Impact of COVID-19 on the Portuguese Hypertension Program

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic is a major concern for patients suffering from hypertension. Continuity of care provided under Primary Care was overlooked during the pandemic, which may have resulted in decreased monitoring of patients with hypertension. Here, we investigated how the COVID-19 pandemic impacted the activity of the Portuguese Hypertension Program. We found a significant decrease in the mean of the monthly number of observations for 2020 compared to previous years. Overall, lockdown measures resulted in significant decreased activity of the hypertension program, specifically in April 2020 and February 2021. Furthermore, by performing a regional analysis for each Regional Health Administration (ARS) of the activity of the hypertension program, we found that in April 2020 there was a significant decrease only in ARS Norte and in February 2021 there was a significant decrease only in ARS LVT and ARS Norte. We concluded there was a significant decrease in the temporal evolution of the proportion of monitored patients in 2020. Furthermore, we speculated that both COVID-19 policy measures and Primary Care based information were useful predictors to understand the time evolution of the activity of the hypertension program during the COVID-19 pandemic. Our findings suggested that the COVID-19 pandemic had a significant impact on the continued care provided to the hypertension community. We provided statistical evidence that a thorough exploration on the health consequences of the COVID-19 pandemic to the hypertension community should be conducted.

1. Introduction

Studies from various countries reported that hypertension, diabetes and cardiovascular diseases were the most prevalent comorbidities among patients suffering from COVID-19 [7, 8, 21]. Specifically, hypertension is considered one of the most important risk factors for COVID-19. A meta-analysis in China found that the prevalence of hypertension in patients with COVID-19 was 17.1% (95% CI 9.9%-24.4%) and showed that hypertension accounted for 28.8% of ICU/severe cases, but only 14.1% of non-ICU/non-severe cases [12]. In fact, there was statistical evidence that having hypertension resulted in a two-fold increased risk of having a severe disease case (Risk Ratio 2.03, 95% CI 1.54-2.68). Furthermore, another meta-analysis showed that the mortality risk of patients infected with COVID-19 was 3.36 times higher in hypertensive patients than in normotensive patients (Odds Ratio 3.36, 95% CI 1.96-5.74) thus concluding, with a 5% significance level, that hypertension led to an increased mortality risk [28].

The COVID-19 pandemic represents a major concern for the hypertension community. Confinement measures for the prevention of COVID-19 have a significant impact on vulnerable populations with comorbidities, such as hypertension. Despite reducing the spread of the SARS-CoV-2 infection, confinement measures hamper regular patient-provider interactions considered essential for the comprehensive monitoring and care of hypertension [2]. In addition, along with delayed care-seeking due to fear of contracting COVID-19, other risk factors arise due to confinement, such as unhealthy diets, reduced physical activity and mental health related concerns which may ultimately lead to health consequences [11]. Furthermore, generally, governments adopted a COVID-19 response focused essentially on hospital care in order to prevent the collapse of the national healthcare systems, thus overlooking the importance of Primary Care in guaranteeing the continuity of care. As a result, access to care for chronic conditions as well as acute complications significantly dropped during the COVID-19 pandemic [24].

The Portuguese National Healthcare System (NHS) provides care and monitoring to patients suffering from hypertension. To assess whether and how the COVID-19 pandemic affected continued care provided to the hypertension community is a vital step to ponder future implications and devise new strategies for forthcoming pandemics.

Here, we attempted to understand and explain the impact of the COVID-19 pandemic on the activity of the Portuguese Hypertension Program. To this end, we analysed observations from the latter publicly available at Transparency. We hypothesised: (1) a decrease in the activity of the program in 2020 compared to previous years; (2) a decrease in the proportion of observed patients under the program during lockdown periods compared to the same periods in previous years; (3) a disproportionate outcome on hypertension continued care under each ARS; (4) a decrease in the temporal trend of observations in 2020 compared to preceding years; (5) a need for incorporating both COVID-19 policy measures and Primary Care based information to model the activity of the hypertension program during the COVID-19 pandemic.

In this study, we concluded that COVID-19 had a significant negative impact on the monitoring of hypertensive patients in Portugal. Therefore, in parallel to the epidemic response, we believe the Portuguese NHS should make further efforts to ensure existing healthcare services, especially Primary Care, keep running in order to avoid additional health consequences.

2. Methods and Materials

2.1. Study area

This analysis presented was focused on mainland Portugal. The first cases of COVID-19 in Portugal were reported on 2nd March 2020. On 3rd March 2020, General Directorate of Health (DGS) started to issue a daily summary of the evolution of COVID-19. The Portuguese government adopted lockdown measures to restrict citizens' mobility to avoid the spread of the SARS-CoV-2 infection. During these periods, citizens were only allowed to leave home only to buy food, medicines or essential goods, to go to work if it was not possible to work from home, or for medical and emergency reasons. The first lockdown lasted between 18th March 2020 [16] and 2nd May 2020 [17], with the second lasting between 15th January 2021 [18] and 30th April 2021 [19].

2.2. COVID-19 in Portugal

The data related to the evolution of COVID-19 in Portugal was downloaded from the publicly available repository covid19pt-data. Data recorded from 26th February 2020 to 31st May 2021 was analysed. Here, data relative to the number of new daily COVID-19 confirmed cases was analysed to characterize the evolution of the COVID-19 pandemic in Portugal. Furthermore, we tested whether the mean number of new daily COVID-19 confirmed cases differed across the Portuguese Regional Health Administrations (ARS), using the non-parametric Kruskal-Wallis test, after detecting non-normality and heteroscedasticity in the data, using the Shapiro-Wilk and Levene tests, respectively. Pairwise comparisons of means were conducted using the Wilcoxon Rank-Sum test with Bonferroni correction. In addition, data related to the number of hospitalizations and deaths was analysed. Finally, the autocorrelation (ACF), partial autocorrelation (PACF) and cross-correlation (CCF) functions were computed for a subset of relevant predictors in order to describe important features of the COVID-19 time evolution, explain how past observations could affect future ones and investigate the relationship between data. The data and statistical analyses were performed using the packages "car" [5] and "stats" [20] in R software version 4.0.4 [20].

2.3. Portuguese Hypertension Program dataset

Data related to the activity of the Portuguese Hypertension Program was obtained from Transparency, an open-access NHS data platform. The dataset contained monthly information, recorded from January 2014 to February 2021, of the proportion of NHS users with arterial hypertension (HT), aged under 65 years, who have had at least one blood pressure (BP) measurement of less than 150/90 mmHg in the past 6 months. Henceforth, users satisfying the aforementioned conditions were designated "patients with condition". An exploratory analysis of the data aggregated by year, month and ARS was conducted using R software version 4.0.4 [20].

2.4. Differences in activity of the hypertension program

Here, in order to assess whether there was a change in the mean number of patients with condition in 2020 compared with previous years, the Kruskal-Wallis test was utilized, since the Shapiro-Wilk test suggested non-normality and the Levene test heteroscedasticity of the data. Two-sided pairwise comparisons of the means for each year were performed using the Games and Howell test [6]. Aiming to confirm the previous results, the same procedure was applied to the detrended number of patients with condition obtained using the function "detrend" with default settings from the R package "pracma" [3]. We excluded 2021 from the previous statistical tests since only data relative to January and February was available. We expected a decrease in the mean number of patients with condition during the COVID-19 pandemic, specifically during the lockdown of 2020 and 2021. Consequently, we investigated whether a decrease occurred during April 2020 and February 2021 compared with the same respective months in past years. Given that the assumptions of the ANOVA test were not satisfied, the Kruskal-Wallis test was used to confirm this expectation. In view of this expectation, pairwise comparisons were performed using the one-sided Wilcoxon Rank-Sum test with Bonferroni correction. In addition, the Games and Howell test was utilized to confirm the previous results. Finally, we tested whether the mean for April 2020 and February 2021 was different from the same respective months in past years across ARS, using the Kruskal-Wallis test for every ARS, after detecting that the assumptions of the One-Way ANOVA test were not satisfied, with exception of ARS Alentejo for which the standard One-Way ANOVA test was performed, since normality using the Shapiro-Wilk test and homogeneity of variance across years using the Levene test were detected. In addition, since we had no expectation on whether the mean of April 2020 and February 2021 across ARS would increase or decrease, we employed two-sided pairwise comparison tests using the Games and Howell test.

2.5. Monthly observation trends across years

The monitoring of patients with condition may have been influenced by the COVID-19 pandemic, as patients could have delayed care-seeking in Primary Care. We suspected that the temporal trend and seasonality observed in the monthly number of patients with condition for 2014-2019 may have been altered due to the imposition of lockdown restrictions and, more broadly, COVID-19. In order to estimate whether these effects resulted in differences in the observed trend and seasonality of the number of patients under the hypertension program in 2020 compared to previous years, we utilized generalised additive models (GAMs) following the methodology of [1, 23]. GAMs are statistical models that can be used to estimate trends as smooth functions of time. Specifically, unlike a standard generalized linear model, GAMs are composed of a sum of smooth functions of covariates instead of or in addition to the standard linear covariate effects [23]. To conduct this analysis, the hypertension program data was aggregated by month and year. Thereafter, a wide range of models using different covariates, covariate interactions and smoothing parameters was tested using observations recorded from January 2014 to December 2020. Smoothing parameter selection was conducted using restricted maximum likelihood (REML) [27]. ANOVA tests were performed to assess the significance of models, covariates and smooth terms. Model fit was assessed using R^2_{adj}, AIC and by visually inspecting the residuals. As stated, the objective of this analysis was to explain the effect of 2020 on the temporal trend of the observations. Nevertheless, when aiming to test the predictive ability of the GAM model, the latter was used to predict the monthly mean number of patients with condition in January and February 2021. Analysis were performed using the "mgcv" [25] and "pracma" [3] packages in R version 4.0.4 software version [20].

2.6. Impact of COVID-19 policy measures and Primary Care access on the hypertension program

Here, we aimed to assess the impact of COVID-19 on the monitoring activity of the Portuguese Hypertension Program by designing a model which considered a wide range of predictors, such as COVID-19 policy measures and Primary Care based information. Here, we considered observations from March 2020 to February 2021. Firstly, data from the Portuguese Hypertension Program was retrieved. Secondly, data related to policy measures imposed by each Portuguese ARS to respond to the negative effects of COVID-19 was obtained using the R package "COVID19" [9]. Thirdly, information of the access and demand of Primary Care Services was obtained from Transparency. Finally, data relative to the evolution of several types of Primary Care appointments was downloaded from Transparency. The dataset used for analysis considered only a subset of relevant predictors, see Appendix 5.5 for further details. We expected that an increase in the severity of COVID-19 policy measures and a decrease in the access to Primary Care services to be mirrored by a decrease in the mean number of observed patients with condition across ARS and time. Consequently, we investigated the effect of COVID-19 policy measures and Primary Care related information (independent variables) in the mean number of observed patients with condition (dependent variable) by fitting several ordinary least squares (OLS) regression models. Nevertheless, given that the Durbin-Watson test was significant for residual autocorrelation, we utilized generalised least squares (GLS) regression models to account for the possibility of unequal error variances and correlations between different errors [4]. The correlation structure between the residuals obtained by the OLS regression models was assessed using the function "auto.arima" from the R package "forecast" [10]. Following the methodology of [22], we fitted two different types of OLS and GLS regression models: (1) simple models with one single COVID-19 policy measure or Primary Care related information at a time and (2) full model with all COVID-19 policy measures and all Primary Care based variables. The ARS of each observation in the data was included in both types of models as a categorical variable. ANOVA likelihood ratio tests between nested models were employed to check the significance of the fixed effect terms and the need for the correlation structure. Model fit was assessed using the AIC, McFadden's Pseudo-R^2 [13], Nagelkerke's Pseudo-R^2 [14] and by analysing the residuals-diagnostic plots. Analysis were performed using the "nlme" [15] package in R software version 4.0.4 [20].

3. Results

3.1. COVID-19 in Portugal

The daily evolution of the total number of new confirmed cases between February 2020 and May 2021 was depicted in Figure 1.

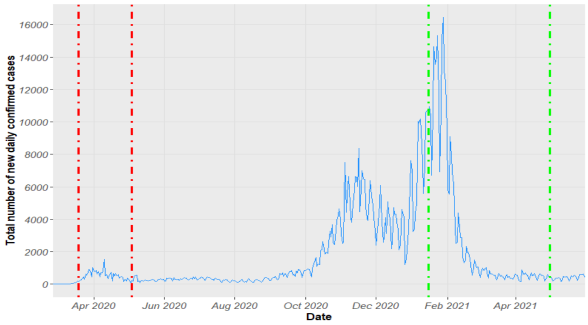


Figure 1: New daily confirmed COVID-19 cases. Each lockdown was represented within each set of colored dashed lines.

Analysis of Figure 1 revealed that there were three distinct COVID-19 waves in Portugal. The red dashed lines correspond to the first lockdown period and wave. Afterwards, the pandemic situation was considered stable. October 2020 until December 2020 corresponded to the second COVID-19 wave. The second lockdown period is represented within the green dashed lines and approximately matches the third COVID-19 wave. The latter was the worst relative to the number of new daily confirmed COVID-19 cases. The barplot of the monthly evolution of the total number of new confirmed COVID-19 cases depicted a similar pattern (Figure 10).

ARS Lisboa e Vale do Tejo (LVT) and ARS Norte registered the highest counts of new daily infected as observed in Figure 11. The boxplot of the daily total number of new confirmed COVID-19 cases for each ARS was presented in Figure 2.

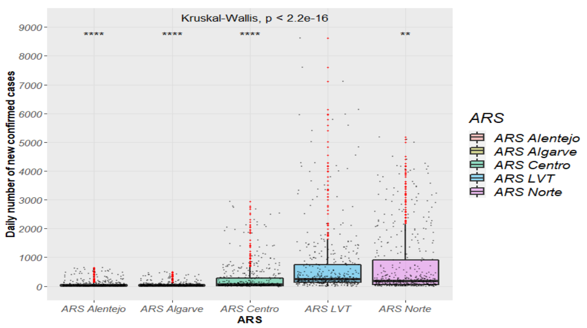


Figure 2: Boxplot of the total number of new confirmed COVID-19 cases for each ARS. Comparison of means performed using the Kruskal-Wallis test. Asterisks indicate significant differences between the mean of each ARS and ARS LVT ($p < 0.05$). Red points represent outliers, according to the Tukey criterion.

As observed from Figure 2, ARS LVT and ARS Norte were most affected by COVID-19. In fact, the aforementioned ARS had the largest variability in the daily number of new confirmed cases. Moreover, both were characterized by a large number of outliers, which corresponded to days with an atypically high number of new confirmed cases. The Kruskal-Wallis test identified significant differences in the means of the daily number of new confirmed COVID-19 cases between ARS $(F = 788.24; \mathrm{p} < 0.001)$. Specifically, as exemplified by Figure 2, all pairwise differences were considered significant $(\mathrm{p} < 0.05)$, with the exception of the pair ARS Alentejo/Algarve.

Another relevant descriptor of the evolution of the pandemic in Portugal refers to the number of COVID-19 based hospitalizations. Figure 3 presented, for each month, the total number of COVID-19 infected patients hospitalized either in Nursery units or Intensive Care Units (ICU).

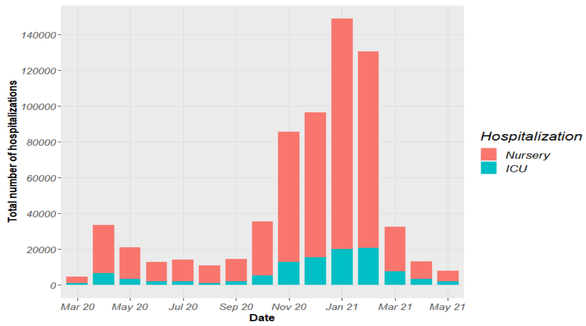


Figure 3: Total number of COVID-19 related hospitalizations in Nursery units and ICU per month.

The fluctuations in the number of hospitalized patients with COVID-19 depicted in Figure 3 followed closely the variations in the daily number of new confirmed COVID-19 cases observed in Figure 1. The third COVID-19 wave had the largest number of hospitalizations.

As indicated by the significant sample autocorrelations observed in Figure 12 (a), there was significant persistence of new confirmed COVID-19 cases from one period to the next, characterized by a weekly seasonality pattern. Figure 13 (a) suggested a similar interpretation with an apparent seasonality pattern. Both Figure 12 (b) and Figure 13 (b) suggested an autoregressive term in the data. The sample CCF between the total number of new confirmed cases and the total number of hospitalizations was presented in Figure 4. As observed, the number of new confirmed cases leads the number of hospitalizations. In fact, according to Figure 4, an above average number of new confirmed cases was likely to lead to an above average number of hospitalizations several days later, as evidenced by the significant positive cross correlation values obtained for negative lags. The results obtained in Figure 4 and Figure 14 were coherent with the values obtained for the Pearson correlation matrix of Figure 15.

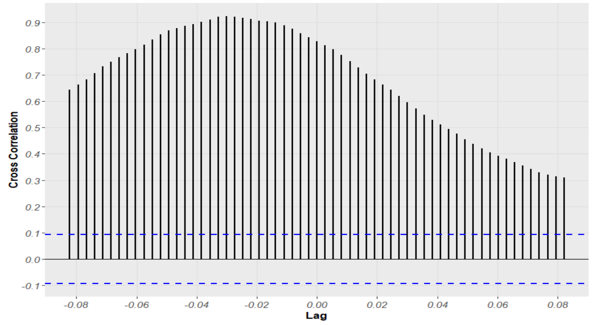


Figure 4: CCF between the total number of new confirmed cases and the total number of hospitalizations.

3.2. Summary of the hypertension program dataset

The entire dataset consisted of 4,711 observations recorded from January 2014 to February 2021. Each observation corresponded to the number of recorded patients with condition for a given Health Center Group (ACES) inserted on a given ARS for a specific month and year. The number of observations for each year was approximately the same, with the exception of 2021, as shown in Figure 16. With the exception of 2020 and 2021, the mean number and mean proportion of patients with condition was approximately identical across previous years. As observed in Figure 17, the ARS with most observations was ARS Norte, followed by ARS LVT. The pattern observed in Figure 5 of the monthly mean proportion of patients with condition across the years displayed seasonality.

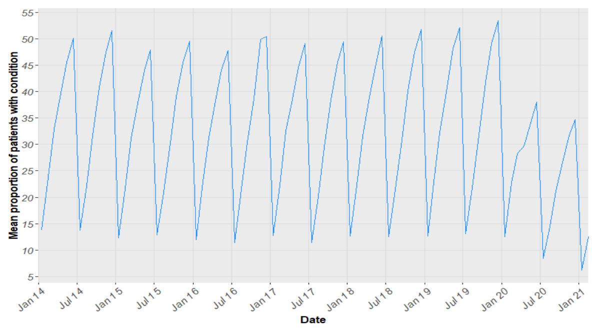


Figure 5: Monthly evolution of the mean proportion of patients with condition from 2014 to 2021.

As demonstrated in Figure 5, generally, on each year, the monthly mean proportion of patients with condition follows an upward trend, which drops abruptly in July, followed by another increasing period until December.

3.3. Differences in activity of the hypertension program

Significant differences were detected in the mean number of patients with condition across the years 2014 to 2020 by the Kruskal-Wallis test $(F = 98.93; \mathrm{p} < 0.001)$. In 2020, according to the one-sided Wilcoxon Rank-Sum test, there was a significant decrease in the mean number of patients with condition compared to the years 2014-2019 $(W = 1608522; \mathrm{p} < 0.001)$. Results from the individual pairwise comparisons between 2020 and each of the previous years were in agreement with the aforementioned results, i.e., the mean number of patients with condition significantly decreased in 2020 $(\mathrm{p} < 0.001)$. The boxplot of Figure 6 corroborates the previous results.

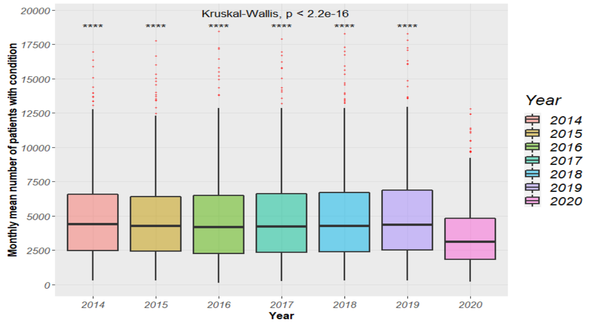


Figure 6: Boxplot of the mean number of patients with condition for each year. Comparison of means performed using the Kruskal-Wallis test. Asterisks indicate significant differences between the mean of each year and 2020 $(\mathrm{p} < 0.001)$. Red points represent outliers, according to the Tukey criterion.

The Kruskal-Wallis test identified significant differences in the detrended mean number of patients with condition among years $(F = 98.56; \mathrm{p} < 0.001)$, as observed in Figure 18. The Games and Howell pairwise comparisons test detected significant differences in 2020 compared to all of the previous years $(\mathrm{p} < 0.001)$.

During April, the month corresponding to the 2020 lockdown, the Kruskal-Wallis test detected significant differences in the mean number of patients with condition among years $(F = 15.70; \mathrm{p} < 0.05)$, as shown in Figure 7. Test results for February were presented in Appendix 6.3.

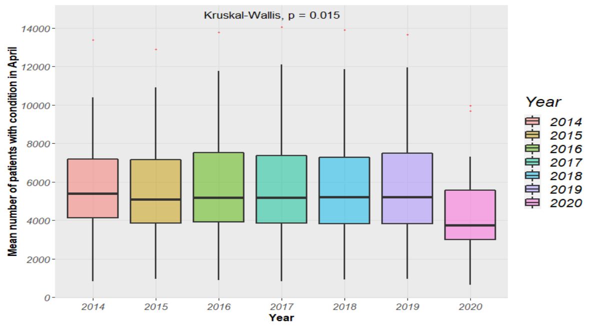


Figure 7: Boxplot of the mean number of patients with condition in April for each year. Comparison of means performed using the Kruskal-Wallis test. Red points represent outliers, according to the Tukey criterion.

In fact, the mean number of patients with condition in 2020 was significantly lower compared to previous years as evidenced by the mean differences and significance test results, presented in Table 1, obtained with the Games and Howell test.

Year	Mean difference	p-value
2014	-1332.27	< 0.1
2015	-1217.73	< 0.1
2016	-1369.71	< 0.1
2017	-1367.27	< 0.1
2018	-1392.47	< 0.05
2019	-1503.69	< 0.05

Table 1: Comparison of the mean number of patients of April 2020 with April of previous years using the Games and Howell test.

By performing an ANOVA test on observations from April recorded in ARS Alentejo, we did not find significant differences in the mean number of patients with condition across years, as evidenced in Figure 19 (a). Moreover, this result was corroborated by the pairwise comparisons which found no significant differences between April 2020 and April of previous years in ARS Alentejo. Similarly, the Kruskal-Wallis test did not identify significant differences in the means of April across years for ARS Algarve, ARS Centro and ARS LVT aggregated data, as depicted in Figures 19 (b), (c), (d). Pairwise comparisons did not report significant differences between April 2020 and the same month in previous years. Nevertheless, the Kruskal-Wallis test found significant differences in the mean number of patients with condition observed in April for the ARS Norte aggregated data $(F = 15.39; \mathrm{p} < 0.05)$, as observed in Figure 19 (e). In fact, pairwise comparisons detected a significant decrease in April 2020 compared to 2014, 2016, 2017 $(\mathrm{p} < 0.05)$ and 2015, 2018, 2019 $(\mathrm{p} < 0.1)$. Analysis of February across years and ARS was presented in Apprendix 6.3.

3.4. Monthly observation trends across years

We were interested in modelling the mean percentage of patients with condition measured each month from 2014 until 2020. Therefore, we fitted the model described by Equation 1.

$$y = \beta_0 + f_{seasonal}(x_1) + x_2 + f_{interaction}(x_1, x_2) \quad (1)$$

where y was the response variable, β_0 was the intercept term, $f_{seasonal}$ and $f_{interaction}$ were smooth functions for the seasonal term and the interaction term between seasonal and trend features. The covariates x_1 and x_2 were selected in order to provide some form of time indicators of within-year and between year variation. Concretely, the mean percentage of patients with condition for each month of each year corresponded to the response variable (y), which was assumed to follow a Binomial distribution. The number of the month of each observation (x_1) was smoothed with a thin plate regression spline $(f_{seasonal})$ with a basis dimension of 12 (number of unique values of the covariate). Since the year was treated as a categorical variable, it was included as a linear predictor in the model (x_2) to account for the trend in the observations and assess whether 2020 had a significant effect on the temporal trend of the data. Thus, no smoothing term was applied to this covariate. The interaction between the trend and seasonal features of the data was modelled with a tensor product interaction [26] applied to both x_1 and x_2 using thin plate regression splines with a number of knots of 12 and 7 for each covariate, respectively. We included a continuous autoregressive term in the model to account for month to month autocorrelation between the number of observations within each year, since the Durbin-Watson test for autocorrelated errors was significant $(\mathrm{p} < 0.001)$ when applied to the model with uncorrelated errors.

Firstly, from the analysis of the GAM fit, it was observed that the hypothesis of zero-effect of the smooth terms were rejected $(\mathrm{p} < 0.001)$. Secondly, the diagnostic plots of Figure 21 were used to visually assess the residuals. The experimental distribution had approximately the same shape as the theoretical distribution, as evidenced by the QQ-plot of the residuals depicted in Figure 21 (a). The histogram of the residuals found in Figure 21 (b) followed approximately a binomial distribution. In Figure 21 (c), the residuals were randomly scattered around the origin as a function of the linear predictors, thus suggesting that their expected value was approximately 0. Figure 21 (d) evidenced a distribution of points aligned with the $y = x$ line, indicative of the GAM's goodness of fit and usefulness to describe the data. The scatterplot of the residuals as a function of the order in which observations were collected, depicted in Figure 21 (e), exhibited normal random noise around the $y = 0$ line suggesting that there was no serial correlation. Thirdly, the number of basis functions used to fit the GAM was appropriate, as evidenced by the k-index values of 0.98 and 1.36 for the smooth terms $f_{seasonal}$ and $f_{interaction}$, respectively. Finally, the concurvity of the GAM yielded values close to 0, suggesting no co-linearity issues.

As evidenced in Table 2, the GAM identified a significant parametric predictor for the year 2020. The coefficient estimate for 2020 was -1.1690, which indicated an overall decrease in the mean percentage of observed patients with condition in that year compared to previous years. Thus, there was a decrease in the temporal trend of the mean percentage of observed patients with condition. The model scored a R^2_{adj} of 0.99 and an AIC of -180.50.

Year	Estimate	SE
2014	-0.7162*	0.0057
2015	-0.8008*	0.0057
2016	-0.7955*	0.0058
2017	-0.7986*	0.0057
2018	-0.7533*	0.0057
2019	-0.7031*	0.0057
2020	-1.1690*	0.0062

Table 2: Parametric coefficients estimated by the generalised additive model assessing temporal trends in the mean percentage of observed patients with condition. SE = standard error. Asteriks indicate significant values $(\mathrm{p} < 0.001)$.

As evidenced in Figure 8, the GAM was able to model the temporal trend of the mean percentage of observed patients with condition for January and February 2021. We note that the model used to obtain the predicted values did not consider year as a categorical variable. Here, the variable year was modelled as a continuous predictor smoothed using a P-spline with 7 knots (one for each considered year).

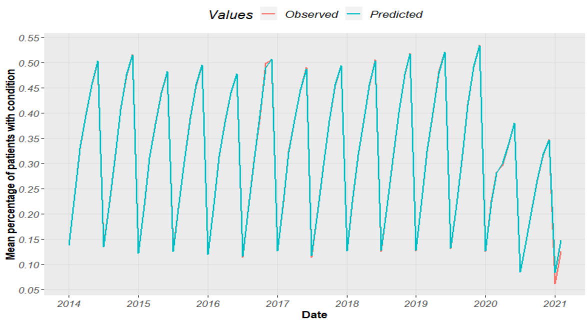


Figure 8: Plot of the observed values and GAM prediction values of the mean percentage of patients with condition for data from January 2014 to February 2021.

3.5. Impact of COVID-19 policy measures and Primary Care access on the hypertension program

A number of simple GLS regression models, with an autocorrelation-moving average correlation structure of order $(2, 1)$, were fitted to the data: (1) M_0, closure of schools/universities, (2) M_1, closure of workplaces, (3) M_2, stay at home requirements, (4) M_3, restrictions on internal movement, (5) M_4, stringency index, (6) I_1, number of appointments in Primary Care, (7) I_2, number of face-to-face appointments in Primary Care, (8) I_3, number of non-present/non-specific appointments in Primary Care, (9) I_4, number of at-home appointments in Primary Care and (10) F, full model with all the aforementioned predictors. Likelihood ratio tests between nested models, suggested that the fixed effect terms and the correlation structure of every model were significant $(\mathrm{p} < 0.001)$.

The residuals-diagnostic plots of the full model, displayed in Figure 22, were visually inspected aiming to evaluate the model assumptions. Firstly, the distribution of the residuals as a function of the fitted values suggested non-linear patterns in the data. In fact, the residuals were not randomly scattered, as evidenced in Figure 22 (a). Secondly, the residuals did not follow a normal distribution, as suggested by the QQ-plot of Figure 22 (b), the histogram of the residuals in Figure 22 (c) and the Shapiro-Wilk test results $(\mathrm{p} < 0.001)$. Finally, the Durbin-Watson test identified significant residual autocorrelation $(\mathrm{p} < 0.05)$, which was corroborated by the decreasing pattern of the residuals, as a function of the observation index, in Figure 22 (d). Moreover, the variance inflation factor identified significant collinearity between predictors in the model. Therefore, the full model did not properly represent the data. Nevertheless, we present our findings in order to provide some insight into the effects of COVID-19 policy measures and Primary Care based information on the activity of the hypertension program.

Figure 9 presented the AIC, McFadden's and Nagelkerke's Pseudo-R^2 for the different models.

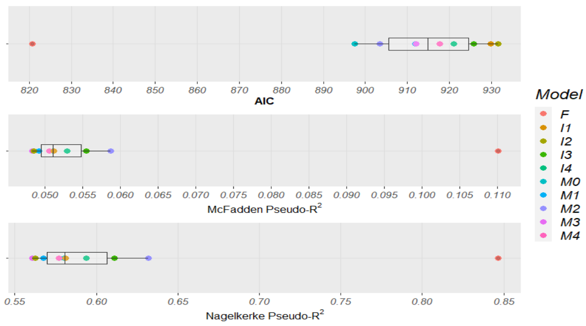


Figure 9: AIC, McFadden's and Nagelkerke's Pseudo-R^2 for the evaluated models (horizontally). One boxplot for each metric was computed based on the distribution of the values obtained by each model for the referred metric.

The full model that combined all predictors yielded the best results across all metrics, i.e., the lowest AIC (820.75) and the highest McFadden's (0.11) and Nagelkerke's (0.85) Pseudo-R^2. With the exception of model F, the variability of the results computed for each simple model on each metric was low, which suggested that no single predictor could be used to completely explain the fluctuations in the number of observed patients with condition during the COVID-19 pandemic. Overall, relative to the simple models, M_2, which used the stay at home requirements categorical predictor and I_3, which considered the number of non-present appointments in Primary Care, yielded the best results. Model M_3, which considered restrictions on internal movement, achieved the lowest McFadden's and Nagelkerke's Pseudo-R^2.

The full model identified significant predictors for the mean number of patients with condition observed in each ARS, for a given month and year, as observed in Table 3. Specifically, the categorical variables closure of schools/universities and stay at home requirements, as well as the continuous predictors stringency index, number of appointments in Primary Care, number of non-present appointments in Primary Care and number of at-home appointments in Primary Care improved the ability of the model to predict the response variable. Nevertheless, as stated, the validity of aforementioned findings was questionable.

4. Discussion

In general terms, between February 2020 and May 2021, Portugal was hit by three distinct COVID-19 waves, which were managed by the Portuguese government through the implementation of a number of policy measures, such as strict lockdown measures, requiring citizens to stay at home. We observed that from November 2020 to February 2021 the Portuguese NHS registered the highest counts of new COVID-19 infections (Figure 1), where ARS Norte and ARS LVT were the most affected regions. In fact, we concluded that there were significant differences in the means, for each ARS, of the daily number of new confirmed COVID-19 cases (Figure 2). We hypothesized that the increased incidence of COVID-19 on ARS Norte and ARS LVT may have resulted in a decline of continued care, which was also delayed. In addition, we speculated that Primary Care may have been overlooked during the COVID-19 pandemic, especially during the periods in which hospitals registered the highest counts of COVID-19 based hospitalizations (Figure 3). Since there was evidence that an above average number of new confirmed cases led to an above average number of COVID-19 based hospitalizations (Figure 4), we conjectured that ARS Norte and ARS LVT would have had the highest number of COVID-19 based hospitalizations.

Overall, data of the Portuguese Hypertension Program was consistently collected across years (Figure 16). We found that ARS Norte and ARS LVT contributed the largest number of registrations to the data, which was expected due to the increased number of ACES in these regions (Figure 17). We observed that the mean proportion of patients with condition was consistently at its lowest in January and July across years. In addition, the mean proportion of patients with condition increased consistently from January to June and from July to December within a given year (Figure 5) and interval timespan of the data. As stated, the hypertension program considered patients which had at least one blood pressure (BP) measurement of less than 150/90 mmHg in the past 6 months. Consequently, patients which had a BP measurement of less than 150/90 mmHg, for instance, in January of a given year, would still be contributing to the mean proportion of patients with condition in June of the same year but not for July thus explaining the observed yearly temporal pattern. However, despite following a similar temporal evolution, the monthly mean proportion of patients with condition was found to be lower in 2020 and 2021 compared to previous years.

A significant decrease was detected in the mean number and detrended mean number of observed patients with condition in 2020 compared to past years, which suggested that the comprehensive monitoring of the hypertensive community may have been neglected (Figure 6, Figure 18). Both the 2020 and 2021 lockdowns had a decreasing effect in the activity of the hypertension program, since the mean number of patients with condition observed in April 2020 (Figure 7) and February 2021 (Figure 20) was found to be significantly lower compared to the same month in previous years. Furthermore, there was significant evidence that in April 2020 the mean number of patients with condition in ARS Norte, which was the most heavily affected ARS, decreased compared to preceding years (Figure 19). In addition, hypertension continued care in ARS LVT and ARS Norte was found to be significantly decreased in February 2021 compared to past years. Interestingly, COVID-19 seemed to have only influenced monitoring in the largest ARS. These results implied that confinement measures and greater COVID-19 incidences resulted in decreased program activity.

We identified, as expected, a significant decrease in the temporal trend of the mean proportion of patients with condition in 2020 compared to previous years (Table 2). The constant temporal evolution of the mean proportion of patients with condition throughout 2014-2019 was found to decrease in 2020, indicating significant influence of COVID-19 on the activity of the hypertension program. The model was able to capture the temporal pattern of the data, thus providing significant estimates and reliable comparisons between 2020 and past years. On the one hand, although the model was designed to study the effects of COVID-19 on the activity of the program, we found it was able to emulate the temporal evolution of the activity of the program in 2021. On the other hand, we observed that the model predicted values which did not match exactly the observed values of 2021 (Figure 8). Therefore, the predictive ability of the model was limited, which may have been caused by the low number of observations in the sample.

On the one hand, the modelling approach used to study the impact of COVID-19 policy measures and Primary Care access on the hypertension program was found to be inappropriate. Concretely, even though the fixed effect terms and the correlation structure of the models was found to be significant, the assumptions for the GLS regression models were not satisfied (Figure 22). A potential issue could have been related to the non-stationary properties of the data which were not explored thoroughly. Furthermore, for each time point (month and year) there were 5 observations in the dataset, each corresponding to one ARS, which may have caused the models to underfit the data. Finally, the application of the median to all COVID-19 policy measure covariates potentially invalidated the usefulness of the data. On the other hand, based on the results of this analysis we suspected that the COVID-19 policy measure "stay at home requirements" and the Primary Care based information "number of non-presential/non-specific appointments" may have been potential meaningful predictors of the activity of the hypertension program during the COVID-19 pandemic. Surprisingly, the COVID-19 policy on "restrictions on internal movement" was found to have been, potentially, the most uninformative predictor. The full model, which yielded, as expected, the best results, demonstrated that COVID-19 policy measures and Primary Care based information explained up to 85% (Figure 9) of the activity of the hypertension program. Therefore, these results suggested that both COVID-19 policy measures and Primary Care based information should probably be used to analyse the evolution of the mean number of patients with condition during the COVID-19 pandemic timespan.

Further studies are necessary to understand the impact of COVID-19 on a local scale, i.e., on the multiple Health Centers Group (ACES) spread across the country. Future work should also analyse the activity of the hypertension program in the years following the COVID-19 pandemic, to ascertain whether the proportion of NHS users with arterial hypertension, aged under 65 years, who have had at least one BP measurement of less than 150/90 mmHg in the past 6 months returns to values similar to those registered before 2020. Furthermore, the decreased monitoring of NHS patients with hypertension during the pandemic may have had implications on the number of deaths by COVID-19 of patients with hypertension. We believe such as investigation would be pivotal to understand the health consequences of the COVID-19 pandemic on this medical community. For instance, data available at COVID-19 Surveillance Data may be used to study such a problem.

5. Conclusion

The COVID-19 pandemic in Portugal had direct implications to the hypertension community which we aimed to study by analysing data of the activity of the Portuguese Hypertension Program. We found that the activity of the program decreased significantly in 2020 as well as during the lockdown periods. In addition, COVID-19 affected the Portuguese ARS disproportionately, both from the incidence of the virus and the activity of the hypertension program point of view. Our results suggested that both COVID-19 policy measures and Primary Care based information could be potential helpful predictors to study the temporal evolution of the activity of the hypertension program during the COVID-19 pandemic. Overall, our findings suggested that COVID-19 had a negative impact on the continued care essential to the hypertension community.

References

[1] M. Basile, L. F. Russo, V. G. Russo, A. Senese, and N. Bernardo. Birds seen and not seen during the covid-19 pandemic: The impact of lockdown measures on citizen science bird observations. *Biological Conservation*, 256:109079, 2021.

[2] D. Beran, S. Aebischer Perone, M. Castellsague Perolini, F. Chappuis, P. Chopard, D. M. Haller, F. Jacquerioz Bausch, H. Maisonneuve, N. Perone, and G. Gastaldi. Beyond the virus: Ensuring continuity of care for people with diabetes during covid-19. *Primary Care Diabetes*, 15(1):16–17, 2021.

[3] H. W. Borchers. *pracma: Practical Numerical Math Functions*, 2021. R package version 2.3.3.

[4] J. Fox and S. Weisberg. *An R companion to applied regression*. Sage publications, 2018.

[5] J. Fox and S. Weisberg. *An R Companion to Applied Regression*. Sage, Thousand Oaks CA, third edition, 2019.

[6] P. A. Games and J. F. Howell. Pairwise multiple comparison procedures with unequal n's and/or variances: A monte carlo study. *Journal of Educational Statistics*, 1(2):113–125, 1976.

[7] G. Grasselli, A. Zangrillo, A. Zanella, M. Antonelli, L. Cabrini, A. Castelli, D. Cereda, A. Coluccello, G. Foti, R. Fumagalli, G. Iotti, N. Latronico, L. Lorini, S. Merler, G. Natalini, A. Piatti, M. V. Ranieri, A. M. Scandroglio, E. Storti, M. Cecconi, A. Pesenti, and C.-. L. I.

Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*, 323(16):1574–1581, 04 2020.

[8] W.-j. Guan, Z.-y. Ni, Y. Hu, W.-h. Liang, C.-q. Ou, J.-x. He, L. Liu, H. Shan, C.-l. Lei, D. S. Hui, et al. Clinical characteristics of coronavirus disease 2019 in china. *New England journal of medicine*, 382(18):1708–1720, 2020.

[9] E. Guidotti and D. Ardia. Covid-19 data hub. *Journal of Open Source Software*, 5(51):2376, 2020.

[10] R. J. Hyndman and Y. Khandakar. Automatic time series forecasting: the forecast package for R. *Journal of Statistical Software*, 26(3):1–22, 2008.

[11] M. Lazzerini, E. Barbi, A. Apicella, F. Marchetti, F. Cardinale, and G. Trobia. Delayed access or provision of care in italy resulting from fear of covid-19. *The Lancet Child & Adolescent Health*, 4(5):e10–e11, 2020.

[12] B. Li, J. Yang, F. Zhao, L. Zhi, X. Wang, L. Liu, Z. Bi, and Y. Zhao. Prevalence and impact of cardiovascular metabolic diseases on covid-19 in china. *Clinical Research in Cardiology*, 109(5):531–538, 2020.

[13] D. McFadden et al. Conditional logit analysis of qualitative choice behavior. 1973.

[14] N. J. D. NAGELKERKE. A note on a general definition of the coefficient of determination. *Biometrika*, 78(3):691–692, 09 1991.

[15] J. Pinheiro, D. Bates, S. DebRoy, D. Sarkar, and R Core Team. *nlme: Linear and Nonlinear Mixed Effects Models*, 2021. R package version 3.1-152.

[16] Presidência da República. Decreto do presidente da república n.º 14-A/2020, March 2020. https://data.dre.pt/eli/decpresrep/14-A/2020/03/18/p/dre (accessed 10 June 2021).

[17] Presidência da República. Decreto do presidente da república n.º 20-A/2020, April 2020. https://data.dre.pt/eli/decpresrep/20-A/2020/04/17/p/dre (accessed 10 June 2021).

[18] Presidência do Conselho de Ministros. Decreto n.º 3-A/2021, January 2021. https://data.dre.pt/eli/dec/3-A/2021/01/14/p/dre (accessed 10 June 2021).

[19] Presidência do Conselho de Ministros. Resolução do conselho de ministros n.º 45-C/2021, April 2021. https://data.dre.pt/eli/resolconsmin/45-c/2021/p/cons/20210604/pt/html (accessed 10 June 2021).

[20] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2021.

[21] S. Richardson, J. S. Hirsch, M. Narasimhan, J. M. Crawford, T. McGinn, K. W. Davidson, , and the Northwell COVID-19 Research Consortium. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*, 323(20):2052–2059, 05 2020.

[22] C. Santamaria, F. Sermi, S. Spyratos, S. M. Iacus, A. Annunziato, D. Tarchi, and M. Vespe. Measuring the impact of covid-19 confinement measures on human mobility using mobile positioning data. a european regional analysis. *Safety Science*, 132:104925, 2020.

[23] G. L. Simpson. Modelling palaeoecological time series using generalised additive models. *Frontiers in Ecology and Evolution*, 6:149, 2018.

[24] J. Thornton. Covid-19: A&e visits in england fall by 25% in week after lockdown. *BMJ*, 369, 2020.

[25] S. Wood. *Generalized Additive Models: An Introduction with R*. Chapman and Hall/CRC, 2 edition, 2017.

[26] S. N. Wood. Low-rank scale-invariant tensor product smooths for generalized additive mixed models. *Biometrics*, 62(4):1025–1036, 2006.

[27] S. N. Wood. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 73(1):3–36, 2011.

[28] M. Zuin, G. Rigatelli, G. Zuliani, A. Rigatelli, A. Mazza, and L. Roncon. Arterial hypertension and risk of death in patients with covid-19 infection: systematic review and meta-analysis. *Journal of Infection*, 81(1):e84–e86, 2020.

6. Supporting Information

This section contains supporting information for the report. Detailed descriptions and analysis of the datasets, implemented models and complementary plots for Section 3 were presented below.

6.1. COVID-19 in Portugal

The plot of the number of new confirmed COVID-19 cases per month was presented in Figure 10.

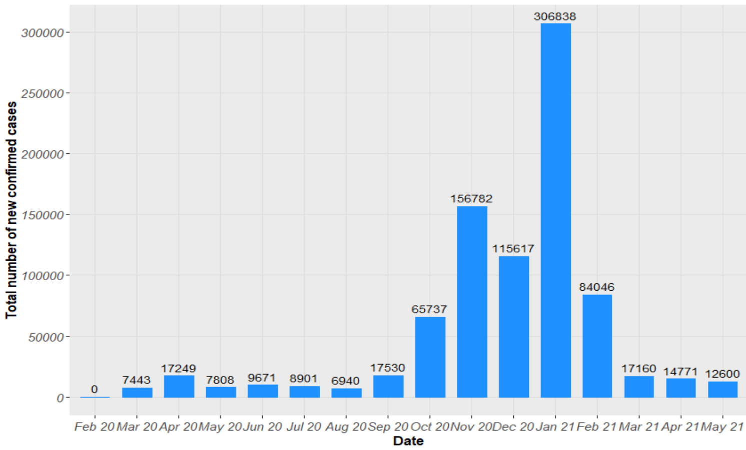


Figure 10: Total number of new confirmed COVID-19 cases per month.

Despite being a coarser visualization of the evolution of the COVID-19 pandemic, Figure 10 provides an indirect measure of the situation of the NHS, which may have directly influenced Primary Care. The plot of the daily total number of new confirmed cases for each ARS was depicted in Figure 11.

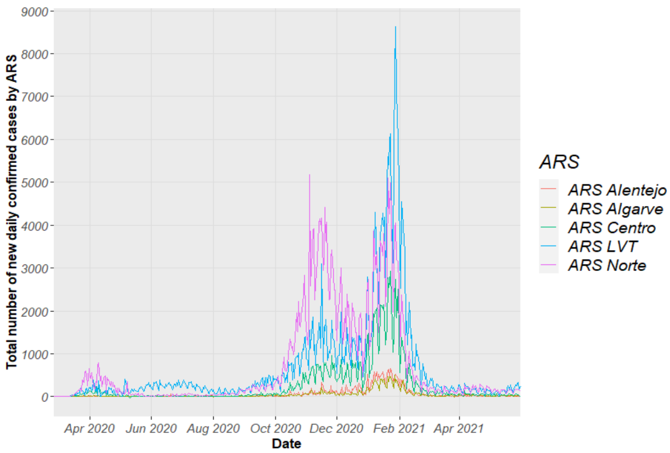
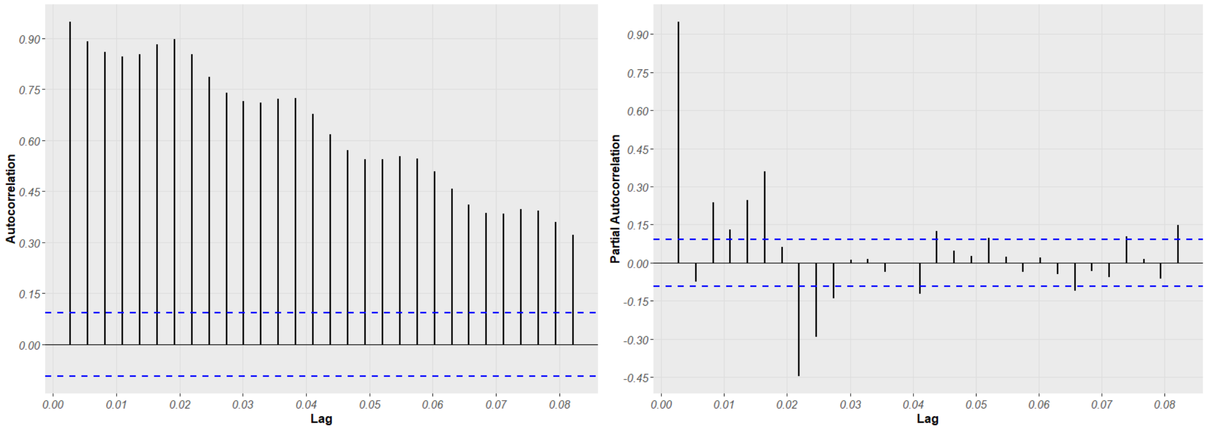


Figure 11: Daily total number of new confirmed COVID-19 cases per ARS.

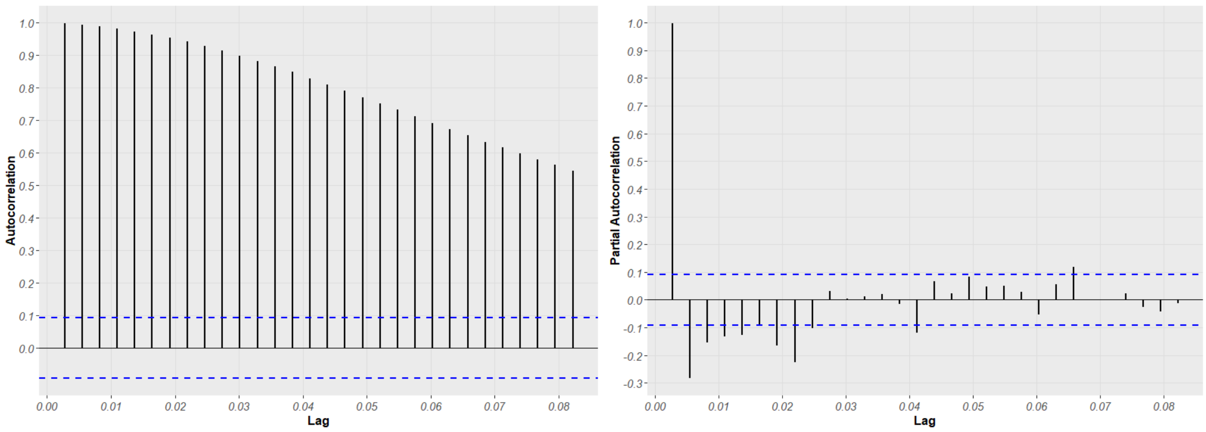
As observed in Figure 11, the most affected ARS were ARS LVT and ARS Norte, particularly during the second and third COVID-19 waves.

The plots of the sample autocorrelation function (ACF) and sample partial autocorrelation function (PACF) with a 95% confidence band for each selected COVID-19 descriptor were presented in Figure 12 and Figure 13.



(a) ACF. **(b)** PACF.

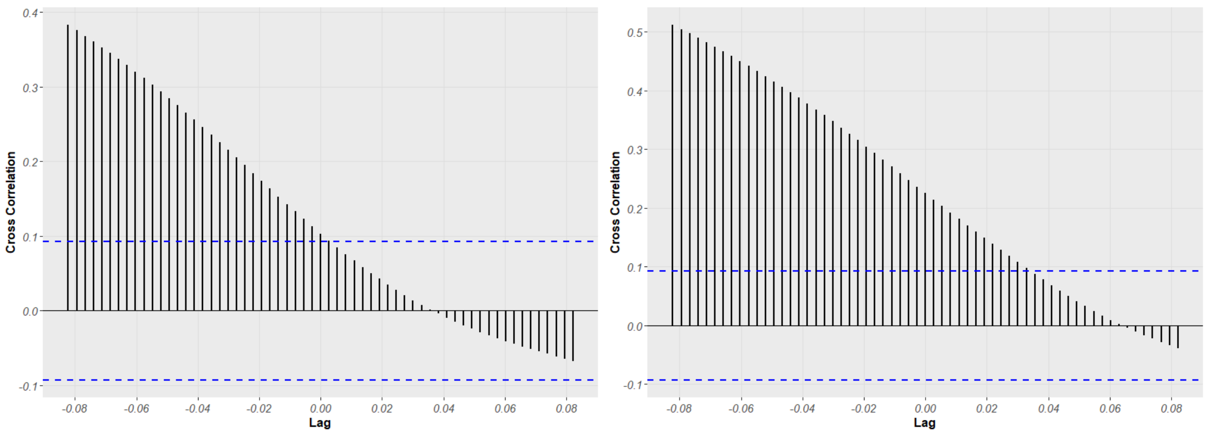
Figure 12: ACF and PACF for the total number of new confirmed COVID-19 cases.



(a) ACF. **(b)** PACF.

Figure 13: ACF and PACF for the total number of COVID-19 hospitalizations.

The plots of the sample cross correlation function (CCF) with a 95% confidence band for each pair of selected variables were depicted in Figure 14



(a) Total number of new confirmed cases and deaths. **(b)** Total number of hospitalizations and deaths.

Figure 14: CCF.

The heatmap of the Pearson correlation matrix, computed on a subset of continuous variables with no temporal features, was depicted in Figure 15.

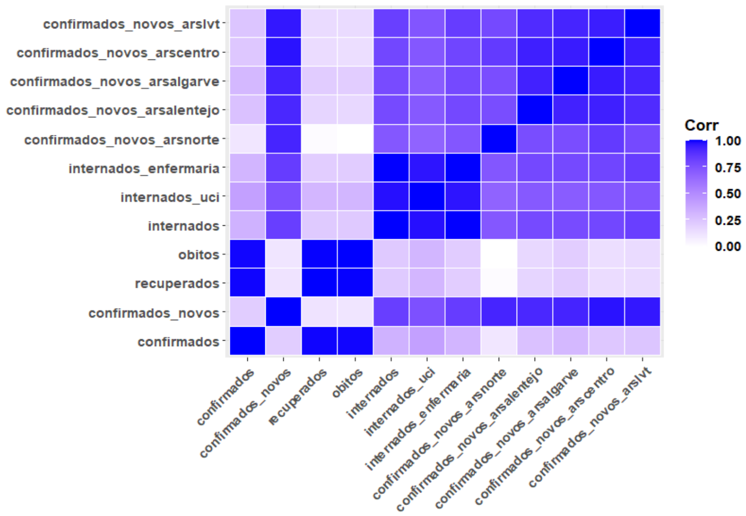


Figure 15: Heatmap of the correlation matrix.

6.2. Summary of Hypertension Program data

Figure 16 presented the total number of recorded observations for each year.

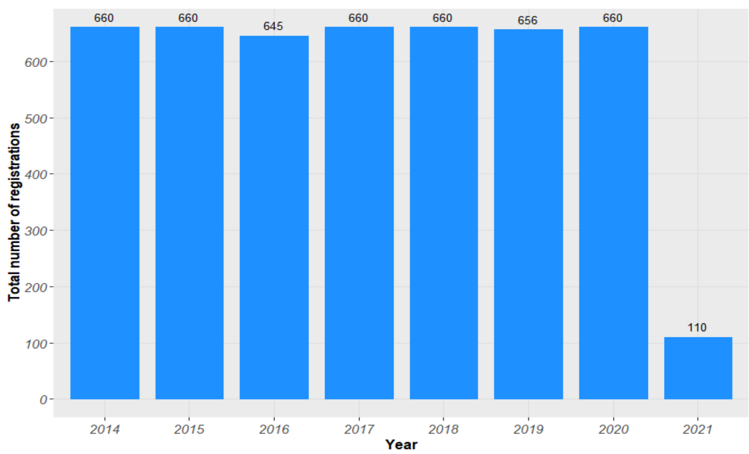


Figure 16: Total number of registrations for each year.

Figure 17 depicted the total number of recorded observations for each ARS.

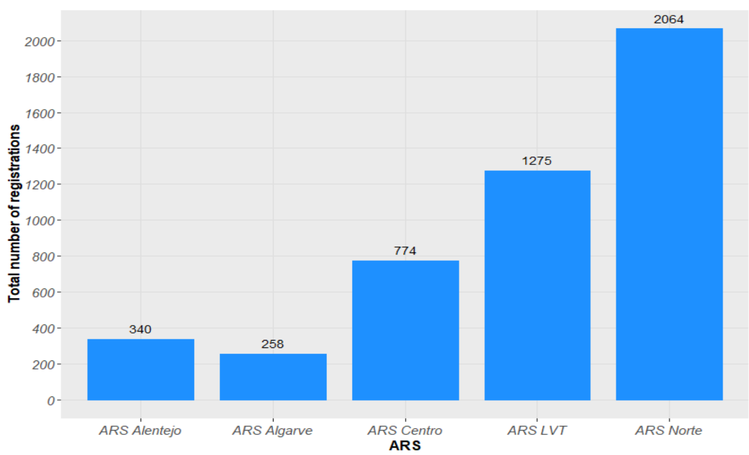


Figure 17: Total number of registrations for each ARS.

6.3. Differences in activity of the hypertension program data

The detrended mean number of patients with condition for each year is represented in Figure 18. Differences between means were computed using the Kruskal-Wallis test and the pairwise comparisons were obtained by a two-sided Wilcoxon Rank-Sum test using 2020 as a reference group.

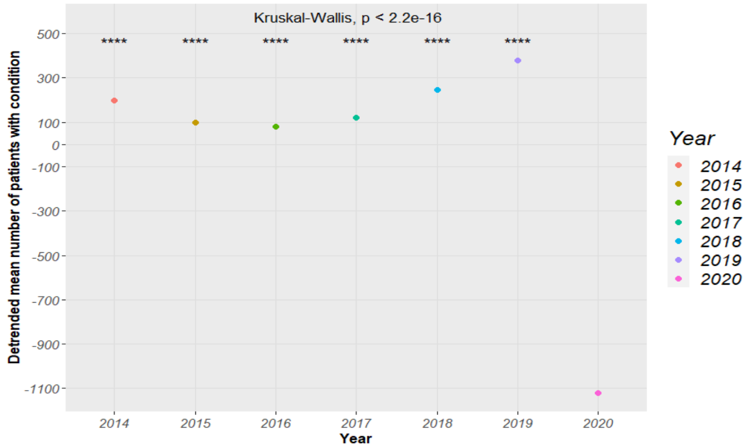
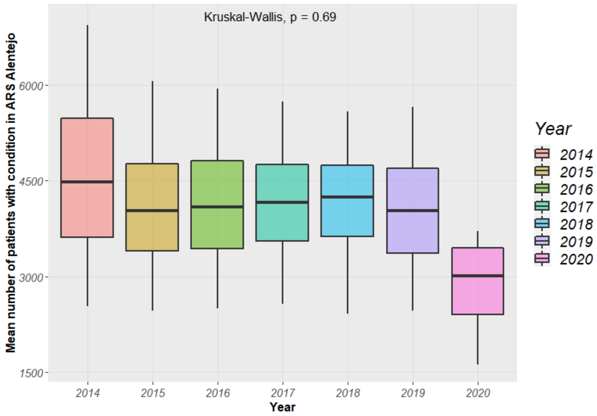
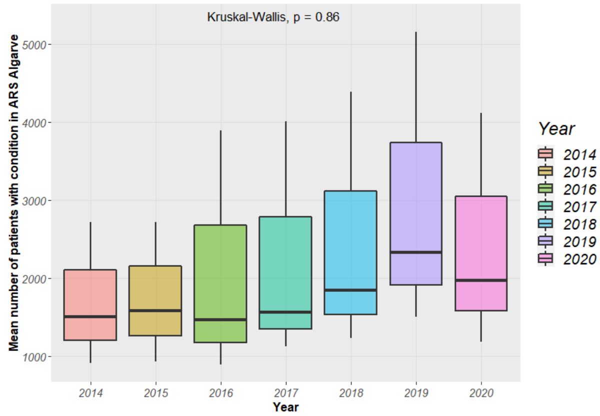


Figure 18: Detrended mean number of patients with condition for each year. Comparison of means performed using the Kruskal-Wallis test. Asterisks indicate significant differences between the detrended mean of each year and 2020 $(p < 0.001)$.

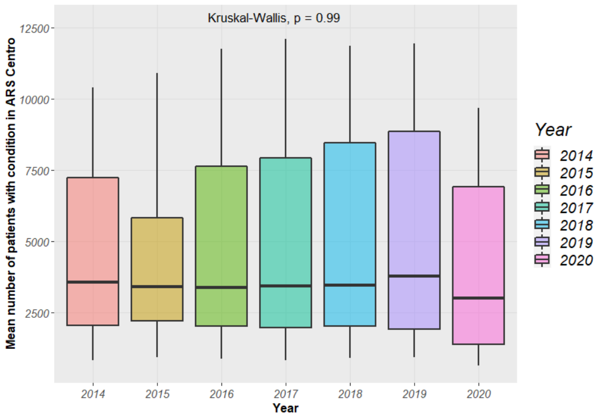
The boxplots of the mean number of patients with condition aggregated by ARS for April of each year were presented in Figure 19.



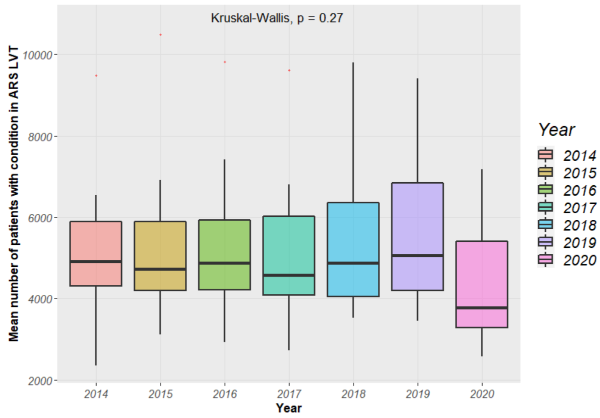
(a) ARS Alentejo.



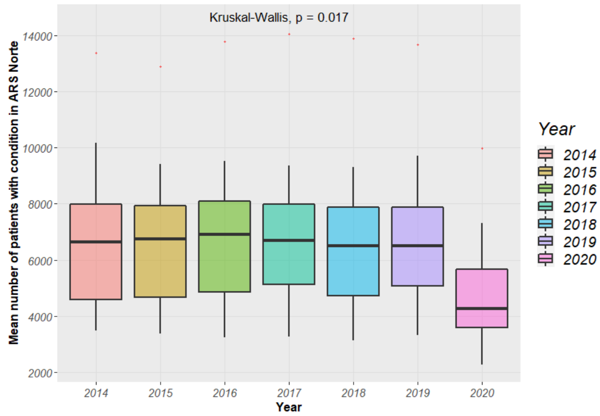
(b) ARS Algarve.



(c) ARS Centro.



(d) ARS LVT.



(e) ARS Norte.

Figure 19: Mean number of patients with condition by ARS for April of each year. Comparison of means performed using the Kruskal-Wallis test. Red points represent outliers, according to the Tukey criterion.

Similarly, the Kruskal-Wallis test identified significant differences in the mean number of patients with condition observed in February across years $(F = 56.67; \mathrm{p} < 0.001)$.

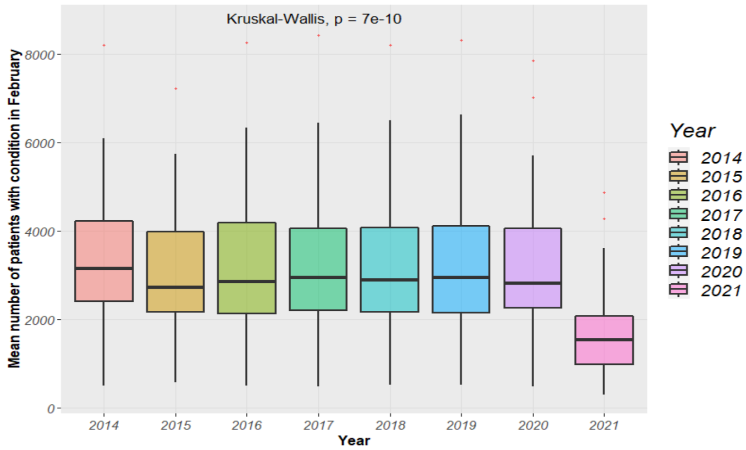


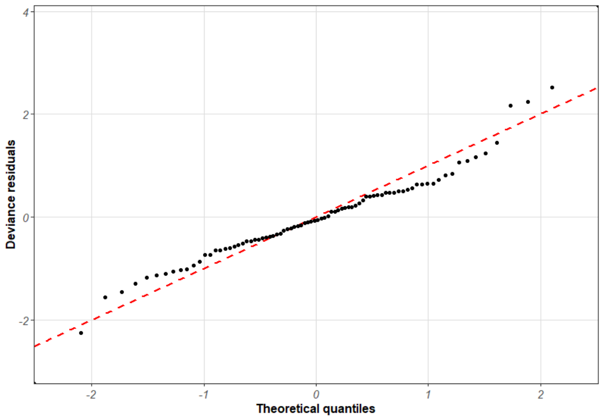
Figure 20: Boxplot of the mean number of patients with condition in February for each year. Comparison of means performed using the Kruskal-Wallis test. Red points represent outliers, according to the Tukey criterion.

Pairwise comparisons between February 2021 and the same month in previous years, using the Games and Howell test, suggested there was a significant decrease in the mean number of patients with condition $(\mathrm{p} < 0.001)$.

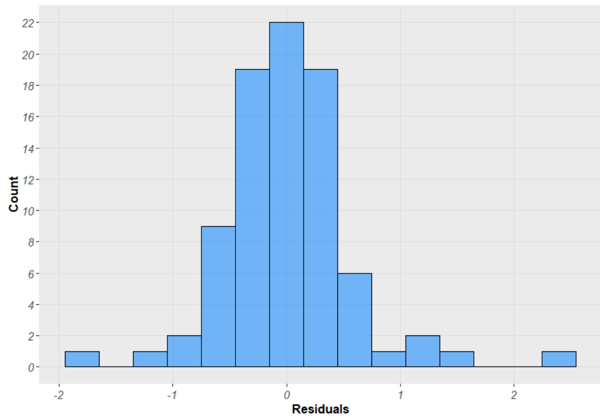
Furthermore, considering each ARS separately, the Kruskal-Wallis identified significant differences in the mean number of observed patients with condition in February for ARS LVT $(F = 31.21; \mathrm{p} < 0.001)$ and ARS Norte $(F = 36.53; \mathrm{p} < 0.001)$. No significant differences were found for the remaining ARS when considering February of each year. The Games and Howell pairwise comparisons identified for both ARS LVT and ARS Norte a significant decrease in February 2021 compared to 2014-2020 $(\mathrm{p} < 0.001)$.

6.4. Monthly observation trends across years

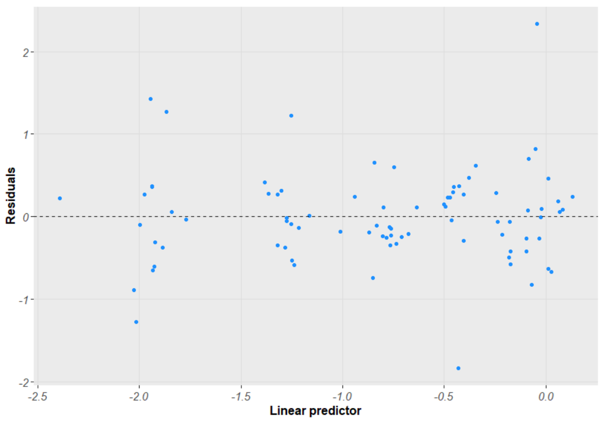
The residuals-diagnostic plots of the GAM described in Section 3.4 were presented in Figure 21.



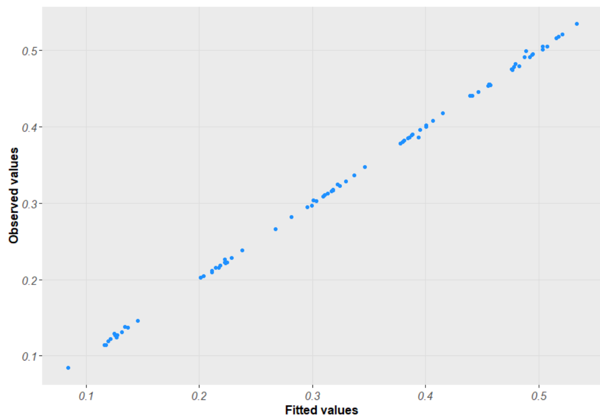
(a) QQ-plot of the residuals.



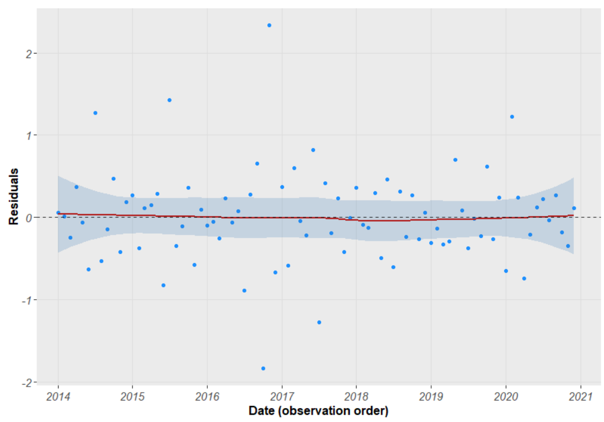
(b) Histogram of the residuals.



(c) Scatterplot of the residuals as a function of the linear predictors.



(d) Scatterplot of the observed values as a function of the fitted values.



(e) Scatterplot of the residuals as a function of the order in which observations were collected. LOESS (Locally Estimated Scatterplot Smoothing) was used to obtain the red line with a 95% confidence band.

Figure 21: Residuals diagnostic plots of the implemented GAM.

6.5. Impact of COVID-19 policy measures and Primary Care access on the hypertension program

As stated in Methods 2.6, the dataset considered data corresponding to the COVID-19 pandemic in Portugal, i.e., from March 2020 to February 2021. Furthermore, the dataset was aggregated by ARS, month and year, since data from the Portuguese Hypertension Program was collected on a monthly basis. The following variables were considered to fit the linear models using generalised least squares:

- ARS;
- Month;
- Year;
- Mean number of patiens with condition for a given ARS, month and year;
- Median of school_closing for a given ARS, month and year;
- Median of workplace_closing for a given ARS, month and year;
- Median of cancel_events for a given ARS, month and year;
- Median of gatherings_restrictions for a given ARS, month and year;
- Median of transport_closing for a given ARS, month and year;
- Median of stay_home_restrictions for a given ARS, month and year;
- Median of internal_movement_restrictions for a given ARS, month and year;
- Mean of stringency_index (combination of COVID-19 policy measures) for a given ARS, month and year;
- Mean number of appointments in Primary Care for a given ARS, month and year;
- Mean number of face-to-face appointments in Primary Care for a given ARS, month and year;
- Mean number of non-present/non-specific appointments in Primary Care for a given ARS, month and year;
- Mean number of at-home appointments in Primary Care for a given ARS, month and year;

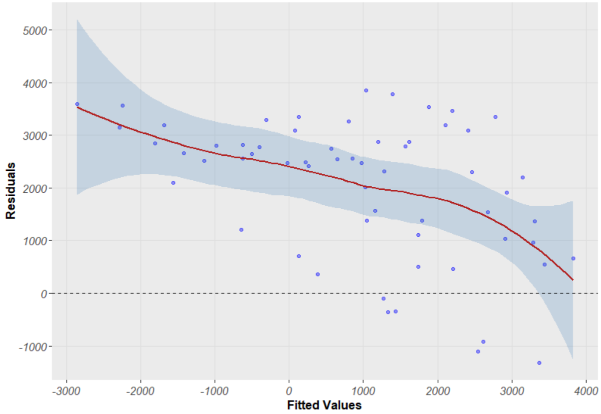
COVID-19 policy measures could take a value from 0 to 2, 3 or 4, indicating the intensity with which the measure was applied. Additional information about the COVID-19 policy measures can be found at COVID-19 Data Hub. For the period comprehended between March 2020 and February 2021, the median of the COVID-19 policy measures *cancel_events*, *gatherings_restrictions* and *transport_closing* was identical for every combination of ARS, month and year. Therefore, these variables were not used to fit the models.

Table 3 presented the results of the ANOVA test applied to the full model described in Section 3.5.

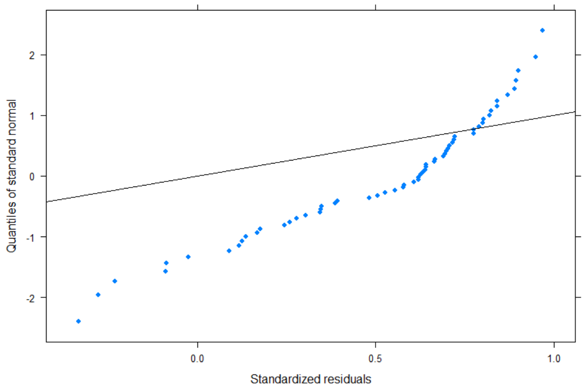
Covariate	p-value
Closure of schools/universities*	0.0203
Closure of workplaces	0.1180
Stay at home requirements*	$<$ 0.0001
Restrictions on internal movement	0.1801
Stringency index*	$<$ 0.0001
Number of appointments*	$<$ 0.0001
Number of face-to-face appointments in PC	0.1144
Number of non-present appointments in PC*	$<$ 0.0001
Number of at-home appointments in PC*	$<$ 0.0001
ARS*	0.0007

Table 3: Results of the ANOVA test performed on the full model which considered all predictors. Asterisks indicate significant covariates ($p < 0.05$).

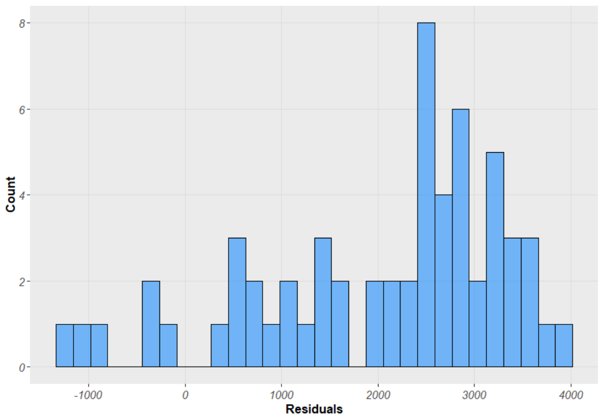
The residuals-diagnostic plots of the full model considering all the COVID-19 policy predictors and the Primary Care based information predictors were presented in Figure 22.



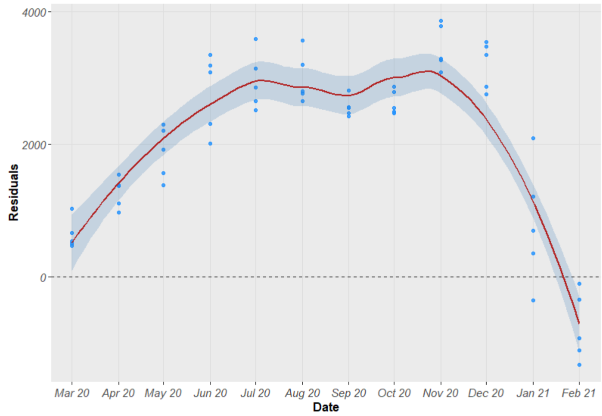
(a) Scatterplot of the residuals as a function of the linear predictors.



(b) QQ-plot of the residuals.



(c) Histogram of the residuals.



(d) Scatterplot of the residuals as a function of the order in which observations were collected.

Figure 22: Residual-diagnostic plots of the full model. LOESS (Locally Estimated Scatterplot Smoothing) was used to obtain the red line with a 95% confidence band in (a) and (d).