UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Instituto de Medicina Preventiva e Saúde Pública

Impact of the COVID-19 pandemic on non-COVID mortality in Continental Portugal

Joana Torres da Silva Fonseca Monteiro

Orientado por:

Prof. Doutor António Vaz Carneiro

Coorientado por:

Dr. Paulo Nicola

JULHO'2021

[This page intentionally left blank]

UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Instituto de Medicina Preventiva e Saúde Pública

Impact of the COVID-19 pandemic on non-COVID mortality in Continental Portugal

Joana Torres da Silva Fonseca Monteiro

JULHO'2021

RESUMO

Introdução: A COVID-19 foi declarada uma pandemia global, em março de 2020. Desde então, o mundo tem enfrentado a pressão por ela criada nos sistemas de saúde, que pode, também, afetar os cuidados de doentes não-COVID-19. Este estudo pretende determinar se a pandemia se associa a um aumento da mortalidade não-COVID-19 e, particularmente, daquela por causas naturais, em Portugal Continental.

Métodos: A partir de dados públicos, agregados e anonimizados, comparámos a mortalidade, nos primeiros 12 meses da pandemia, com a sua *baseline*, a níveis nacional e regional. Correlacionámos, também, a mortalidade com indicadores de utilização dos cuidados de saúde e com fatores que se poderiam associar a diferenças na mortalidade, tais como medidas de saúde pública, casos de COVID-19 e a temperatura média diária.

Resultados: A mortalidade não COVID-19, quer natural nacional, quer regional, por todas as causas, esteve frequentemente acima da *baseline* e, durante várias semanas, registou-se excesso de mortalidade. Não houve correlação entre as consultas médicas nos cuidados de saúde primários e a mortalidade, com exceção daquelas ao domicílio, no Alentejo e no Centro, as regiões mais envelhecidas do Continente, que aumentaram com a mortalidade. Quanto ao seguimento de doenças crónicas, cirurgias urgentes e urgências triadas como cor de laranja ou amarelas, observou-se uma associação entre a sua diminuição e o aumento da mortalidade.

Conclusões: A pandemia teve impacto na mortalidade, resultando numa diminuição da mortalidade por acidentes de viação e num aumento da mortalidade não-COVID-19, por causas naturais e por todas as causas. Assim, cuidados de saúde que poderiam evitar a morte parecem ter estado comprometidos quando a pressão no sistema era maior e, simultaneamente, a população poderá ter hesitado na procura de cuidados. No entanto, também parece existir um esforço para manter o seguimento dos indivíduos mais frágeis.

Palavras-chave: COVID-19; mortalidade não-COVID-19; excesso de mortalidade; cuidados de saúde; Portugal Continental.

ABSTRACT

Introduction: COVID-19 was declared a global pandemic in March 2020. Since then, the world has been fighting the distress it has imposed on healthcare systems, which may affect the care of non-COVID-19 patients. This study aims to determine whether and to what extent the pandemic is associated with an increase in non-COVID-19 mortality, especially from natural causes, in Continental Portugal.

Methods: Using aggregated anonymized data from public databases, we compared mortality during the first 12 months of the pandemic to its baseline, at national and regional levels. Mortality data were also correlated with indicators of the use of health care and with factors possibly be associated with changes in mortality, namely public health measures, COVID-19 cases, and daily mean temperature.

Results: National natural-cause and regional all-cause non-COVID-19 mortality were often above their baseline, and during several weeks excess mortality was recorded. There was no correlation between primary care medical appointments and mortality, the exception being Alentejo and Centro, the most elderly regions of Continental Portugal, where at-home medical appointments increased with mortality. As for the follow-up of chronic illnesses, urgent surgeries, and emergency room attendances triaged as orange and yellow, an association between their decrease and the increase in mortality was observed.

Conclusions: During its first 12 months, the pandemic impacted mortality, leading to a decrease in mortality from traffic accidents, and an increase in natural- and all-cause non-COVID-19 mortality. Thus, health care that could have prevented death seems to have gotten compromised when the pressure on the system was higher, which was also when people may have been more hesitant to seek health care. However, there might have been an effort to maintain the follow-up of more fragile individuals during those times.

Keywords: COVID-19; non-COVID-19 mortality; excess mortality; health care; Continental Portugal.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ARDS – Acute respiratory distress syndrome

ARS – Administração Regional de Saúde – Health Administrative Region

BI-CSP – Bilhete de Identidade dos Cuidados de Saúde Primários

COVID-19 – Coronavirus disease 2019

DGS – Direção-Geral da Saúde

EuroMOMO – European monitoring of excess mortality for public health action

GAPIC – Gabinete de Apoio à Investigação Científica, Tecnológica e Inovação

INE – Instituto Nacional de Estatística

IPMA – Instituto Português do Mar e da Atmosfera

LVT – Lisboa e Vale do Tejo

MERS – Middle East respiratory syndrome

MERS-CoV – Middle East respiratory syndrome coronavirus

NUTS – Nomenclature des unites territoriales statistiques – Nomenclature of territorial units for statistics

SARS – Severe acute respiratory syndrome

SARS-CoV – Severe acute respiratory syndrome coronavirus

WHO – World Health Organization

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure **Page**

[This page intentionally left blank]

GENERAL INTRODUCTION

PREVIOUS CORONAVIRUS EPIDEMICS

Coronaviruses are a family of enveloped, single-stranded RNA viruses widely found in humans, other mammals, and birds, generally causing gastrointestinal, neurological, and respiratory diseases. HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 are the strains most commonly found in clinical practice, responsible for mild upper respiratory disease in immunocompetent individuals (Cui et al., 2019; Wiersinga et al., 2020).

In 2002-2003, the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) emerged from palm civets within the Guangdong Province, China, becoming the first coronavirus ever reported to cause severe disease in humans. SARS-CoV was responsible for several outbreaks of atypical pneumonia, ultimately leading to a worldwide epidemic, spreading to 29 countries, infecting 8,096 people, and killing 813. Not long after, in 2012, another highly pathogenic coronavirus – the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) – emerged from dromedary camels and caused an outbreak of atypical pneumonia in Middle Eastern countries (Morens & Fauci, 2020; Zhong et al., 2003).

Since they are highly prevalent, widely distributed, genetically diverse, and highly recombinogenic, and considering the increasing human-animal interface activities, novel and more pathogenic coronaviruses are likely to periodically emerge in humans (Cui et al., 2019; Zhu et al., 2020).

EMERGING OF THE NEW CORONAVIRUS PANDEMIC

In late December 2019, several health facilities reported clusters of cases of atypical pneumonia of unknown etiology in the city of Wuhan, Hubei Province, China. The first reported cases were characterized by fever; imaging characteristics of pneumonia or acute respiratory distress syndrome (ARDS); and reduced or normal white blood cell count with lymphopenia. However, after treatment with antibiotics for 3 to 5 days, there

was no significant improvement (Boni et al., 2020; ProMED - International Society for Infectious Diseases, 2019).

In early January 2020, a novel SARS-like coronavirus – later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was isolated and preliminarily identified as the probable cause of the Wuhan pneumonia clusters (Tan et al., 2020; World Health Organization, 2020f; Wu et al., 2020; Zhu et al., 2020). Although the exact origin remains uncertain, those cases were epidemiologically linked to the Wuhan South China Seafood Market, an open-air wet market. That is particularly relevant since, similarly to SARS and MERS, SARS-CoV has a zoonotic origin, presumably in bats (Zhou et al., 2020) or pangolins (Lam et al., 2020).

During the following months, a series of events, including the fast worldwide dissemination of the virus, led the WHO to initially classify this disease as a public health emergency of international concern (World Health Organization, 2020e) and later as a global pandemic (World Health Organization, 2020d).

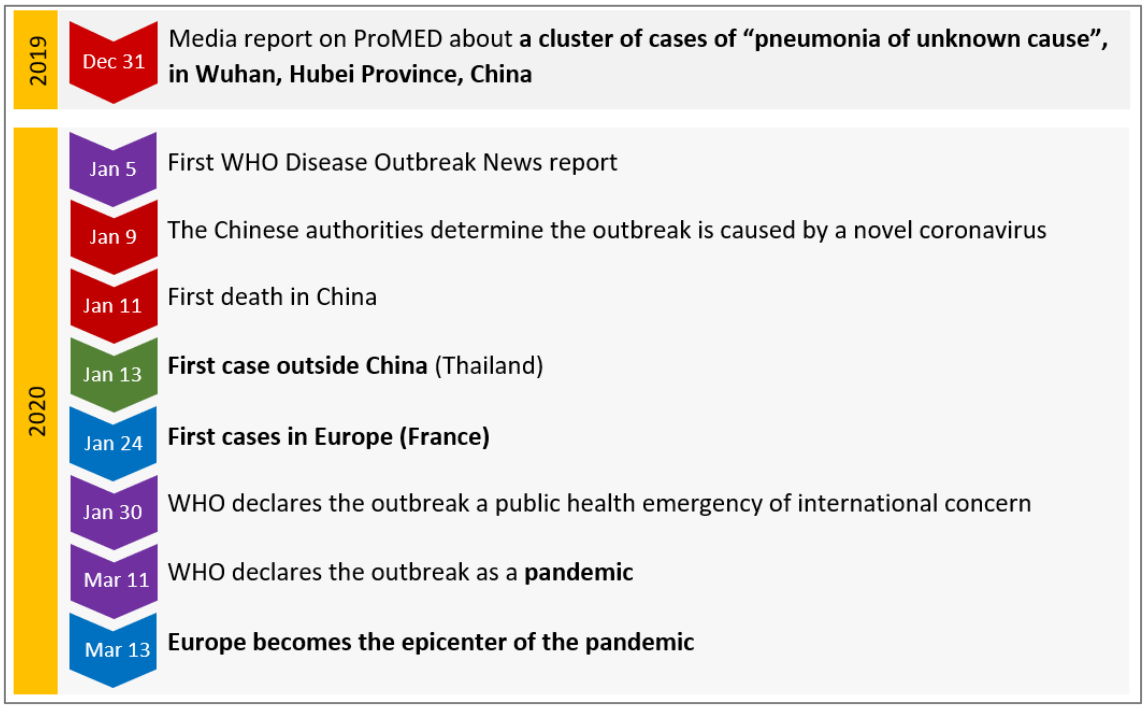


Figure 1 – World timeline of the beginning of the pandemic (World Health Organization, 2020c).

CORONAVIRUS DISEASE 2019 (COVID-19)

Infection with SARS-CoV-2 can be either asymptomatic or symptomatic, presenting itself as the coronavirus disease 2019 (COVID-19), which includes a wide spectrum of symptoms (World Health Organization, 2020b). 81% of those who become symptomatic have milder manifestations, such as fever, dry cough, fatigue, anosmia or dysgeusia, and do not require hospitalization; 14% may develop severe symptoms, such as shortness of breath or chest pain, and may require hospitalization; and 5% have critical manifestations and life-threatening complications requiring admission to intensive care units, namely respiratory failure, septic shock, and multiorgan dysfunction, ultimately leading to death (Wiersinga et al., 2020). After exposure, the mean incubation period for COVID-19 is approximately 5-6 days (Guan et al., 2020), but symptoms can appear as late as 14 days after exposure (Lauer et al., 2020; World Health Organization, 2020a).

COVID-19 PANDEMIC IN PORTUGAL

The first cases of COVID-19 in Portugal were reported on March 2nd, 2020 (Direção-Geral da Saúde, 2020a, 2020b) and the first death occurred 14 days later (Direção-Geral da Saúde, 2020c). Due to the uprising severity of the pandemic across Europe and to avoid a possible future overburden of the healthcare system – similarly to what had happened in countries like Italy, Spain, or France – the State of National Emergency was enacted and restrictions were imposed: a nationwide stay-at-home order; the closure of workplaces and businesses, encouraging remote work; the closure of schools; and the prohibition of events and religious services or celebrations that could lead to large gatherings (Presidência da República, 2020).

Following this, deconfinement took place in different phases, and restrictions were gradually lifted. However, after the summer holidays, the number of cases started increasing. New restrictions, such as curfews, were imposed. Following the Christmas celebrations, the incidence of COVID-19 increased dramatically, and so did the number of general hospital admissions, admissions to Intensive Care Units, and deaths. A new stay-at-home order was then imposed as an effort to ease the pressure on the healthcare system.

CHANGES IN THE USE OF HEALTH CARE IN OTHER COUNTRIES

The COVID-19 pandemic has changed the use of health care in Portugal and throughout the world. Some studies have already shown a considerable decline in elective procedures, medical appointments, and hospital admissions; in the use of preclinical and clinical emergency care; and emergency hospital admissions (Mulholland et al., 2020; Vieira et al., 2020). However, in Waldshut, Germany, there was an increase in the use of the keyword "presumed death" in ambulance services and in the number of primary deaths recorded by the ambulance services, which correlated significantly with the decrease in the total number of emergency admissions (Kortüm et al., 2020). There was also an increase in the percentage of patients requiring hospitalization after visiting the emergency room, and in hospital mortality, suggesting a higher severity of disease presentation upon hospital admission (Lyall & Lone, 2020; Ojetti et al., 2020).

MORTALITY MONITORING

Mortality is one of the basic indicators of health. Its monitoring is pivotal for public health planning and plays a central role during pandemics, contributing to monitoring both the progression of the pandemic and its impact on public health, due to the overburden of healthcare systems. Mortality monitoring is also essential to determine the impact of increasingly more common extreme weather conditions – such as heat and cold waves – which may result in periods of excess mortality (EuroMOMO, n.d.-c).

As defined by the EuroMOMO project – European monitoring of excess mortality for public health action – the mortality baseline is modeled using a Poisson regression corrected for overdispersion and fitted on a valid historical period, with a maximum of 5 years (EuroMOMO, n.d.-b). The z-score is then calculated to represent the distance of the observed mortality to the historical mean, measured in standard deviation units. Excess mortality is defined as an increase in mortality from the baseline of more than two z-scores, and it can be either low ($2 < z \leq 4$), moderate ($4 < z \leq 7$), high ($7 < z \leq 10$), very high ($10 < z \leq 15$), or extremely high ($z > 15$) (EuroMOMO, n.d.-a).

Nevertheless, whether mortality data from 2020-2021 can be compared to homologous periods of 2015-2019 may be controversial. The periods during which there was a nationwide stay-at-home order can be thought of as being similar to the period of summer holidays, with less commuting, a lower risk of infectious diseases, and fewer traffic accidents. This would have a protective effect and lead to a reduction in expected mortality to levels closer to those of summer periods, at least in some age groups (Nogueira et al., 2020).

INCREASE IN MORTALITY DURING THE COVID-19 PANDEMIC IN PORTUGAL

Preliminary data indicates total mortality has been generally higher than the baseline for 2020 since March. From mid-March to May, total mortality was noticeably higher than non-COVID-19 mortality, and their difference corresponded to COVID-19 mortality. Between June and September, non-COVID-19 mortality almost overlapped with total mortality, and mortality was yet higher than the baseline. Furthermore, during several weeks of the year, total mortality was not only higher than the baseline but also higher than the maximum number of deaths during the same weeks of 2015-2019 (Instituto Nacional de Estatística, 2020c, 2020d, 2020a, 2020b, 2021a).

THE PROJECT

This study is part of a major project named “Impact of the COVID-19 pandemic on the use of medical care and non-COVID-19 mortality in Portugal”. It was funded by *Gabinete de Apoio à Investigação Científica, Tecnológica e Inovação* (GAPIC), and developed together with Patrícia Mendes – a fellow sixth-year medical student, who was responsible for the part regarding the use of medical care – and Margarida Ribeiro – a Biostatistics master student. Hence, any similarities between our theses do not constitute plagiarism, but rather represent common aspects of joint work.

The ideation of the project started with a conceptual model of hypotheses to explain possible changes in non-COVID-19 mortality and in the use of health care during the

pandemic. According to those hypotheses, the pandemic can contribute to an increase in mortality: directly, by increasing COVID-19 mortality; and indirectly, by increasing non-COVID-19 mortality, namely due to aspects related with the impact of the pandemic on healthcare. On the one hand, people might be avoiding health care. On the other hand, healthcare services might be experiencing difficulties in answering peoples' needs, resulting in longer waiting times. Besides that, there might have been a decrease in preventive care and an increase in telemedicine, perhaps resulting in a higher proportion of patients with uncontrolled chronic illnesses. Heat and cold waves may also lead to an increase in mortality (Figure 2).

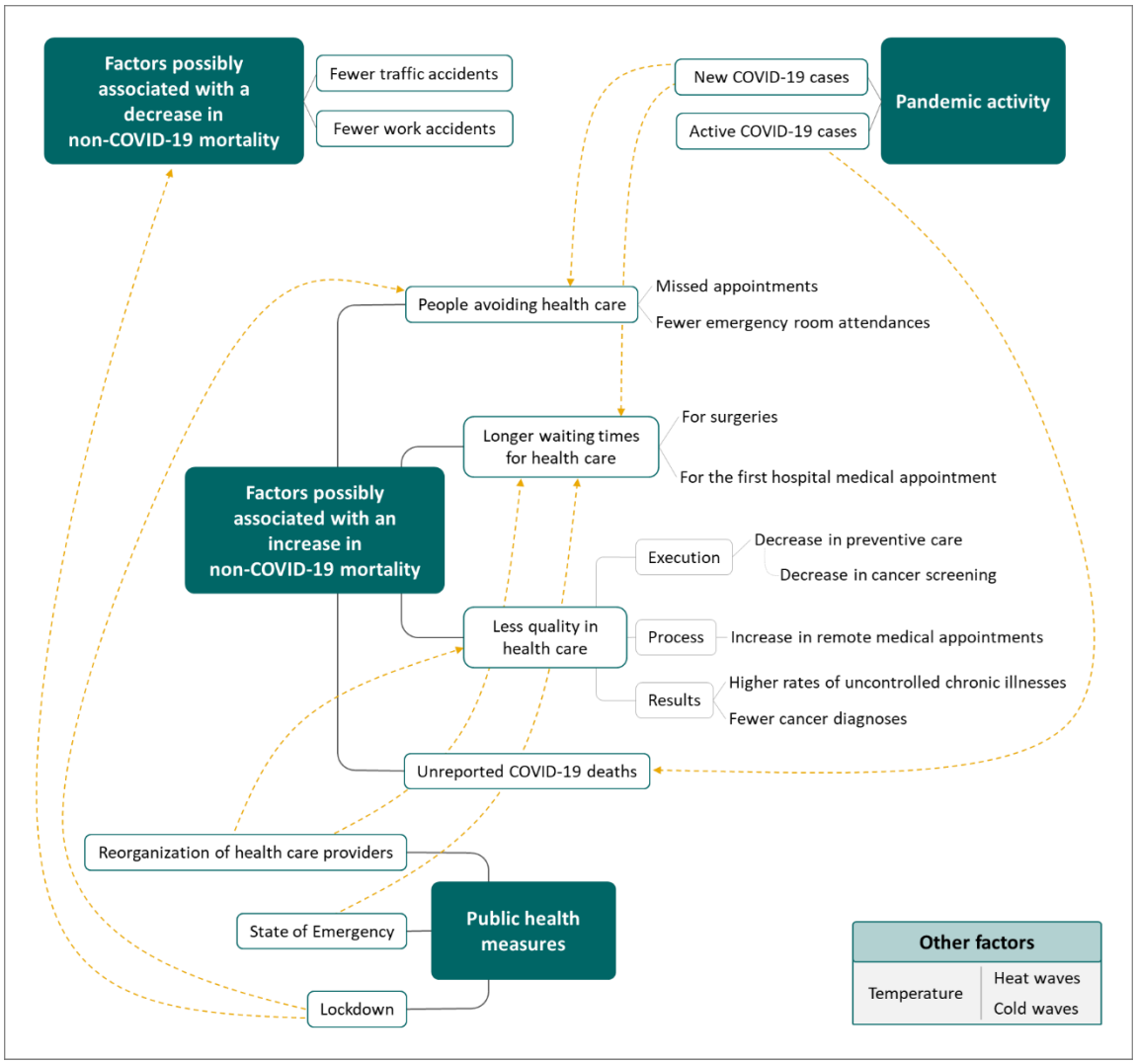


Figure 2 – Conceptual model of pre-established hypotheses.

Findings on Changes in the Use of Medical Care in Continental Portugal

We analyzed changes in the use of health care in Continental Portugal and its five regions – Alentejo, Algarve, Centro, Lisboa e Vale do Tejo (LVT) and Norte – during a pre--pandemic reference period – January and February 2020 – and a pandemic period, divided into three-month subperiods – March to May, June to August, September to November, and December 2020 to February 2021. These subperiods were compared, when possible, with their homologous subperiods from 2015-2019, and their difference was statistically significant when – using Student's *t*-test when the assumption of normality was met or Wilcoxon test for data not following a normal distribution – the *p*-value was less than 0.05.

Appointments in primary care decreased in the pandemic period, the highest loss having been registered in the beginning of the pandemic, between March and May 2020. There was, however, a significant increase in remote appointments, contributing to a positive total annual balance (Figure 3). Also in Primary Care, there was a decrease in adequate follow-up of chronic illnesses and in the incidence of thrombosis/stroke (Figure 4). As for cancer screening, it remained similar to the previous 5 years, although breast cancer screening, as well as breast and colorectal cancer new diagnoses, decreased steadily and significantly throughout the year (Figure 5).

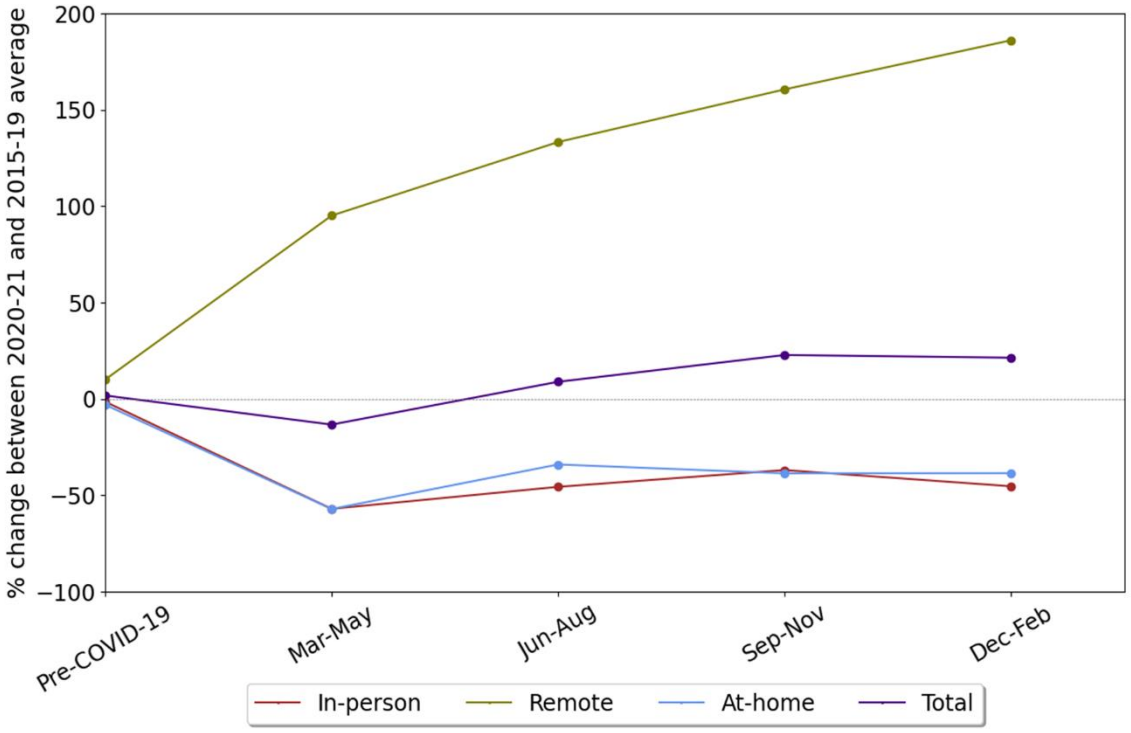


Figure 3 – Changes in the number of primary care medical appointments, when compared to 2015-2019.

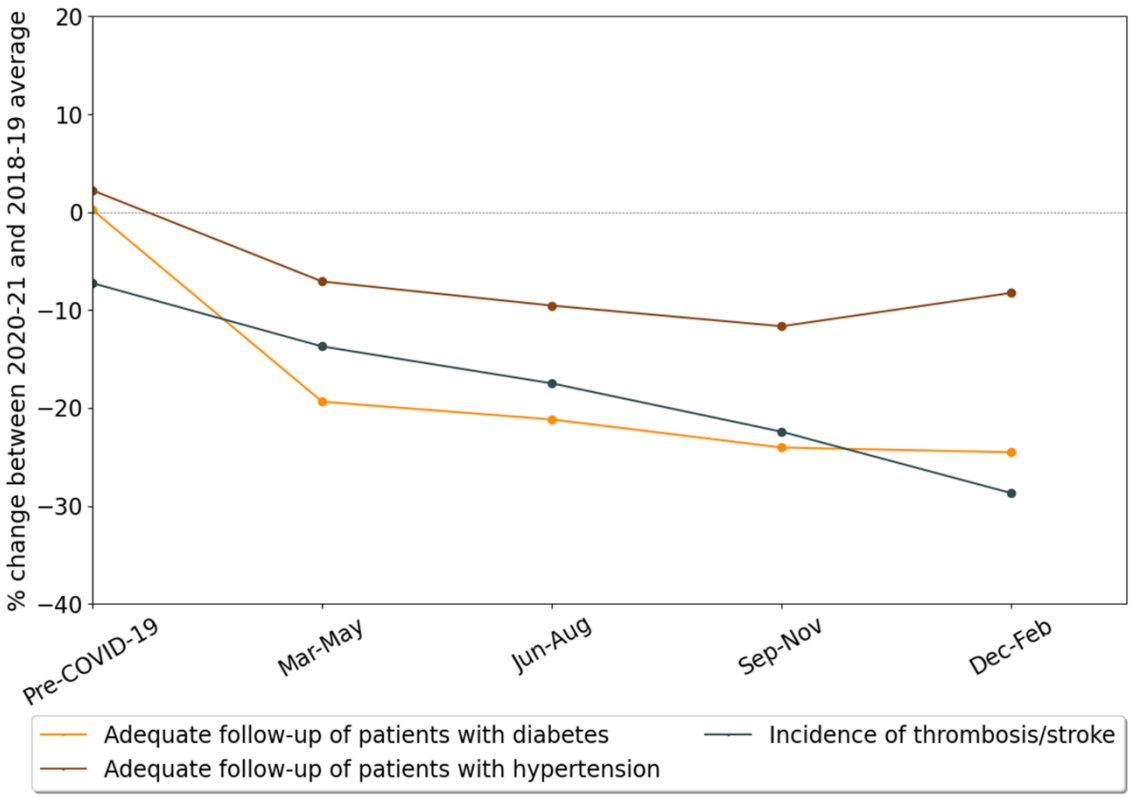


Figure 4 – Changes in the indexes of adequate follow-up of chronic illnesses (diabetes and hypertension) and in the incidence of stroke/thrombosis, when compared to 2018-2019.

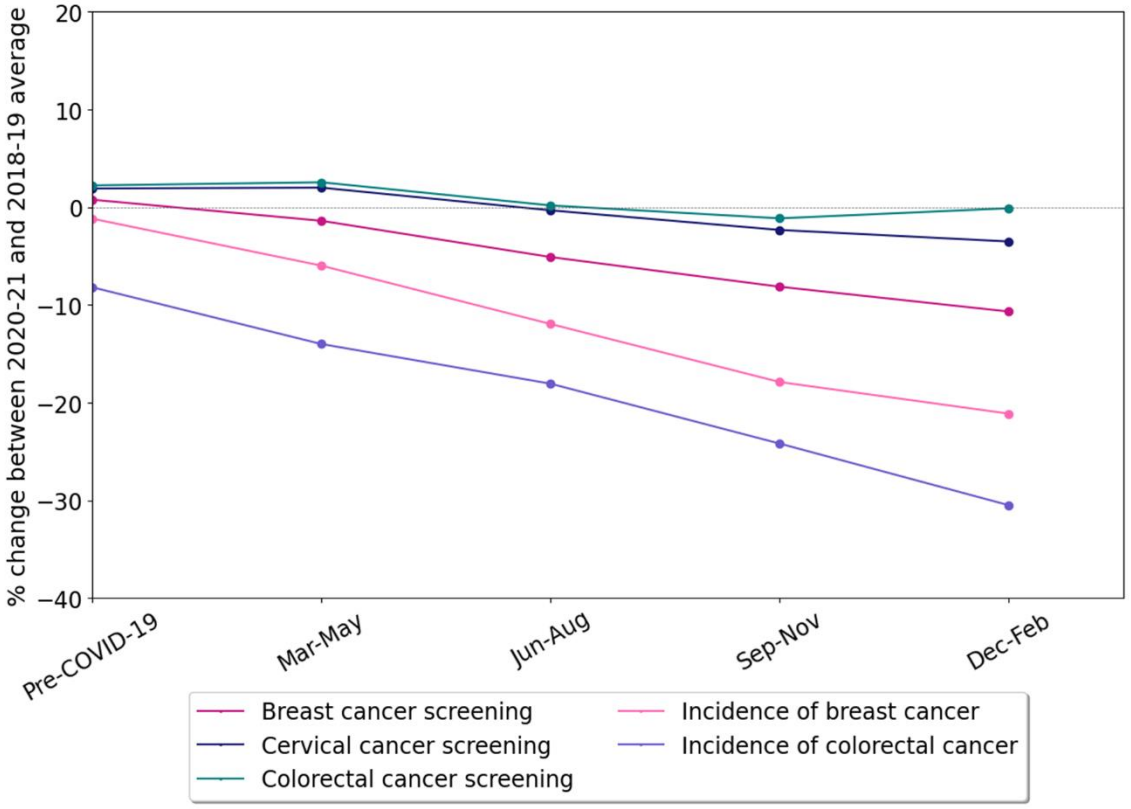


Figure 5 – Changes in cancer screening and diagnosis, when compared to 2018-2019.

In hospitals, there was a significant decrease in medical appointments and in people awaiting their first appointment within the adequate response time (Figure 6), surgeries (Figure 7), ambulance service calls, and emergency room attendances (Figure 8).

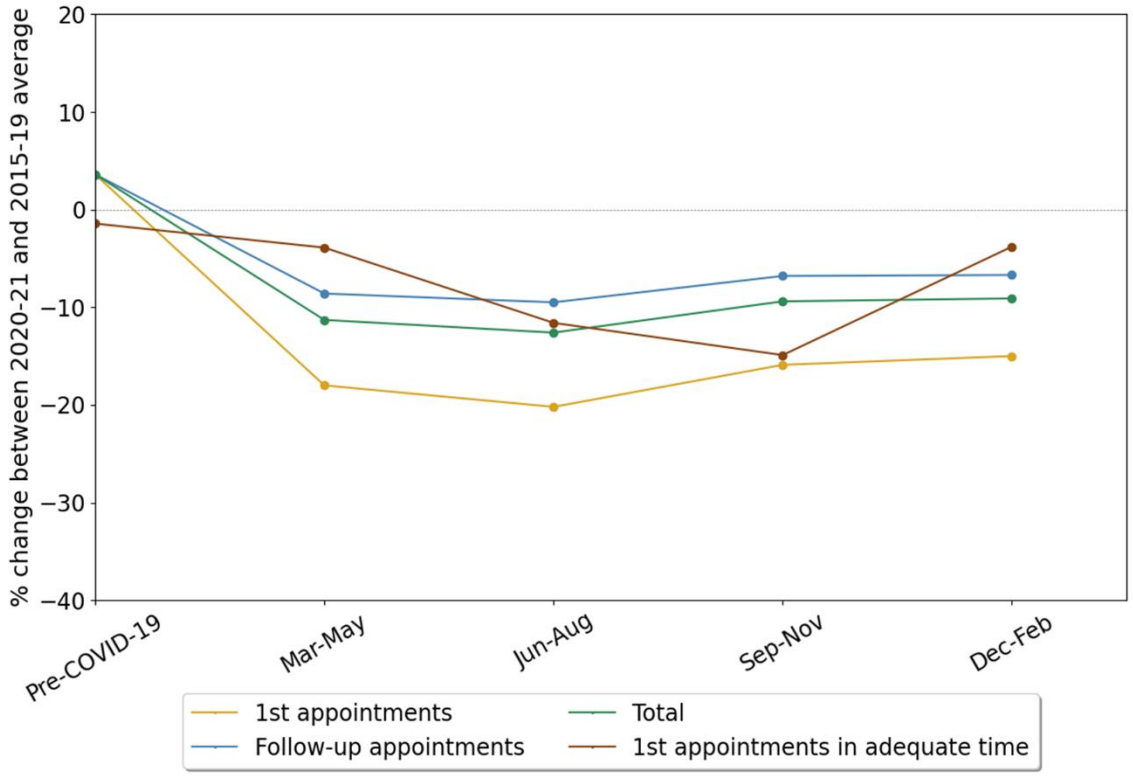


Figure 6 – Changes in hospital medical appointments and waiting times, when compared to 2015-2019.

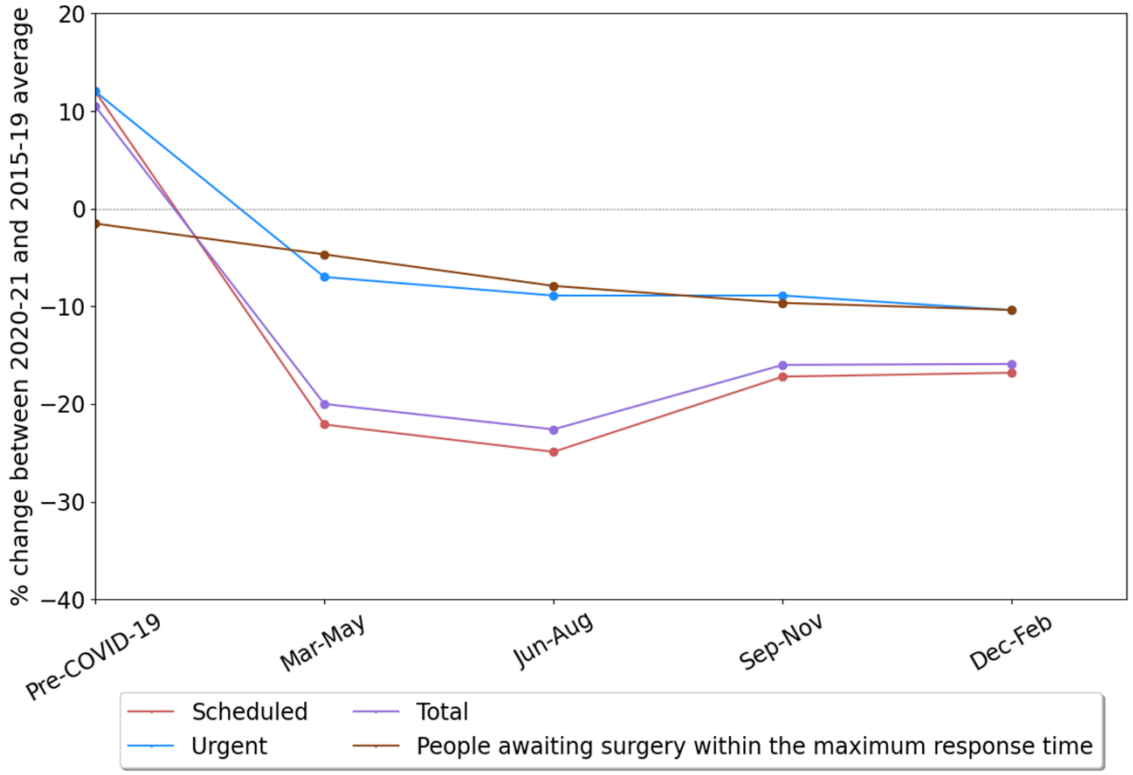


Figure 7 – Changes in the number of surgeries and waiting times, when compared to 2015-2019.

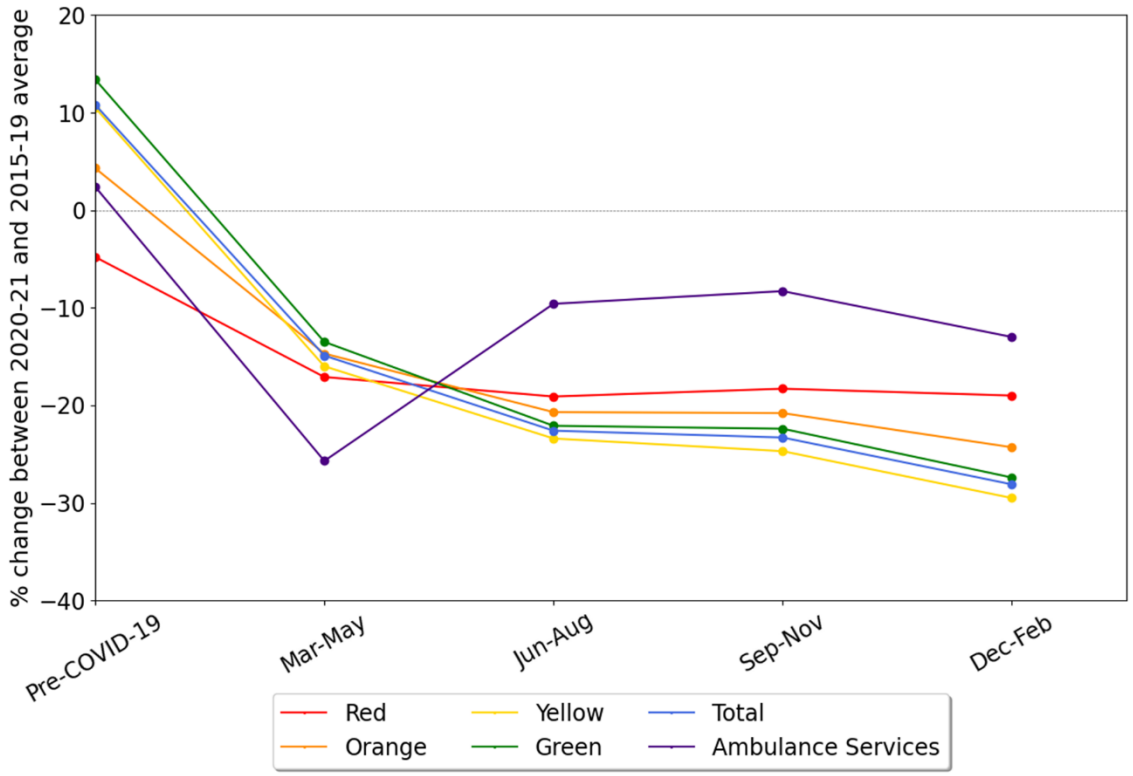


Figure 8 – Changes in emergency room attendances (by the Manchester Triage System) and in ambulance service calls.

ARTICLE

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), firstly identified in Wuhan, China, in late 2019. Its rapid spread around the world led to a worldwide pandemic which, a year after its start, still poses important challenges to countries and a considerable burden on their healthcare systems. Other studies have already shown a substantial decline in elective procedures, medical appointments, and hospital admissions; in the use of preclinical and clinical emergency care; and in emergency hospital admissions (Mulholland et al., 2020; Vieira et al., 2020).

An excess in all-cause mortality associated with the COVID-19 pandemic was expected, both as a direct consequence of the pandemic itself, and indirectly, due to its impact on the use of health care. Other countries and regions have already reported an excess in all-cause mortality only partially attributable to COVID-19-mortality (Kortüm et al., 2020). In Portugal, preliminary data indicates total mortality has been generally higher than the baseline for 2020 since March; between June and September, its increase was mainly due to non-COVID-19 mortality; and in October there was an increase in mortality directly attributable to COVID-19. During several weeks of the year, mortality was not only higher than the baseline but also above the maximum values for 2015-2019 (Instituto Nacional de Estatística, 2021b).

Mortality monitoring during pandemics contributes to monitoring both the progression of the pandemic and its impact on public health, especially due to the overburden of healthcare systems (EuroMOMO, n.d.-c). Studying all-cause and natural-cause excess mortality during the COVID-19 pandemic can provide a better understanding of what may have gotten neglected – in terms of population health – and identify key action points for the upcoming months and future pandemics. It can also provide better knowledge on the value of regular access to quality healthcare and on how variations in these aspects may affect mortality. Therefore, understanding which

factors, other than COVID-19 itself, may be contributing to increasing natural-cause mortality is essential for future public health planning and action in future pandemics.

This study aims to estimate the extent of excess non-COVID-19 mortality in Continental Portugal during the first year of the COVID-19 pandemic, with an emphasis on natural-cause mortality, and to explore correlations which may explain said excess.

METHODS

Study Design and Setting

We carried out an ecological study with public data from Continental Portugal. It comprehends a total of 61 weeks, including a pre-pandemic period – from week 1 of 2020 (starting on December 30th, 2019) to week 9 of 2020 (ending on March 1st, 2020) – and a 12-month pandemic period – from week 10 of 2020 (starting on March 2nd, 2020) to week 8 of 2021 (ending on February 28th, 2021) – corresponding to the first year of the pandemic in Portugal.

Variables and Data Sources

We collected anonymized aggregated data from official public databases. The underlying data sources used in this study are as follows:

Sistema de Informação dos Certificados de Óbito – Vigilância Eletrónica da Mortalidade (SICO e-VM) captures national mortality data by region, cause, and place of death.

Portal da Transparência gathers information from several official sources regarding a) emergency room attendances by level of the Manchester Triage System; b) ambulance service calls; c) medical appointments in primary care – presential, remote or at-home – and in hospitals – first or follow-up; d) number of surgeries by type – scheduled or urgent; and e) waiting times for surgery and for the first hospital medical appointment. This data is provided for Continental Portugal, by month and region.

Bilhete de Identidade dos Cuidados de Saúde Primários (BI-CSP) centralizes information from Primary Care Units in Continental Portugal, namely data concerning indicators of adequate chronic disease follow-up, incidence of stroke/thrombosis and cancer screening/new diagnoses.

Direção-Geral da Saúde has a COVID-19 portal where daily reports on new COVID-19 cases and deaths are provided, at a regional level, as well as the number of nationwide active COVID-19 cases.

Instituto Português do Mar e da Atmosfera (IPMA) is Portugal's national weather service, allowing us to obtain the 2020-2021 national mean daily temperature.

Based on our study on the impact of the pandemic on the use of medical care, we gathered data concerning medical appointments in primary care and hospitals; surgeries; emergency room attendances by the Manchester Triage System and ambulance service calls; adequate follow-up of chronic illnesses and incidence of stroke/thrombosis; and cancer screening and new diagnoses, by health administrative region (ARS) of Continental Portugal (Alentejo, Algarve, Centro, Lisboa e Vale do Tejo (LVT), and Norte) – these five ARS correspond to the five NUTS II from Continental Portugal: Alentejo, Algarve, Centro, Lisboa Metropolitan Area, and Norte, respectively.

Different types of mortality were included in this study. We collected national natural-cause and regional all-cause mortality data from which we subtracted the number of known COVID-19 deaths, guaranteeing only non-COVID-19 mortality data were considered. We also analyzed the number of deaths by accidents or suicide, as well as mortality by place of death.

Restrictiveness Index

A daily regional and continental index was developed to represent the restrictions imposed since March 2020 (Figure 9*Figure 9* – Daily continental restrictiveness index). This index includes nationwide and local measures and reflects the percentage of the population of Continental Portugal affected by different levels of restrictions, based on INE/Pordata resident population estimates for 2019 (Pordata, 2021).

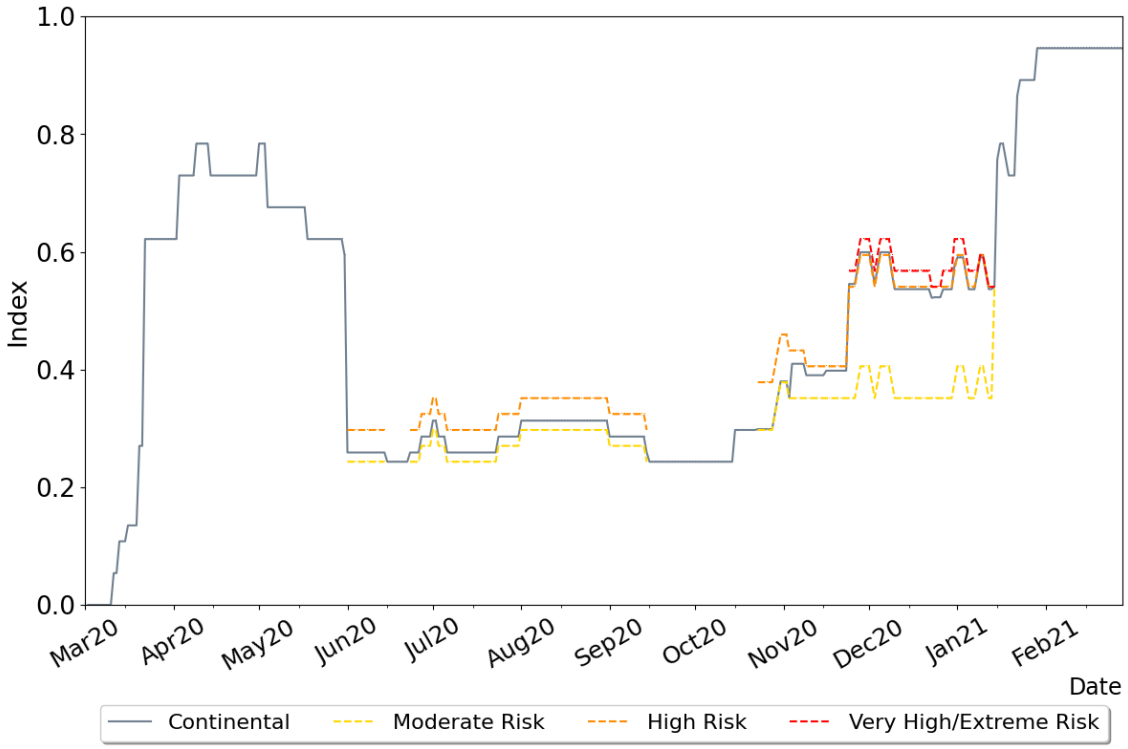


Figure 9 – Daily continental restrictiveness index, from March 2nd, 2020, to February 28th, 2021.

Statistical Methods

For this analysis, the mortality baseline for 2020-2021 corresponds to the 2015-2019 average weekly mortality. The extent of changes in mortality from the baseline is given as the following:

$$z\text{-}score_w = \frac{x_w - \mu_w}{\sigma_w},$$

where x is the 2020-2021 mortality in an ISO week w; μ is the mean 2015-2019 mortality in ISO week w; σ is the population standard deviation from the 2015-2019 mean in ISO week w. Excess mortality was observed if the z-score is higher than 2. No z-score was obtained for week 53 as only 2015 and 2020 had 53 weeks. Therefore, the population standard deviation is zero and the z-score $[(x_w - \mu_w)/0]$ becomes undefined.

For whenever excess regional all-cause or national natural-cause non-COVID-19 mortality was documented, we calculated the correlation between the excess in mortality and the mean temperature. This analysis was done for two periods: warmer weeks (ISO weeks 19 to 43); and colder weeks (ISO weeks 44 to 18). According to previous studies, the cold might take 2-10 days to affect mortality, while hot temperatures might affect it within 3-4 days (Guo et al., 2014). Thus, we considered a lag of two weeks between cold weeks and mortality, and a one-week lag for warm ones.

For the first 12 months of the pandemic, we correlated all mortality data with the restrictiveness index, and with new and active COVID-19 cases. Regional all-cause and national natural-cause non-COVID-19 mortality were also correlated with medical appointments in primary care and hospitals; surgeries; emergency room attendances and ambulance service calls; indexes of adequate follow-up of chronic illnesses and incidence of stroke/thrombosis; and cancer screening and new diagnoses.

We used Pearson correlation coefficient when the relationship between two variables was linear and Spearman correlation coefficient when it was nonlinear. In both cases, the correlation was considered significant when the *p*-value was less than 0.05.

We used R, R Studio (R version 4.0.3), and Python (version 3.8.5) to carry out the analyses and to produce figures.

RESULTS

Changes in Mortality from the Baseline

National all-cause non-COVID-19 mortality is mainly influenced by that of natural causes as it represents the large majority of deaths, making all-cause mortality follow the natural-cause mortality trend (Figure 10).

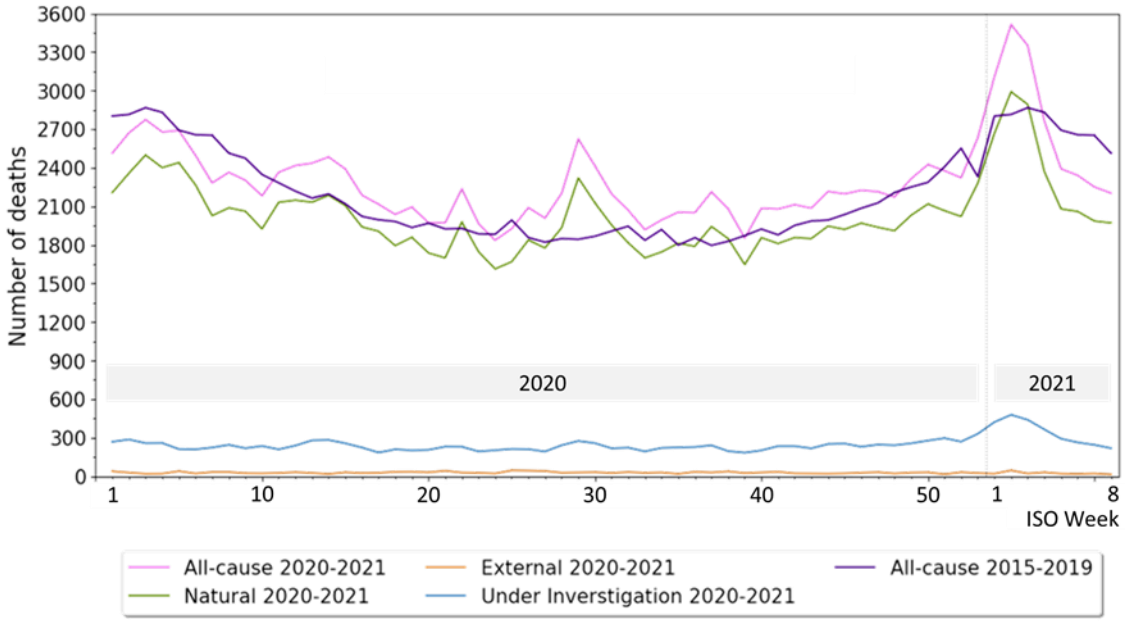


Figure 10 – Non-COVID-19 mortality in Portugal, by cause.
All-cause mortality = Natural-cause (≈89.6%) + external-cause (≈1.5%) + under investigation (≈8.9%)

Natural-cause non-COVID-19 mortality during the pandemic period was often above its baseline (Figure 11), a behavior that was similar for all-cause non-COVID-19 mortality in all regions of Continental Portugal.

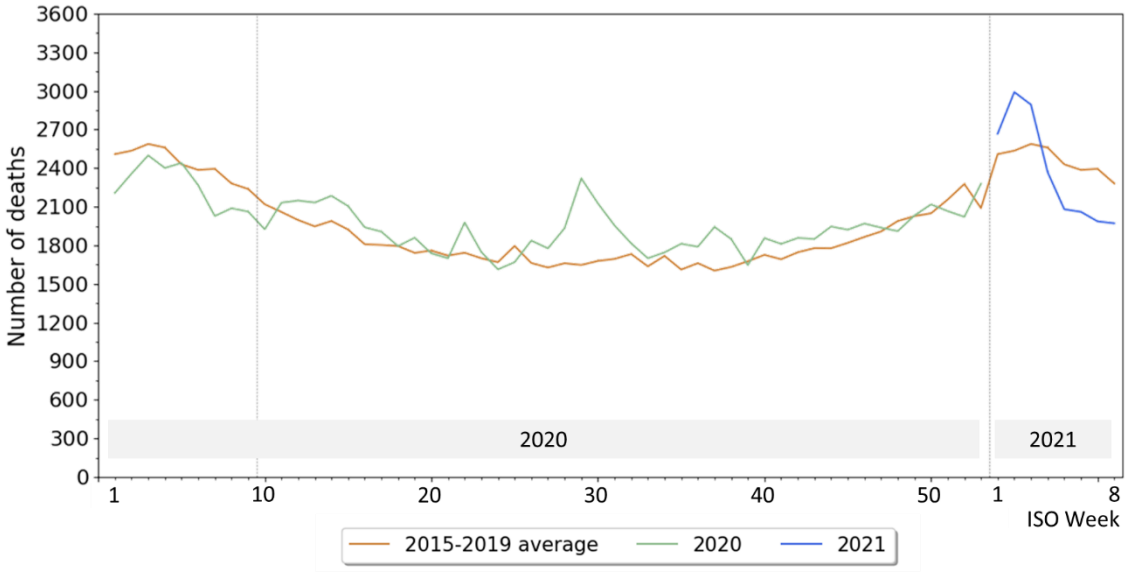


Figure 11 – Natural-cause non-COVID-19 mortality in Portugal.
The left vertical line marks the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021.

However, excess natural-cause non-COVID-19 mortality was registered mainly around weeks 26 to 30, and 35 to 41, when the weekly z-score exceeded 2 (Figure 12).

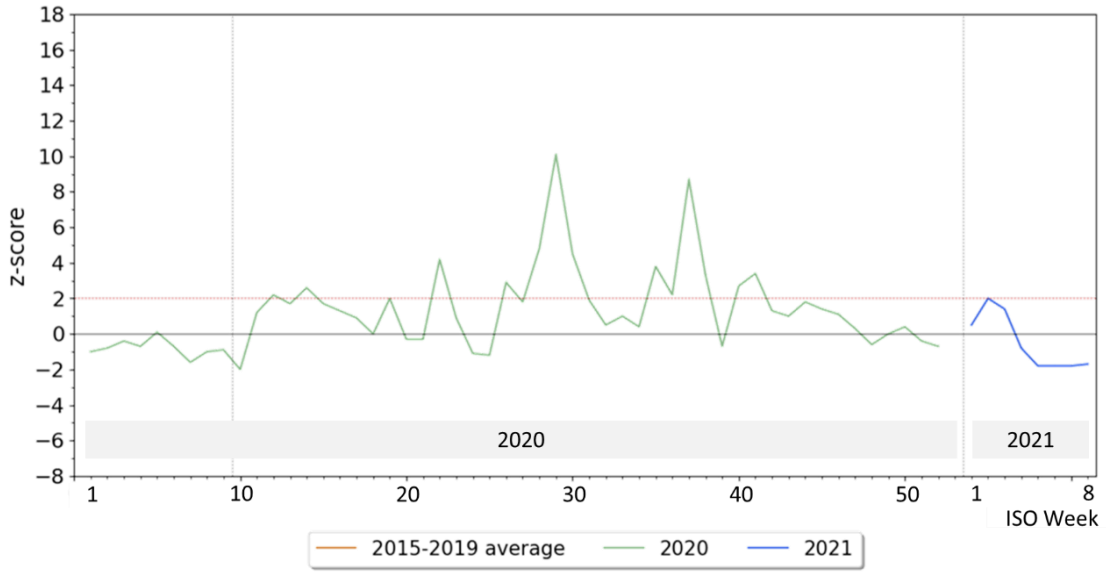


Figure 12 – Weekly z-score for natural-cause non-COVID-19 mortality in Portugal.
The left vertical line marks the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021. The red horizontal line marks z-score=2, above which there is excess mortality.

This too was similar for all-cause non-COVID-19 mortality in all five regions of Continental Portugal, but in Alentejo, Algarve and LVT, there was also excess mortality in the first weeks of 2021 (Figure 13).

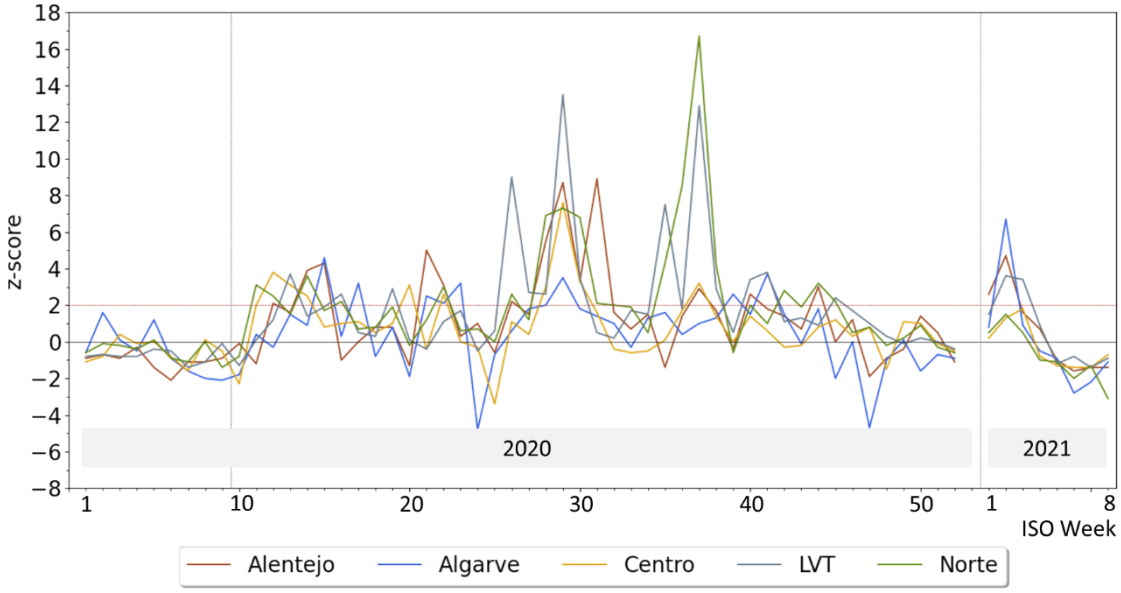


Figure 13 – Weekly z-score for all-cause non-COVID-19 mortality in Continental Portugal, by region.
The left vertical line marks the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021. The red horizontal line marks z-score=2, above which there is excess mortality.

Mortality by traffic accident (Figure 14), as well as by other types of accident or presumed suicide, was below the baseline during most of the 12-month pandemic period.

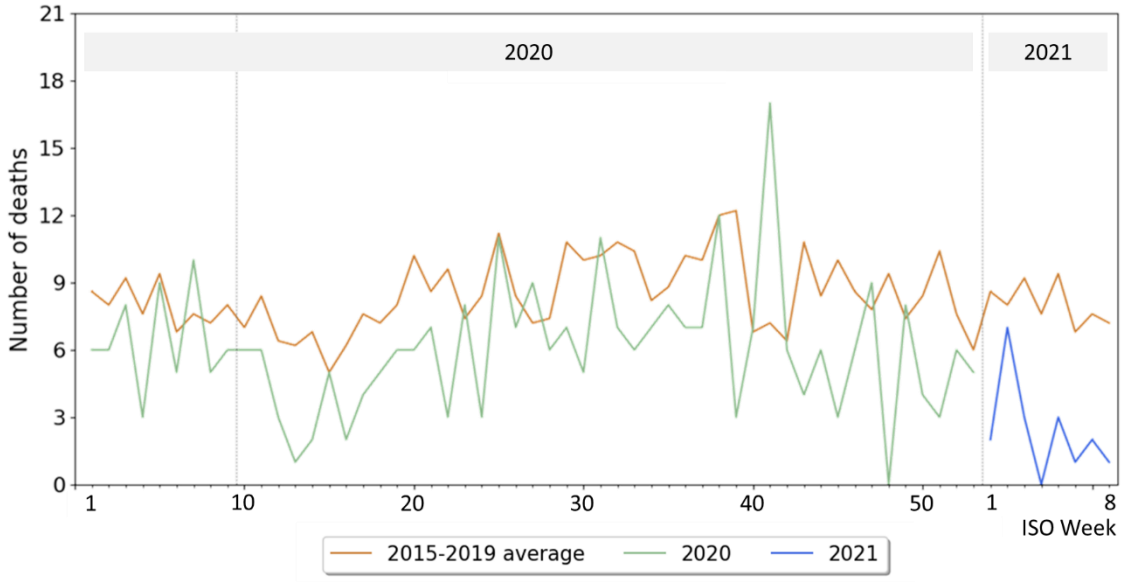


Figure 14 – Mortality by traffic accident in Portugal.
The left vertical line marks the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021.

Their z-scores ranged mainly between -2 and 0, which represents a reduction in mortality, despite being within the expected 2σ distance from the baseline (Figure 15).

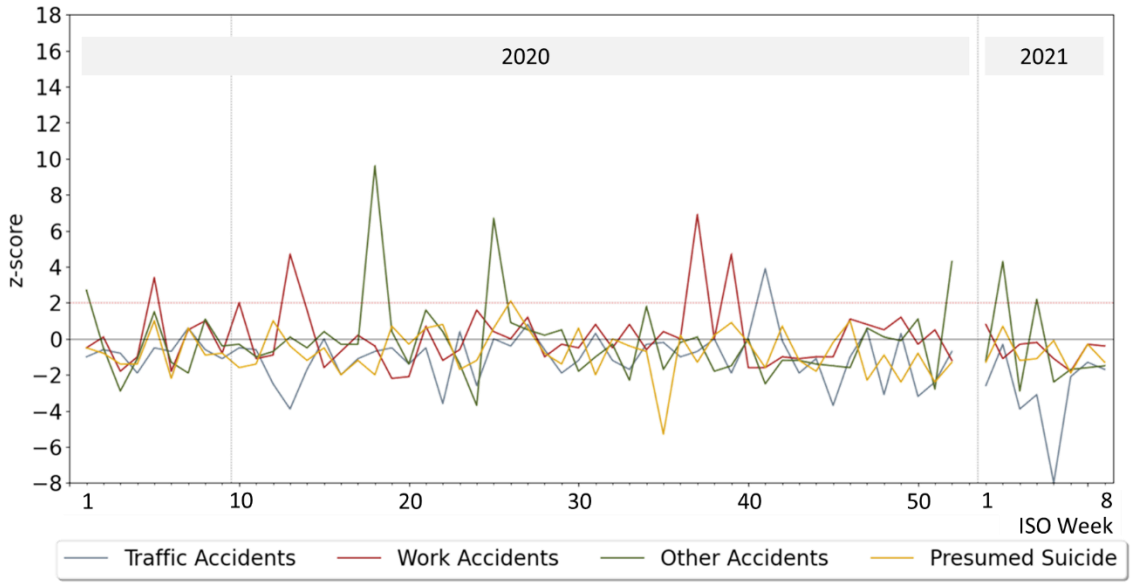


Figure 15 – Weekly z-score for mortality by presumed suicide and accidents in Continental Portugal.
The left vertical line marks the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021. The red horizontal line marks z-score=2, above which there is excess mortality.

Mortality in health institutions persistently exceeded 2 z-scores from week 28 onwards while at-home deaths were much higher than the historical average starting in week 12 (Figure 16).

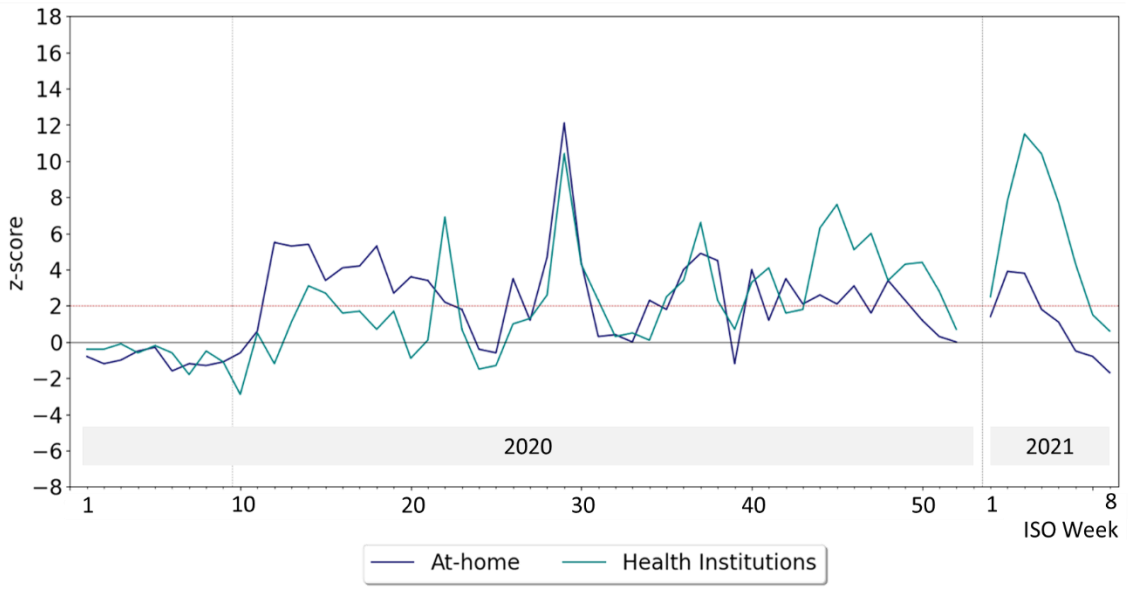


Figure 16 – Weekly z-score for mortality, by place of death.
The left vertical line marks the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021. The red horizontal line marks z-score=2, above which there is excess mortality.

Excess Mortality and Temperature

In the weeks during which excess mortality was registered, there was a positive correlation between the national daily mean temperature and the increase in deaths from the baseline for all-cause non-COVID-19 mortality in warm weeks (Table 1).

Table 1 – Correlation between the increase in mortality – in weeks of excess mortality – and the mean temperature during: a) the previous week and the week of excess mortality, when that excess occurred during a warm week; or b) the previous two weeks and the week of excess mortality, when that excess was reported in a cold week. Significant correlations are marked in bold.

		Mean temperature	
	Non-COVID-19 mortality	*Coefficient*	*p*-value
Warm weeks (19-43)	Natural-cause	0.48	0.1
	All-cause	**0.46**	**<0.001**
Cold weeks (44-18)		0.26	0.21

Mortality and the Pandemic

There was an overall significant correlation between the number of deaths during the first 12 months of the pandemic and: a) the restrictiveness index; b) the number of new COVID-19 cases; and c) the number of active COVID-19 cases. That correlation was positive for regional all-cause and national natural-cause non-COVID-19 mortality, mortality in health institutions and at-home deaths; and negative for traffic accident mortality (Table 2 and Table 3).

Table 2 – Correlation between the number of regional all-cause and natural-cause non-COVID-19 deaths during the pandemic period and the restrictiveness index, the number of new COVID-19 cases, and the number of active COVID-19 cases. Significant correlations are marked in bold.

		Restrictiveness index		New COVID-19 cases		Active COVID-19 cases	
		Coefficient	*p*-value	*Coefficient*	*p*-value	*Coefficient*	*p*-value
Non-COVID-19 mortality							
All-cause	Alentejo	0.1	0.08	**0.62**	**<0.001**	**0.42**	**<0.001**
	Algarve	0.07	0.2	**0.43**	**<0.001**	0.12	0.36
	Centro	**0.23**	**<0.001**	**0.55**	**<0.001**	**0.35**	**<0.001**
	LVT	**0.26**	**<0.001**	**0.66**	**<0.001**	**0.55**	**<0.001**
	Norte	**0.13**	**0.01**	**0.41**	**<0.001**	**0.28**	**0.02**
Natural-cause	National	**0.25**	**<0.001**	**0.52**	**<0.001**	**0.37**	**<0.001**

Table 3 – Correlation between the number deaths by presumed suicide or accident and by place of death, during the pandemic period, and the restrictiveness index, the number of new COVID-19 cases, and the number of active COVID-19 cases. Significant correlations are marked in bold.

	Restrictiveness index		New COVID-19 cases		Active COVID-19 cases	
	Coefficient	*p*-value	*Coefficient*	*p*-value	*Coefficient*	*p*-value
Suicide / Accidents						
Presumed suicide	-0.23	0.09	-0.17	0.19	**-0.26**	**<0.001**
Work accidents	-0.09	0.51	-0.07	0.6	**-0.15**	**<0.001**
Traffic accidents	**-0.54**	**<0.001**	**-0.28**	**0.02**	**-0.37**	**<0.001**
Other accidents	0.01	0.92	0.15	0.24	-0.06	0.22
Place of death						
Health institution	**0.42**	**<0.001**	**0.87**	**<0.001**	**0.91**	**<0.001**
Home	**0.32**	**0.02**	**0.73**	**<0.001**	**0.67**	**<0.001**

Mortality and Healthcare

Overall, there was no correlation between primary care medical appointments and mortality (Table 4).

Table 4 – Correlations between primary care medical appointments during the pandemic period and their difference from 2015-2019, and national natural-cause non-COVID-19 mortality. *Pandemic* represents the values from 2020-2021 whereas *difference* represents their difference to 2015-2019. Borderline significant correlations are marked with *.

	National natural-cause non-COVID-19 mortality			
	Pandemic		Difference	
	Coefficient	*p*-value	*Coefficient*	*p*-value
In-person	0.45	0.11	0.26	0.36
Remote	-0.04	0.9	-0.07	0.82
At-home	0.53	0.05*	0.22	0.44

The exception was for at-home medical appointments in Alentejo and Centro, where both the absolute number of appointments in 2020-2021 and its difference from the 2015-2019 average correlated positively with national natural-cause non-COVID-19 mortality. The number of appointments in 2020-2021 also correlated positively with regional all-cause non-COVID-19 mortality, but only in Alentejo did the difference in at-home appointments from the 2015-2019 average correlate significantly with all-cause non-COVID-19 mortality (Table 5).

Table 5 – Correlations between at-home primary care appointments and national natural-cause and regional all-cause non-COVID-19 mortality. Significant correlations are marked in bold.

		Non-COVID-19 mortality			
		National natural-cause		Regional all-cause	
		Coefficient	*p*-value	*Coefficient*	*p*-value
At-home medical appointments	Appointments in 2020-2021				
	Alentejo	**0.74**	**<0.001**	**0.74**	**<0.001**
	Algarve	0.17	0.55	0.05	0.86
	Centro	**0.67**	**0.01**	**0.64**	**0.01**
	LVT	0.37	0.19	0.21	0.47
	Norte	0.36	0.36	0.39	0.17
	Difference in appointments from the 2015-2019 average				
	Alentejo	**0.62**	**0.02**	**0.62**	**0.02**
	Algarve	0.19	0.52	-0.28	0.33
	Centro	**0.57**	**0.03**	0.47	0.09
	LVT	0.06	0.84	-0.1	0.73
	Norte	0.02	0.95	0.02	0.94

A similar behavior was registered for the difference between 2020-2021 and 2015--2019 in hospital appointments, scheduled surgeries, and for the percentage of first appointments in adequate time (Table 6).

Table 6 – Correlations between hospital medical appointments and surgeries and national natural-cause non-COVID-19 mortality. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2015-2019. Borderline significant correlations are marked with *. Significant correlations are marked in bold.

			National natural-cause non-COVID-19 mortality	
			Coefficient	*p*-value
Continental	Hospital medical appointments			
	First	Pandemic	-0.49	0.06
		Difference	**0.59**	**0.02**
	Follow-up	Pandemic	-0.5	0.06
		Difference	**0.55**	**0.04**
	First appointments in adequate time	Pandemic	**0.55**	**0.04**
		Difference	**0.62**	**0.02**
	Surgeries			
	Scheduled	Pandemic	-0.47	0.08
		Difference	**0.62**	**0.01**
	Urgent	Pandemic	-0.5	0.05*
		Difference	0.46	0.08

There was, however, a negative correlation between urgent surgeries and national natural-cause non-COVID-19 mortality (Table 6). This was accompanied by a decrease in emergency room attendances triaged as orange or yellow, but not by a decrease in ambulance service calls (Table 7).

Table 7 – Correlations between emergency room attendances (by level of the Manchester Triage System) and ambulance service calls, and national natural-cause non-COVID-19 mortality. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2015-2019. Borderline significant correlations are marked with *. Significant correlations are marked in bold.

			National natural-cause non-COVID-19 mortality	
			Coefficient	*p*-value
Continental	Red	Pandemic	-0.5	0.06
		Difference	**0.56**	**0.03**
	Orange	Pandemic	-0.51	0.05*
		Difference	0.5	0.06
	Yellow	Pandemic	-0.51	0.05*
		Difference	0.47	0.07
	Green	Pandemic	-0.5	0.06
		Difference	0.48	0.07
	Ambulance service calls	Pandemic	0.5	0.07
		Difference	0.29	0.32

In primary care, both for Continental Portugal and in general for all regions, the follow-up of patients with diabetes and hypertension decreased with all-cause regional non-COVID-19 mortality and with national natural non-COVID-19 mortality, and its difference to 2018-2019 was smaller for higher numbers of deaths (Table 8). However, there was no correlation with the incidence of stroke/thrombosis.

Table 8 – Correlations between the adequate follow-up of diabetes and hypertension and the incidence of stroke/thrombosis, and national natural-cause non-COVID-19 mortality. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2018-2019. Significant correlations are marked in bold.

			National natural-cause non-COVID-19 mortality	
			Coefficient	*p*-value
Continental	Adequate follow-up of patients with diabetes	Pandemic	**-0.67**	**0.01**
		Difference	**0.61**	**0.02**
	Adequate follow-up of patients with hypertension	Pandemic	**-0.58**	**0.03**
		Difference	**0.63**	**0.02**
	Incidence of stroke / thrombosis	Pandemic	0.04	0.89
		Difference	-0.06	0.85

DISCUSSION

The aim of this study was to analyze the impact of the pandemic on non-COVID-19 mortality in Continental Portugal, particularly on natural-cause mortality, during the first year of the pandemic. We focused on natural-cause mortality as it represents most deaths, and because any changes in the use of health care with a significant impact on people's health, and ultimately leading to death, would reflect itself almost exclusively on mortality by natural causes and its potential excess. However, mortality by external causes cannot be excluded from this analysis: for instance, a decrease in accidents, associated with the different levels of restrictions, could contribute to lowering mortality (Nogueira et al., 2020). Given that external-cause mortality represents about 1.5% of all-cause mortality, its changes – the reduction in mortality by accidents and presumed suicide during the 12-month pandemic period – are not expected to have a significant impact on all-cause mortality. Regardless, the pandemic impacted mortality by traffic accidents, which were lower and decreased the most from the baseline when the restrictiveness index and the new and active COVID-19 cases were higher.

As for mortality by place of death, as expected during such a large pandemic, there was an increase in mortality in health institutions, higher with the worsening of the pandemic. However, with the data available, we could not determine to what extent the pandemic explains that increase. A similar and unexpected behavior was registered for at-home mortality, which might indicate more people avoided health care following events that ultimately led to their death, being those COVID-19 related or not.

During the pandemic period, there were several weeks of excess mortality. In tendentially warmer weeks, a significant correlation was found between temperature and said excess, it being higher with higher daily mean temperatures. Yet, there was no correlation between the temperature in colder weeks and excess mortality, which means other factors were contributing to that excess.

The worsening of the pandemic, represented by either the restrictiveness index or the number of new or active cases COVID-19, seems to have generally affected mortality. This reinforces the idea that health care provision, specifically that which could contribute to preventing death, becomes compromised when the pressure on the

healthcare system is higher – in this case, due to the pandemic. Moreover, the positive correlation between mortality and active cases COVID-19 – i.e., with disease activity – – may be related with the existence of COVID-19 deaths not notified as such.

In general, the number of at-home appointments during 2020-2021 and their difference to 2015-2019 correlated significantly with all-cause non-COVID-19 mortality in Alentejo and Centro regions. This is particularly relevant since at-home appointments are mostly for the elderly population. Those are the regions of Continental Portugal with the highest proportion of people aged over 65 years and an older population demands more health care. Even though for lower mortality there was a decrease in the number of at--home appointments, when compared to 2015-2019, there was a tendency of growth with the increase in mortality. Ultimately, for the highest numbers of deaths, the number of at-home appointments was higher than that of 2015-2019. The follow-up of patients with diabetes or hypertension followed a similar trend when correlated with national natural-cause non-COVID-19 mortality, and their difference to the 2018-2019 values was lower when mortality was higher, approaching the levels of follow-up from previous years. The same was registered for hospital medical appointments, when compared to 2015-2019. Since mortality was also higher during worse periods of the pandemic – with higher new COVID-19 cases – this recovery both in appointments and in follow-up of chronic diseases, as well as the increase in at-home appointments, might represent an effort to maintain the follow-up of more fragile patients.

Regarding urgency and emergency, there was an overall decrease in urgent surgeries with higher non-COVID-19 mortality, which is in accordance with the simultaneous decrease in urgencies triaged as orange and yellow in Continental Portugal. Even though higher mortality cannot be solely attributed to the decrease in emergency room attendances, to a certain degree, it might mean people were more hesitant to seek health care despite suffering from more serious health conditions.

Limitations

One of the main limitations of this study is the fact that we did not consider any time lags between the observation of healthcare indicators and mortality. For instance, the loss in follow-up of patients with chronic illnesses does not have immediate effects.

Unless serious complications were already present, it is very unlikely that inadequate follow-up would result in mortality in such a short period of time.

Not being able to distinguish between deaths caused by COVID-19 and those of people who were infected, but died as a direct consequence of another disease, may contribute to an overestimation of COVID-19 mortality and, consequently, to an underestimation of non-COVID-19 natural mortality and corresponding excess. If confirmed, that would only reinforce our conclusions as they would be based on conservative estimates and results. Besides that, not having access to the specific cause of death for non-COVID-19 deaths also limits our analysis, as we are unable to relate losses in health care provision to possible increases in deaths by specific diseases or complications.

Another important limitation was not having had access to regional data from ÍCARO, and national and regional data from FRIESA, two indexes which estimate the effect of temperature in mortality and would have helped us estimate whether the excess mortality recorded in certain weeks was totally or partially attributable to temperature.

CONCLUSIONS

The COVID-19 pandemic impacted non-COVID-19 deaths independently of excess mortality having been recorded. With higher restrictiveness indexes and higher number of new and active cases COVID-19, mortality was higher. The pandemic also seems to have had an indirect impact on mortality by limiting the response capacity of the healthcare system. However, with higher mortality, there also seems to have been an effort to recover the follow-up of more fragile patients.

This study might contribute to better understanding the effect losses in health care can have in mortality during a pandemic, and to establish priorities when planning the reorganization of healthcare services during a pandemic or when designing emergency plans for extreme situations.

Further studies, with more specific data, are needed to provide additional insight into certain observations, such as the several periods of excess at-home mortality.

REFERENCES

Boni, M. F., Lemey, P., Jiang, X., Lam, T. T. Y., Perry, B. W., Castoe, T. A., Rambaut, A., & Robertson, D. L. (2020). Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic. *Nature Microbiology*, *5*(11), 1408–1417. https://doi.org/10.1038/s41564-020-0771-4

Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. In *Nature Reviews Microbiology* (Vol. 17, Issue 3, pp. 181–192). Nature Publishing Group. https://doi.org/10.1038/s41579-018-0118-9

Direção-Geral da Saúde. (2020a). *Comunicado - Casos de infeção por novo Coronavírus (02/03/2020)*.

Direção-Geral da Saúde. (2020b). *Relatório de Situação N.º 1 - 03/03/2020*.

Direção-Geral da Saúde. (2020c). *Relatório de Situação N.º 15 - 17/03/2020*.

EuroMOMO. (n.d.-a). *Map of z-scores by country*. https://www.euromomo.eu/graphs-and-maps/#map-of-z-scores

EuroMOMO. (n.d.-b). *Methods*. https://www.euromomo.eu/how-it-works/methods/

EuroMOMO. (n.d.-c). *Rationale*. https://www.euromomo.eu/how-it-works/rationale/

Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D. S. C., Du, B., Li, L., Zeng, G., Yuen, K.-Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., … Zhong, N. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*, *382*(18), 1708–1720. https://doi.org/10.1056/nejmoa2002032

Guo, Y., Gasparrini, A., Armstrong, B., Li, S., Tawatsupa, B., Tobias, A., Lavigne, E., De Sousa Zanotti Stagliorio Coelho, M., Leone, M., Pan, X., Tong, S., Tian, L., Kim, H., Hashizume, M., Honda, Y., Guo, Y. L. L., Wu, C. F., Punnasiri, K., Yi, S. M., … Williams, G. (2014). Global variation in the effects of ambient temperature on mortality: A systematic evaluation. *Epidemiology*, *25*(6), 781–789. https://doi.org/10.1097/EDE.0000000000000165

Instituto Nacional de Estatística. (2020a). *A mortalidade em Portugal no contexto da pandemia COVID-19 (Semanas 1 a 46 de 2020)*.

Instituto Nacional de Estatística. (2020b). *A mortalidade em Portugal no contexto da pandemia COVID-19 (Semanas 1 a 48 de 2020)*.

Instituto Nacional de Estatística. (2020c). *Mortality in Portugal in the Context of the COVID-19 pandemic (Weeks 1 to 42 of 2020)*.

Instituto Nacional de Estatística. (2020d). *Mortality in Portugal in the context of the COVID-19 pandemic (Weeks 1 to 44 of 2020)*.

Instituto Nacional de Estatística. (2021a). *A mortalidade em Portugal no contexto da pandemia COVID-19 (Semanas 1 a 52 de 2020)*.

Instituto Nacional de Estatística. (2021b). *Mortality in Portugal in the Context of the COVID-19 pandemic (Weeks 8 and 9 of 2021)*.

Kortüm, S., Frey, P., Becker, D., Ott, H.-J., & Schlaudt, H.-P. (2020). *Corona-Independent Excess Mortality Due to Reduced Use of Emergency Medical Care in the Corona Pandemic: A Population-Based Observational Study*. Cold Spring Harbor Laboratory Press. https://doi.org/10.1101/2020.10.27.20220558

Lam, T. T. Y., Jia, N., Zhang, Y. W., Shum, M. H. H., Jiang, J. F., Zhu, H. C., Tong, Y. G., Shi, Y. X., Ni, X. B., Liao, Y. S., Li, W. J., Jiang, B. G., Wei, W., Yuan, T. T., Zheng, K., Cui, X. M., Li, J., Pei, G. Q., Qiang, X., … Cao, W. C. (2020). Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature*, *583*(7815), 282–285. https://doi.org/10.1038/s41586-020-2169-0

Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., Azman, A. S., Reich, N. G., & Lessler, J. (2020). The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Annals of Internal Medicine*, *10*. https://doi.org/10.7326/M20-0504

Lyall, M. J., & Lone, N. I. (2020). *Higher clinical acuity and 7-day hospital mortality in non-COVID-19 acute medical admissions: prospective observational study*. https://doi.org/10.1101/2020.06.26.20098434

Morens, D. M., & Fauci, A. S. (2020). Emerging Pandemic Diseases: How We Got to COVID-19. *Cell*, *182*(5), 1077-1092. https://doi.org/10.1016/j.cell.2020.08.021

Mulholland, R. H., Wood, R., Stagg, H. R., Fischbacher, C., Villacampa, J., Simpson, C. R., Vasileiou, E., McCowan, C., Stock, S. J., Docherty, A. B., Ritchie, L. D., Agrawal, U., Robertson, C., Murray, J. L. K., MacKenzie, F., & Sheikh, A. (2020). Impact of COVID-19 on accident and emergency attendances and emergency and planned hospital admissions in Scotland: an interrupted time-series analysis. *Journal of the Royal Society of Medicine*, *0*(0), 1–10. https://doi.org/10.1177/0141076820962447

Nogueira, P. J., De Araújo Nobre, M., Nicola, P. J., Furtado, C., & Vaz Carneiro, A. (2020). Excess mortality estimation during the COVID-19 pandemic: Preliminary data from Portugal. *Acta Medica Portuguesa*, *33*(6), 376–383. https://doi.org/10.20344/amp.13928

Ojetti, V., Covino, M., Brigida, M., Petruzziello, C., Saviano, A., Migneco, A., Candelli, M., & Franceschi, F. (2020). Non-covid diseases during the pandemic: Where have all other emergencies gone? *Medicina (Lithuania)*, *56*(10), 1–10. https://doi.org/10.3390/medicina56100512

Pordata. (2021). *Resident population, estimates at December 31st, 2019*. https://www.pordata.pt/en/DB/Municipalities/Search+Environment/Table

Presidência da República. (2020). Decreto do Presidente da República n.º 14-A/2020 de 18 de março. *Diário Da República*, *55*(1.ª Série), 13-(2)-13-(4). www.dre.pt

ProMED - International Society for Infectious Diseases. (2019). *Undiagnosed Pneumonia - China (Hubei): Request for Information*. https://promedmail.org/promed-post/?id=6864153 #COVID19

Tan, W., Zhao, X., Ma, X., Wang, W., Niu, P., Xu, W., Gao, G. F., & Wu, G. (2020). A Novel Coronavirus Genome Identified in a Cluster of Pneumonia Cases - Wuhan, Chine 2019-2020. *CCDC Weekly*, *2*(4), 61–62. http://weekly.chinacdc.cn/fileCCDCW/journal/img/cover/8d108282-5bd8-49fe-a7df-48f6249518b1.pdf#page=15

Vieira, A., Peixoto, V. R., Aguiar, P., Zampaglione, G., Sousa, P., & Abrantes, A. (2020). *Excesso de mortalidade, mortalidade colateral e resposta dos serviços de saúde em Portugal em tempos de COVID-19*.

Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. In JAMA - Journal of the American Medical Association (Vol. 324. *JAMA - Journal of the American Medical Association*, *324*(8), 782–793. https://doi.org/10.1001/jama.2020.12839

World Health Organization. (2020a). *Coronavirus disease (COVID-19) Q&A*. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19

World Health Organization. (2020b). *Coronavirus Symptoms*. https://www.who.int/health-topics/coronavirus#tab=tab_3

World Health Organization. (2020c). *Timeline: WHO's COVID-19 response*. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline

World Health Organization. (2020d). *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

World Health Organization. (2020e). *WHO Director-General's statement on IHR Emergency Committee on Novel Coronavirus (2019-nCoV)*. https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov)

World Health Organization. (2020f). *WHO Statement regarding cluster of pneumonia cases in Wuhan, China*. https://www.who.int/china/news/detail/09-01-2020-who-statement-regarding-cluster-of-pneumonia-cases-in-wuhan-china

Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. Nature, 579(7798), 265–269. https://doi.org/10.1038/s41586-020-2008-3

Zhong, N. S., Zheng, B. J., Li, Y. M., Poon, L. L. M., Xie, Z. H., Chan, K. H., Li, P. H., Tan, S. Y., Chang, Q., Xie, J. P., Liu, X. Q., Xu, J., Li, D. X., Yuen, K. Y., Peiris, J. S. M., & Guan, Y. (2003). Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet*, *362*(9393), 1353–1358. https://doi.org/10.1016/S0140-6736(03)14630-2

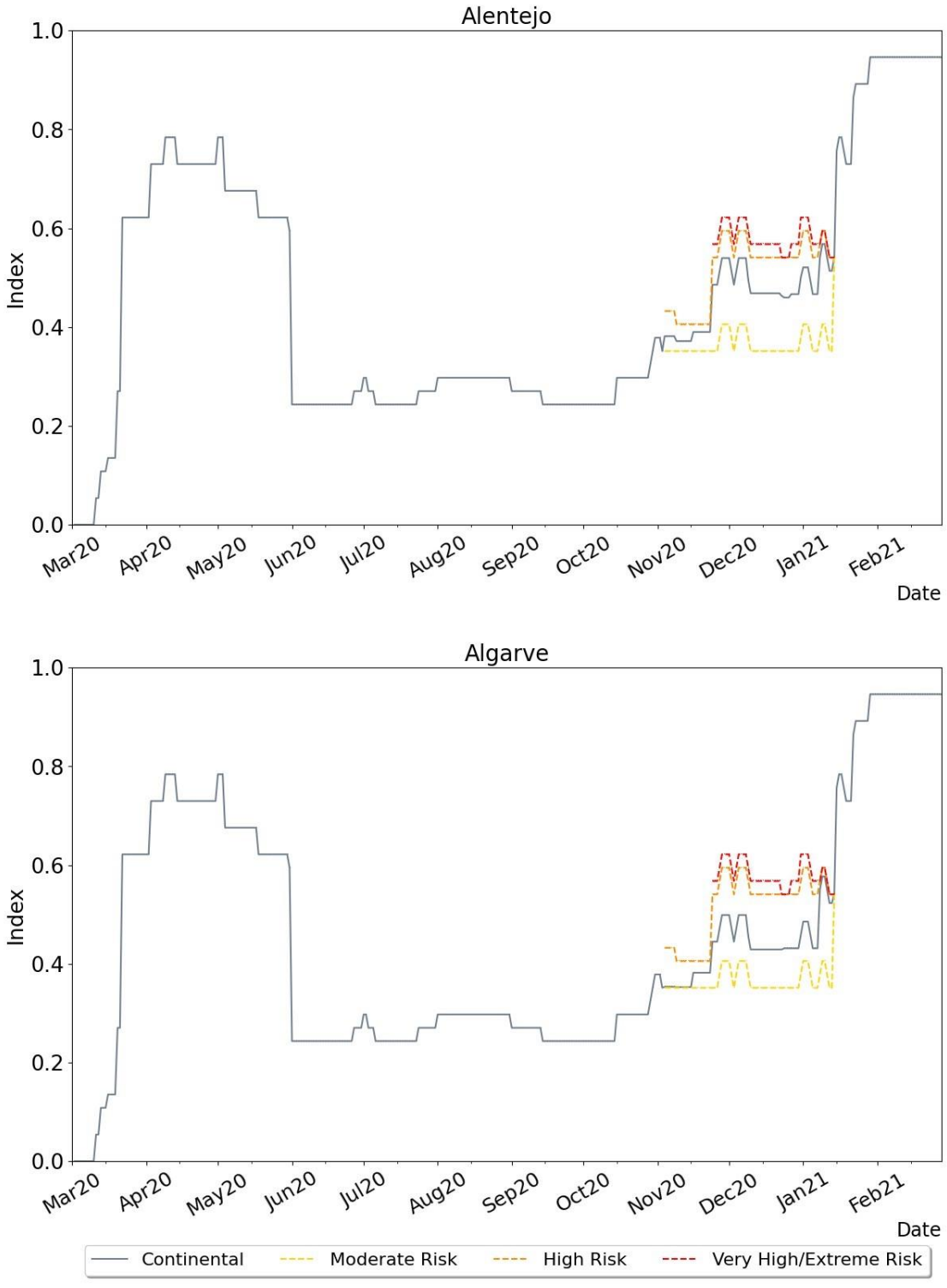
Zhou, P., Yang, X. Lou, Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. Di, Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., … Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., & Tan, W. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, *382*(8), 727–733. https://doi.org/10.1056/nejmoa2001017

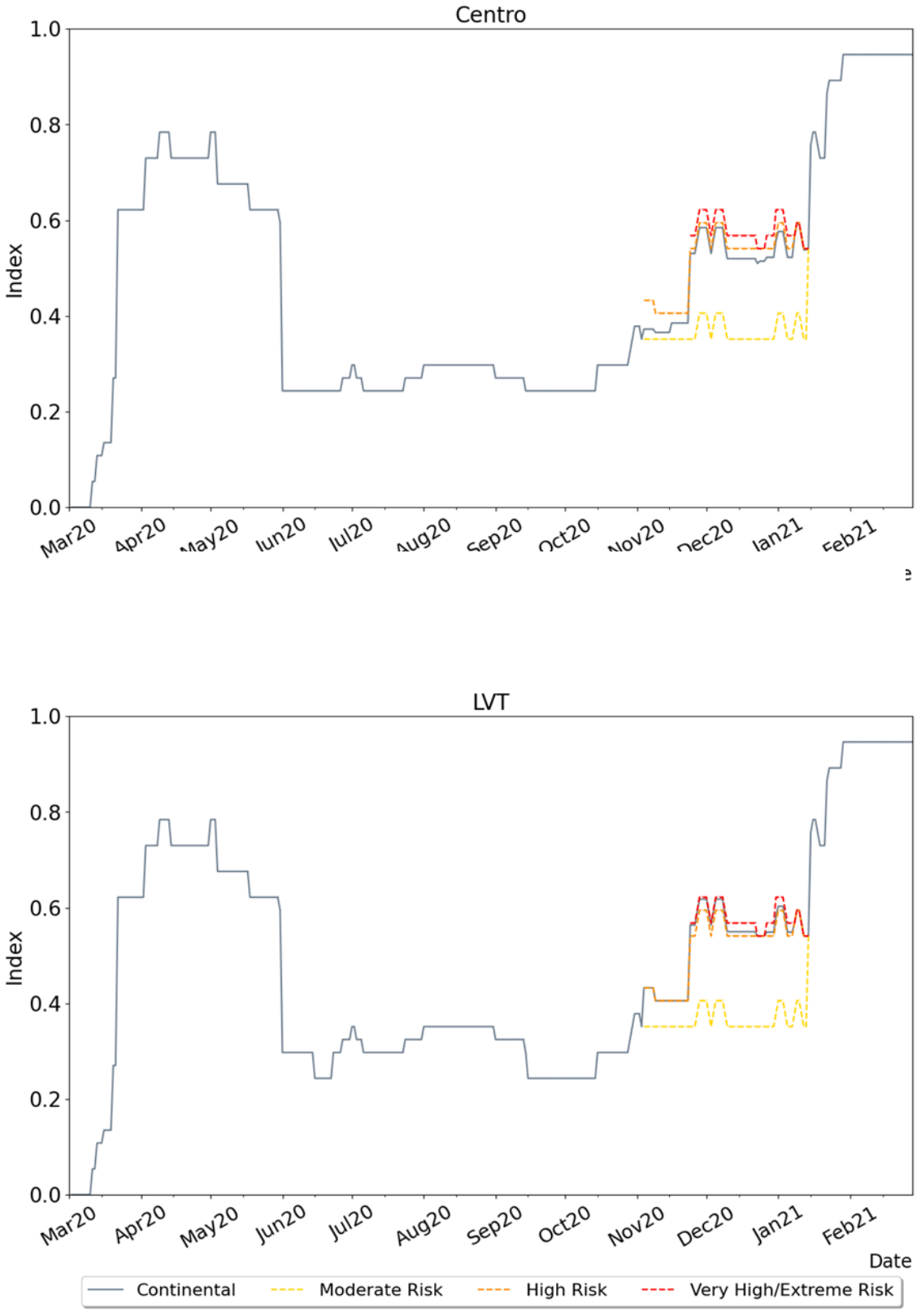
[This page intentionally left blank]

APPENDIX

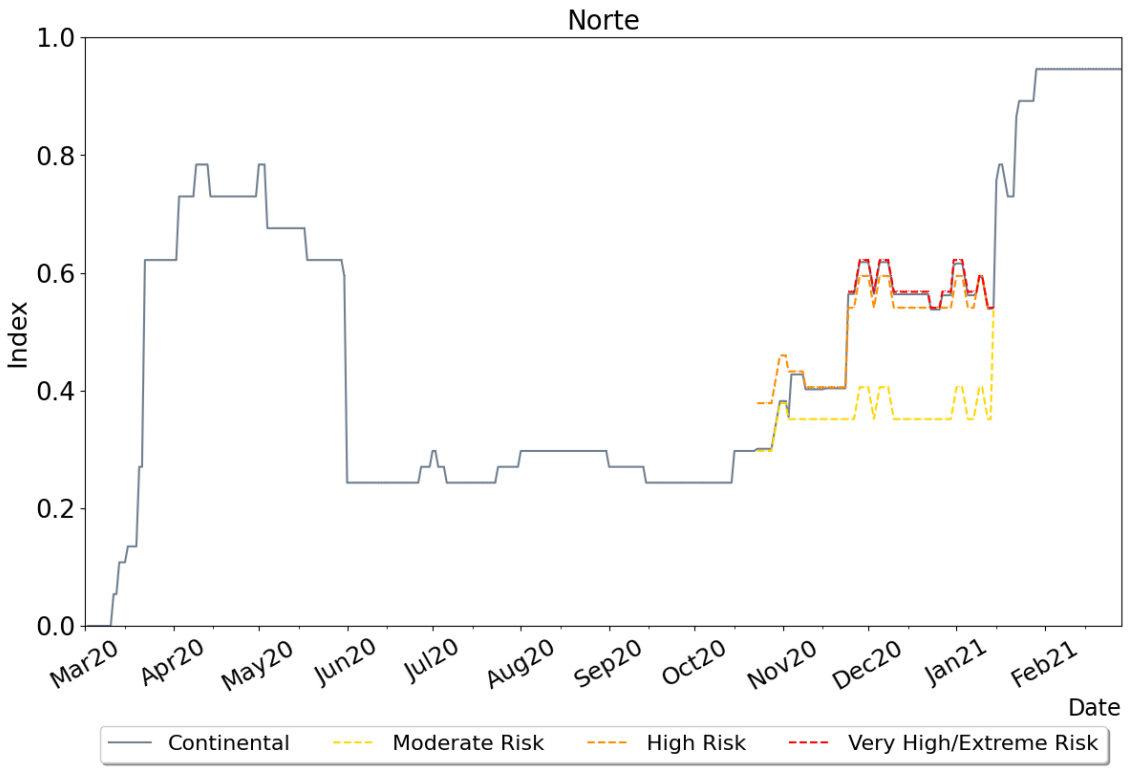
RESTRICTIVENESS INDEX



Supplementary Figure 1 – Daily restrictiveness index in Alentejo and Algarve regions, from March 2nd, 2020, to February 28th, 2021.



Supplementary Figure 2 – Daily restrictiveness index in Centro and LVT regions, from March 2nd, 2020, to February 28th, 2021.



Supplementary Figure 3 – Daily restrictiveness index in Norte region, from March 2nd, 2020, to February 28th, 2021.

Supplementary Table 1 – Items used to calculate the continental daily restrictiveness index. The higher the level within a certain item, the stronger the restrictions. The final score of an item corresponds to the product between the level best suiting the description of the restrictions imposed, and the percentage of the population of Continental Portugal under said restrictions. The maximum total score (considering 100% of the population is under all maximum levels of restrictions) is 36. Therefore, we divided the sum of the levels of all items by 36 in order to obtain an index ranging from 0 to 1.
To calculate the regional daily restrictiveness indexes, instead of using the percentage of the population of Continental Portugal to calculate the final score of an item, we used the percentage of the population of each region under different levels of restrictions.

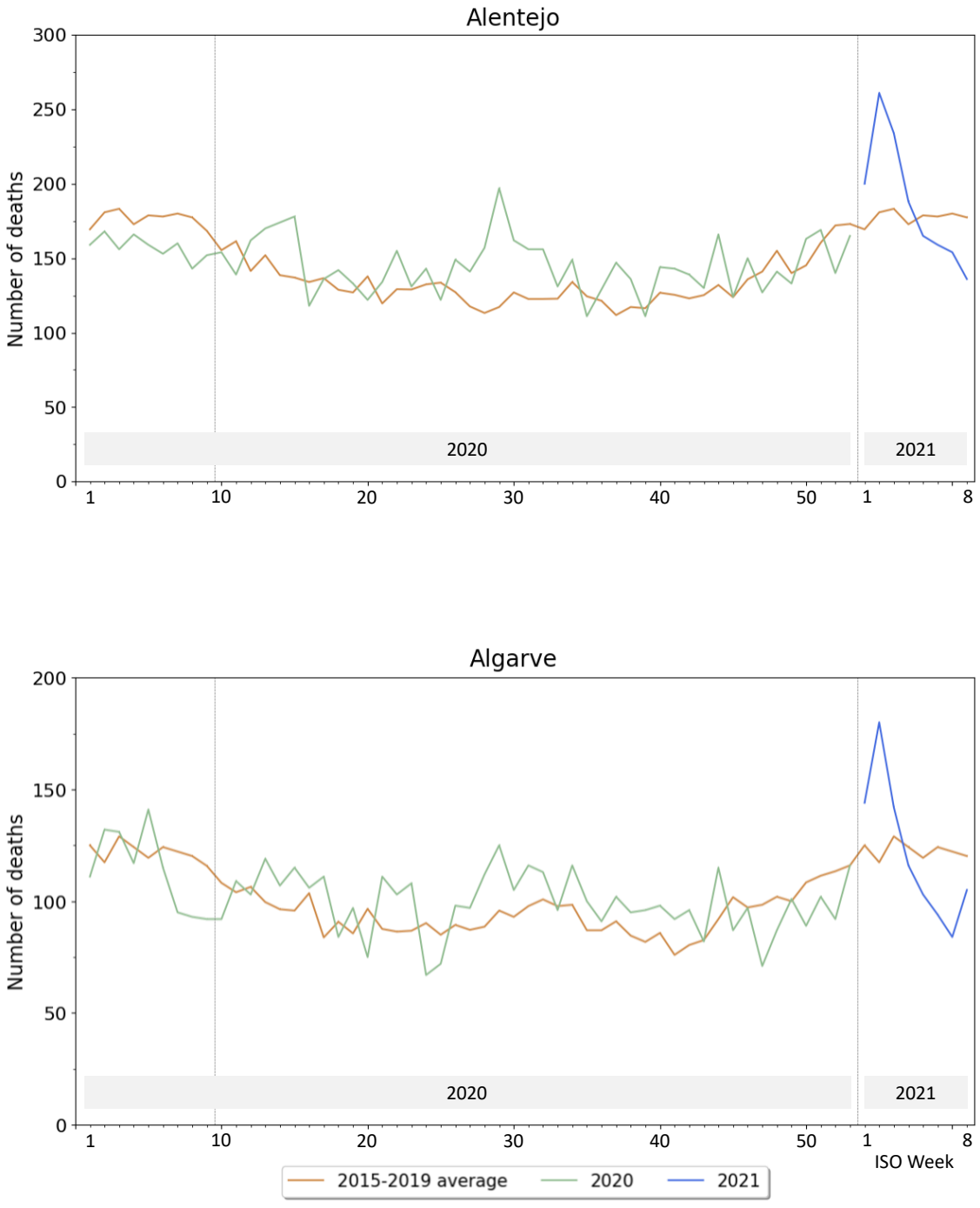
	Items	Level
Circulation	Public roads	
	No restrictions	0
	Curfew: from 11pm to 5am	1
	Curfew: 11pm to 5am (weekdays); 1pm to 5am (weekends and holidays)	2
	General stay-at-home order	3
	Circulation between municipalities	
	Allowed	0
	Forbidden from 11pm or until 5/6am	1
	Forbidden during a whole day or during all weekends	2
	Forbidden for more than 5 consecutive days	3

Items		Level
CIRCULATION	Land borders	
	Open	0
	Closed	1
	Air borders	
	Open	0
	External borders closed (some exceptions)	1
	External borders closed (some exceptions) and/or flight restrictions within the EU or to important Portuguese communities	2
	All borders (external and internal) closed. Only essential justified travels allowed	3
MASKS	No recommendation/obligation	0
	Mandatory in closed spaces	1
	Recommended on public roads, whenever social distancing is not possible	2
	Mandatory on public roads, whenever social distancing is not possible	3
VISITING PEOPLE IN INSTITUTIONS	Allowed	0
	Forbidden	1
BUSINESSES	Open shops, restaurants, and other services	
	Stores with more than 400m^2 or in shopping centers; cinemas, theaters, and auditoria; pools, gyms, casinos, tattoo shops	0
	Stores outside shopping centers and with no more than 400m^2; restaurants, cafés; museums, palaces, art galleries; markets	1
	Stores outside shopping centers and with no more than 200m^2; hairdressers, manicure; bookshops, auto centers; libraries and archives	2
	All closed, apart from those selling essential goods and services	3
	Closing times for businesses	
	Regular schedule	0
	8pm to 11pm	1
	8pm to 1am (weekdays); 1pm to 5pm (weekends or holidays)	2

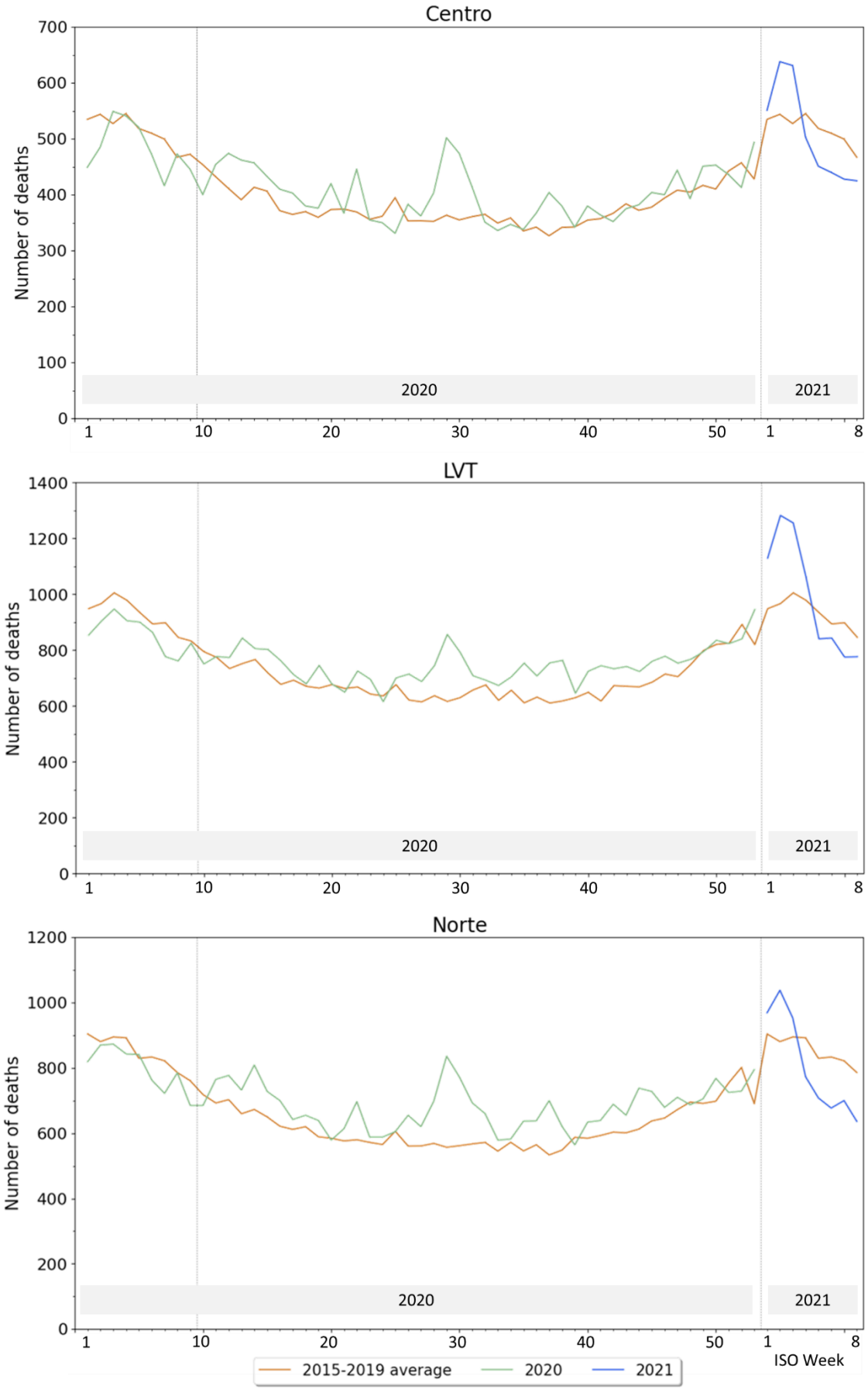
	Items	Level
Businesses	Closing times for restaurants	
	Regular schedule	0
	8pm to 1am	1
	8pm to 1am (weekdays); 1pm to 5pm (weekends or holidays)	2
	Consumption of alcoholic beverages on public roads	
	Allowed	0
	Forbidden	1
Gatherings	Limit of people in a group	
	None	0
	20 people	1
	10 people	2
	6 people or less	3
	Religious ceremonies	
	Allowed	0
	Forbidden	1
	Limit of people in other events	
	None	0
	50 people	1
	20 people	2
	10 people	3
	5 people	4
	Other events forbidden	5
Education and Work	Schools and universities	
	Open	0
	Partially closed or with exams	1
	Holidays or closed	2
	Work	
	Regular	0
	Partially remote (recommendation)	1
	Partially remote (mandatory)	2
	Entirely remote (mandatory)	3

Index = $\frac{Sum}{36}$

NON-COVID-19 ALL-CAUSE MORTALITY BY REGION OF CONTINENTAL PORTUGAL

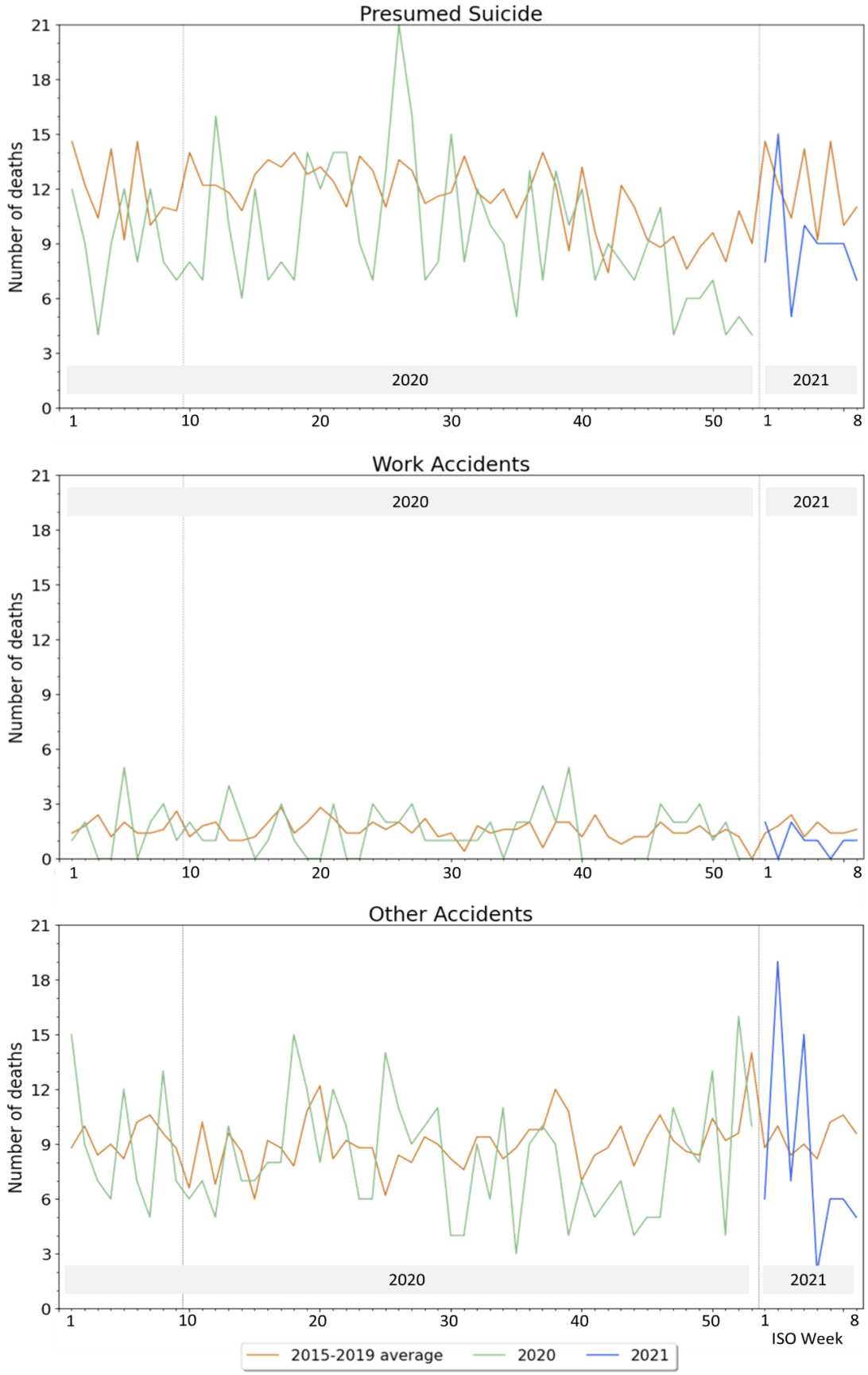


Supplementary Figure 4 – All-cause non-COVID-19 mortality in Alentejo and Algarve regions.
The left vertical line represents the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021.



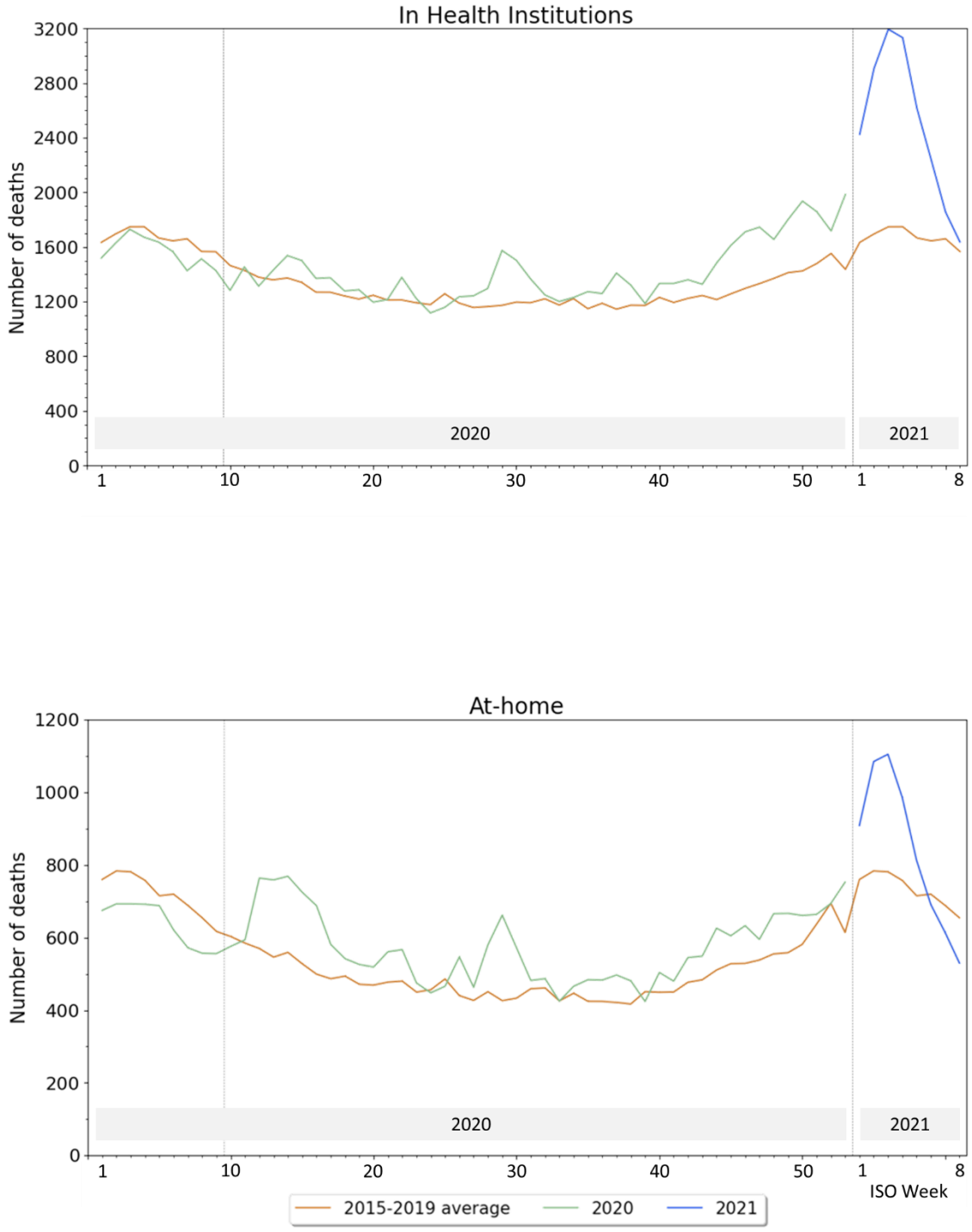
Supplementary Figure 5 – All-cause non-COVID-19 mortality in Centro, LVT and Norte regions.
The left vertical line marks the end of the pre-pandemic period; the right one separates 2020 from 2021.

NATIONAL MORTALITY BY PRESUMED SUICIDE OR ACCIDENT



Supplementary Figure 6 – Mortality by presumed suicide and accidents, other than traffic accidents. The left vertical line marks the end of the pre-pandemic period; the right one separates 2020 from 2021.

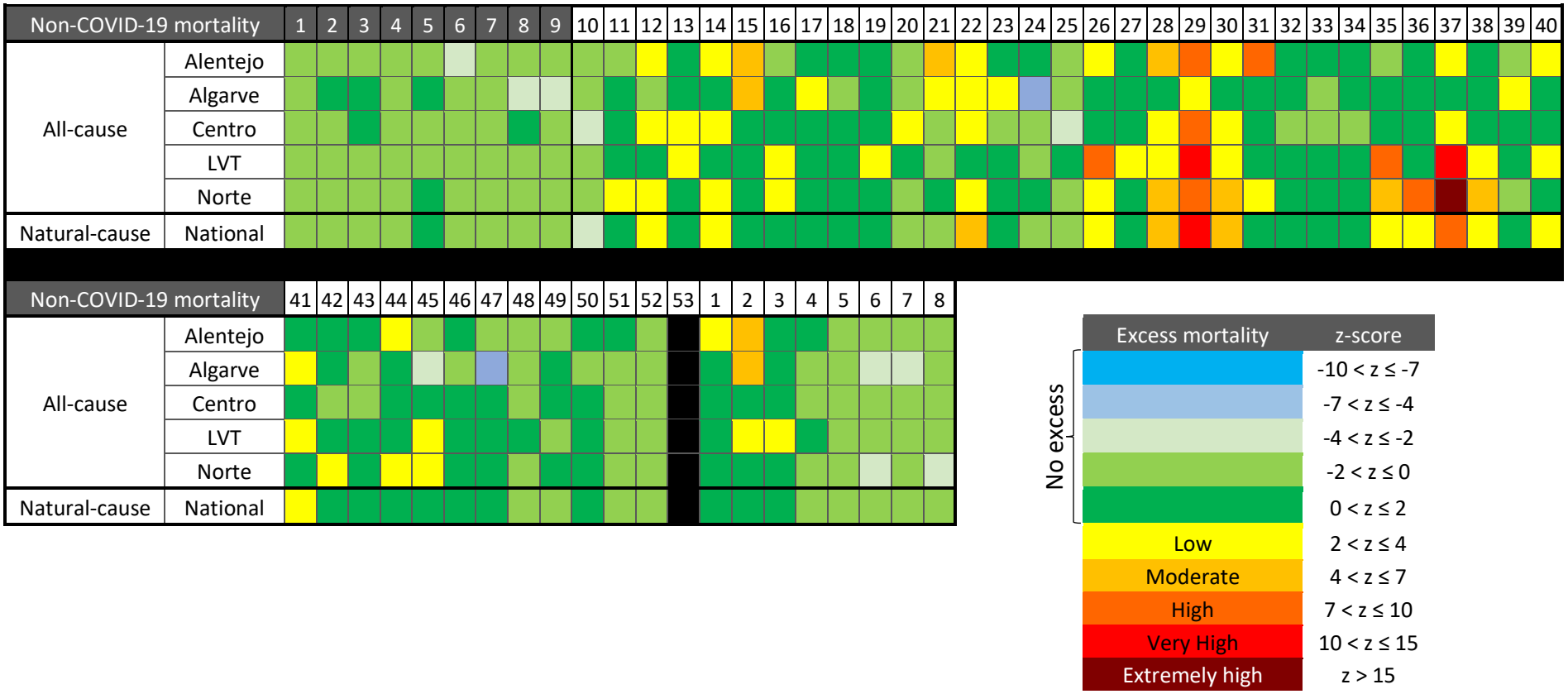
NATIONAL MORTALITY BY PLACE OF DEATH



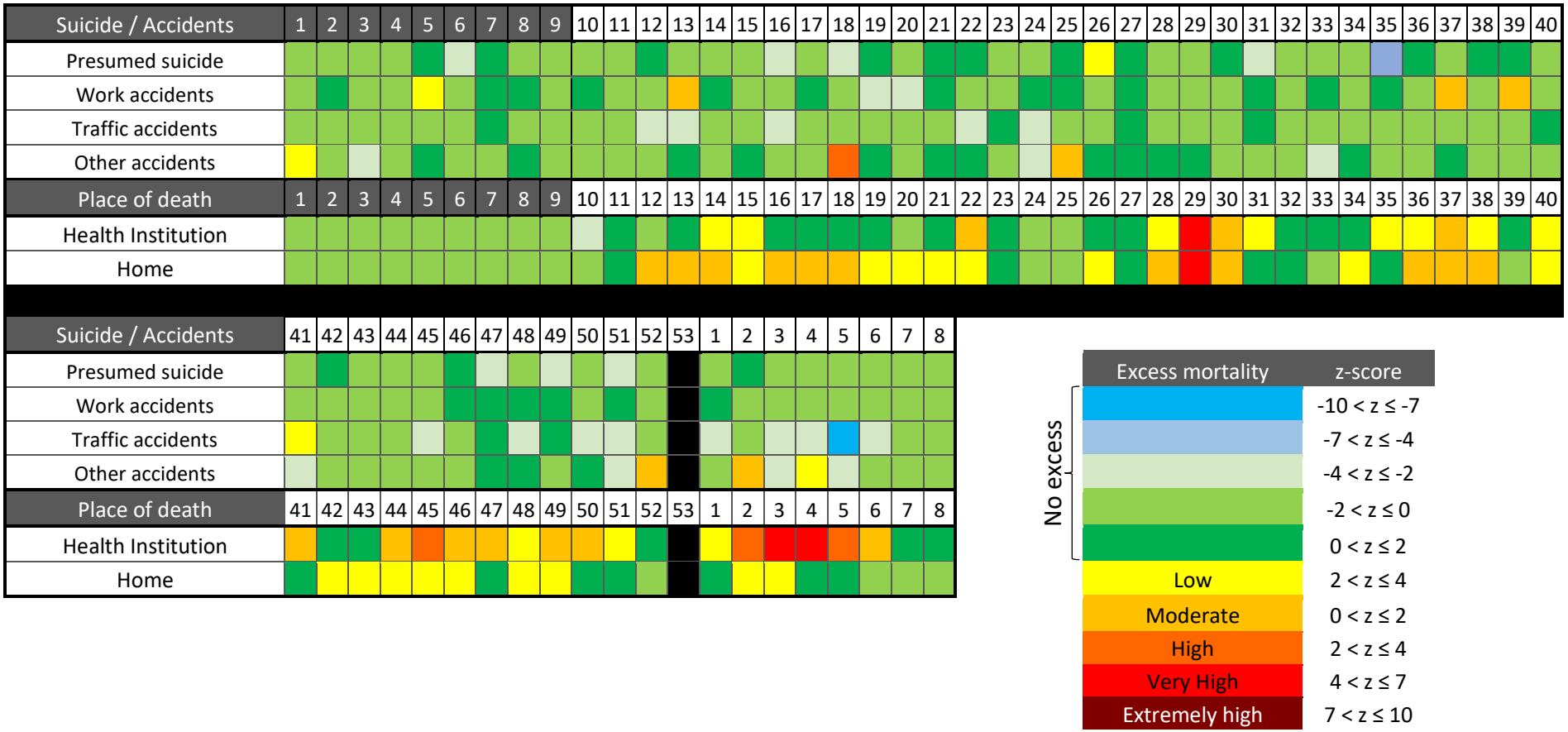
Supplementary Figure 7 – Mortality by place of death.
The left vertical line represents the end of the pre-pandemic period (week 9/2020); the right vertical line separates 2020 from 2021

EXCESS MORTALITY AND Z-SCORES BY WEEK

Supplementary Table 2 – Excess regional all-cause and national natural-cause non-COVID-19 mortality by week, starting on week 1/2020 and ending on week 8/2021, according to the definition of z-score. The first 9 weeks correspond to the pre-pandemic period and the following ones correspond to the pandemic period, from March 2nd, 2020, to February 28th, 2021. As, between 2015 and 2019, only 2015 had 53 weeks, the population standard deviation from the 2015-2019 baseline cannot be calculated and, consequently, neither can we obtain the z-score for that week.



Supplementary Table 3 – Excess mortality by presumed suicide or accidents and by place of death, by week, starting on week 1/2020 and ending on week 8/2021, according to the definition of z-score. The first 9 weeks correspond to the pre-pandemic period and the following ones correspond to the pandemic period, from March 2nd, 2020, to February 28th, 2021. As, between 2015 and 2019, only 2015 had 53 weeks, the population standard deviation from the 2015-2019 baseline cannot be calculated and, consequently, neither can we obtain the z-score for that week.



CORRELATIONS BETWEEN MORTALITY, THE RESTRICTIVENESS INDEX AND COVID-19 CASES

Supplementary Table 4 – Correlations between mortality and the restrictiveness index, new COVID-19 cases, and active COVID-19 cases. The analysis was done for both mortality during the pandemic period of 2020-2021, and for the difference in mortality from the 2015-2019 baseline. The correlation with the difference in mortality helps us understand whether the increase in the restrictiveness index and/or new and/or active COVID-19 cases relates to a decrease or increase in mortality from the baseline. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2015-2019. Significant correlations are marked in bold. Borderline significant correlations are marked with *.

		Restrictiveness index				New COVID-19 cases				Active COVID-19 cases			
		Pandemic		Difference		Pandemic		Difference		Pandemic		Difference	
		Coefficient	*p*-value	*Coefficient*	*p*-value	*Coefficient*	*p*-value	*Coefficient*	*p*-value	*Coefficient*	*p*-value	*Coefficient*	*p*-value
Non-COVID-19 mortality													
All-cause	Alentejo	0.1	0.08	-0.19	0.18	**0.62**	**<0.001**	**0.26**	**0.04**	**0.42**	**<0.001**	0.09	0.5
	Algarve	0.07	0.2	-0.2	0.16	**0.43**	**<0.001**	0.09	0.48	0.12	0.36	-0.07	0.58
	Centro	**0.23**	**<0.001**	-0.17	0.24	**0.55**	**<0.001**	0.13	0.31	**0.35**	**<0.001**	-0.05	0.71
	LVT	**0.26**	**<0.001**	**-0.47**	**<0.001**	**0.66**	**<0.001**	-0.14	0.28	**0.55**	**<0.001**	-0.25	0.05*
	Norte	**0.13**	**0.01**	0.25	0.08	**0.41**	**<0.001**	**0.76**	**<0.001**	**0.28**	**0.02**	**0.62**	**<0.001**
Natural-cause (National)		**0.25**	**<0.001**	**-0.37**	**0.01**	**0.52**	**<0.001**	0.1	0.47	**0.37**	**<0.001**	-0.11	0.38
Suicide / Accidents													
Presumed suicide		-0.23	0.09	-0.25	0.07	-0.17	0.19	-0.07	0.57	**-0.26**	**<0.001**	**-0.13**	**0.01**
Work accidents		-0.09	0.51	-0.15	0.27	-0.07	0.6	-0.03	0.8	**-0.15**	**<0.001**	-0.1	0.06
Traffic accidents		**-0.54**	**<0.001**	**-0.37**	**0.01**	**-0.28**	**0.02**	**-0.27**	**0.03**	**-0.37**	**<0.001**	**-0.29**	**<0.001**
Other accidents		0.01	0.92	-0.06	0.66	0.15	0.24	0.1	0.45	-0.06	0.22	**-0.18**	**<0.001**
Place of death													
Health institution		**0.42**	**<0.001**	0.25	0.06	**0.87**	**<0.001**	**0.89**	**<0.001**	**0.91**	**<0.001**	**0.83**	**<0.001**
Home		**0.32**	**0.02**	0.02	0.9	**0.73**	**<0.001**	**0.53**	**<0.001**	**0.67**	**<0.001**	**0.14**	**<0.001**

CORRELATIONS BETWEEN VARIABLES RELATED TO HEALTH CARE USE AND MORTALITY

Supplementary Table 5 – Correlations between primary care-related variables and mortality – national natural-cause non-COVID-19 mortality for continental values, and regional all-cause non-COVID-19 mortality for regional values. The analysis was done for both the values of said variables during the pandemic period of 2020-2021, and for their difference to those from a) 2015-2019, for appointments; b) 2018-2019, for all other variables. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2015-2019 or 2018-2019. Significant correlations are marked in bold. Borderline significant correlations are marked with *.

		Non-COVID-19 mortality			
		Pandemic		Difference	
		Coefficient	*p*-value	*Coefficient*	*p*-value
Primary care medical appointments					
In-person	Continental	0.45	0.11	0.26	0.36
	Alentejo	0.05	0.87	-0.15	0.62
	Algarve	0.23	0.44	0.1	0.74
	Centro	0.41	0.15	0.2	0.5
	LVT	0.28	0.32	0.08	0.79
	Norte	0.53	0.05*	0.31	0.28
Remote	Continental	-0.04	0.9	-0.07	0.82
	Alentejo	0.5	0.07	0.4	0.15
	Algarve	0.22	0.45	-0.18	0.54
	Centro	-0.08	0.78	-0.01	0.98
	LVT	0.23	0.43	0.05	0.88
	Norte	-0.15	0.62	-0.16	0.59

At-home	Continental	0.53	0.05*	0.22	0.44
	Alentejo	**0.74**	**<0.001**	**0.62**	**0.02**
	Algarve	0.05	0.86	-0.28	0.33
	Centro	**0.64**	**0.01**	0.47	0.09
	LVT	0.21	0.47	-0.1	0.73
	Norte	0.39	0.17	0.02	0.94
Indexes of adequate follow-up of chronic illnesses					
Diabetes	Continental	**-0.67**	**0.01**	**0.61**	**0.02**
	Alentejo	**-0.71**	**<0.001**	0.37	0.2
	Algarve	**-0.8**	**<0.001**	0.48	0.08
	Centro	**-0.62**	**0.02**	**0.62**	**0.02**
	LVT	**-0.65**	**0.01**	0.36	0.21
	Norte	**-0.6**	**0.02**	0.53	0.05*
Hypertension	Continental	**-0.58**	**0.03**	**0.63**	**0.02**
	Alentejo	**-0.67**	**0.01**	0.37	0.2
	Algarve	**-0.79**	**<0.001**	0.3	0.29
	Centro	-0.5	0.07	**0.65**	**0.01**
	LVT	**-0.57**	**0.03**	0.35	0.22
	Norte	-0.51	0.06	0.53	0.05*
Incidence of stroke / thrombosis					
	Continental	0.04	0.89	-0.06	0.85
	Alentejo	-0.05	0.86	-0.27	0.34
	Algarve	0.17	0.56	-0.19	0.52
	Centro	0.14	0.62	0.02	0.93
	LVT	-0.23	0.42	-0.23	0.42
	Norte	0.12	0.69	0.03	0.91

Supplementary Table 6 – Correlations between hospital care-related variables and mortality – national natural-cause non-COVID-19 mortality for continental values, and regional all-cause non-COVID-19 mortality for regional values. The analysis was done for both the values of said variables during the pandemic period of 2020-2021, and for their difference to those from 2015-2019. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2015-2019. Significant correlations are marked in bold. Borderline significant correlations are marked with *.

		Non-COVID-19 mortality			
		Pandemic		Difference	
		Coefficient	*p*-value	*Coefficient*	*p*-value
Hospital medical appointments					
First	Continental	-0.49	0.06	**0.59**	**0.02**
	Alentejo	-0.48	0.07	0.32	0.24
	Algarve	**-0.54**	**0.04**	-0.37	0.17
	Centro	-0.5	0.06	0.36	0.19
	LVT	-0.43	0.11	0.31	0.26
	Norte	-0.4	0.13	0.27	0.33
Follow-up	Continental	-0.5	0.06	**0.55**	**0.04**
	Alentejo	-0.48	0.07	0.23	0.41
	Algarve	**-0.54**	**0.04**	-0.15	0.7
	Centro	-0.51	0.05*	0.26	0.35
	LVT	-0.43	0.11	0.27	0.34
	Norte	-0.42	0.11	0.15	0.61
First appointments in adequate time	Continental	**0.55**	**0.04**	**0.62**	**0.02**
	Alentejo	**0.67**	**0.01**	**0.59**	**0.03**
	Algarve	-0.38	0.18	0.18	0.55
	Centro	**0.6**	**0.02**	**0.55**	**0.04**
	LVT	0.39	0.17	0.42	0.13
	Norte	0.47	0.09	0.4	0.15

Surgeries					
Scheduled	Continental	-0.47	0.08	**0.62**	**0.01**
	Alentejo	-0.47	0.08	0.28	0.31
	Algarve	-0.51	0.05*	0.4	0.14
	Centro	-0.48	0.07	0.46	0.08
	LVT	-0.41	0.13	0.35	0.2
	Norte	-0.39	0.15	0.25	0.38
Urgent	Continental	-0.5	0.05*	0.46	0.08
	Alentejo	-0.49	0.06	0.18	0.52
	Algarve	**-0.54**	**0.04**	0.24	0.38
	Centro	-0.52	0.05*	0.33	0.23
	LVT	-0.43	0.11	0.2	0.48
	Norte	-0.42	0.12	0.26	0.36
People awaiting surgery within the maximum response time	Continental	0.28	0.32	0.15	0.6
	Alentejo	0.19	0.49	0.04	0.88
	Algarve	0.19	0.49	0.23	0.42
	Centro	0.51	0.05*	**0.58**	**0.02**
	LVT	-0.13	0.63	-0.64	0.84
	Norte	0.21	0.45	0.04	0.89

Supplementary Table 7 – Correlations between urgency and emergency-related variables and mortality – national natural-cause non-COVID-19 mortality for continental values, and regional all-cause non-COVID-19 mortality for regional values. The analysis was done for both the values of said variables during the pandemic period of 2020-2021, and for their difference to those from 2015-2019. *Pandemic* represents the numbers from 2020-2021 whereas *difference* represents their difference to 2015-2019. Significant correlations are marked in bold. Borderline significant correlations are marked with *.

		Non-COVID-19 mortality			
		Pandemic		Difference	
		Coefficient	*p*-value	*Coefficient*	*p*-value
Emergency room attendances by level of the Manchester Triage System					
Red	Continental	-0.5	0.06	**0.56**	**0.03**
	Alentejo	-0.47	0.07	-0.12	0.66
	Algarve	-0.52	0.05*	0.36	0.18
	Centro	-0.52	0.05*	0.42	0.12
	LVT	-0.44	0.1	0.33	0.23
	Norte	-0.41	0.13	0.43	0.11
Orange	Continental	-0.51	0.05*	0.5	0.06
	Alentejo	-0.5	0.06	0.14	0.61
	Algarve	-0.52	0.05*	0.38	0.16
	Centro	-0.51	0.05*	0.45	0.09
	LVT	-0.45	0.09	0.28	0.31
	Norte	-0.42	0.12	0.33	0.22
Yellow	Continental	-0.51	0.05*	0.47	0.07
	Alentejo	-0.5	0.06	0.14	0.63
	Algarve	-0.52	0.05*	0.36	0.18
	Centro	-0.51	0.05*	0.41	0.13
	LVT	-0.46	0.09	0.25	0.37
	Norte	-0.41	0.13	0.3	0.27

Green	Continental	-0.5	0.06	0.48	0.07
	Alentejo	-0.51	0.05*	0.12	0.67
	Algarve	-0.51	0.05*	0.4	0.13
	Centro	-0.51	0.05*	0.39	0.15
	LVT	-0.45	0.09	0.26	0.35
	Norte	-0.4	0.14	0.36	0.19
Ambulance service calls					
	Continental	0.5	0.07	0.29	0.32