



Exploring the interplay between climate, population immunity and SARS-CoV-2 transmission dynamics in Mediterranean countries



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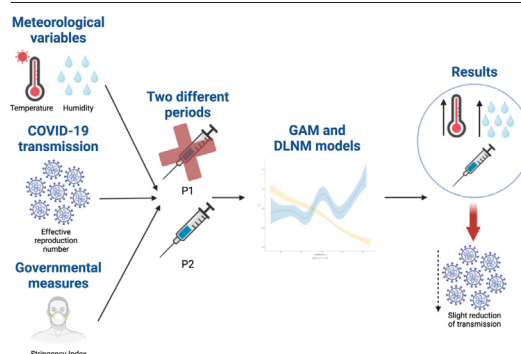
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HIGHLIGHTS

- There were inconsistent findings regarding the impact of meteorological factors on SARS-CoV-2 transmission.
- Population immunity is a confounding factor in the study of the seasonality of COVID-19.
- Temperature and specific humidity did not affect transmission of the disease when the population lacked immunity.
- With enough immunization coverage, there is a slight decrease in the transmission of SARS-CoV-2 during warmer periods

GRAPHICAL ABSTRACT



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ABSTRACT

The relationship between SARS-CoV-2 transmission and environmental factors has been analyzed in numerous studies since the outbreak of the pandemic, resulting in heterogeneous results and conclusions. This may be due to differences in methodology, considered variables, confounding factors, studied periods and/or lack of adequate data. Furthermore, previous works have reported that the lack of population immunity is the fundamental driver in transmission dynamics and can mask the potential impact of environmental variables. In this study, we aimed to investigate the association between climate variables and COVID-19 transmission considering the influence of population immunity. We analyzed two different periods characterized by the absence of vaccination (low population immunity) and a high degree of vaccination (high level of population immunity), respectively. Although this study has some limitations, such as the restriction to a specific climatic zone and the omission of other environmental factors, our results indicate that transmission of SARS-CoV-2 may increase independently of temperature and specific humidity in periods with low levels of population immunity while a negative association is found under conditions with higher levels of population immunity in the analyzed regions.

Abbreviations: COVID-19, Coronavirus disease 2019; dfs, degrees of freedom; GAM, Generalized Additive Model; OxCGRT, Oxford COVID-19 Government Response Tracker; P1, Period with low population immunity; P2, Period with a certain degree of population immunity due to vaccination; R_{eff} , effective reproductive number; RR, Relative Risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SH, Specific Humidity; SI, Stringency Index.

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1. Introduction

Since the onset of the COVID-19 pandemic, great efforts have focused on studying the influence of environmental factors on the transmission of the disease. One key area of research is the seasonal pattern of COVID-19 transmission, which exhibits increased transmission in cold and dry

environments (Martinez, 2018), as observed in other respiratory viruses such as influenza and human coronaviruses (Baker et al., 2018; Moriyama et al., 2020).

Despite the extensive research on this topic, many of the studies were preliminary and showed inconsistent findings (Carlson et al., 2020). Specifically, regarding the influence of temperature, different works have reported a negative correlation between temperature and disease transmission, with some showing a considerable impact on the number of new cases and on the variation of the effective reproductive number (R_e) (D'Amico et al., 2022; Fontal et al., 2021; Hoogeveen et al., 2022; Ma et al., 2021; Yamasaki et al., 2021; Yin et al., 2022). However, other studies have reported small effects (Bashir et al., 2020; Briz-Redón and Serrano-Aroca, 2020; Meyer et al., 2020) or no association whatsoever between temperature and transmission (Kassem, 2020; Liu et al., 2022; O'Reilly et al., 2020; Pan et al., 2021).

The inconsistency between the different studies may be attributed to various factors, such as i) the analysis period selected, especially at the initial stages of the pandemic when a considerable number of cases and deaths were not reported (Chatterjee, 2020; Pifarré i Arolas et al., 2021); ii) the use of an inadequate and limited methodology that may have introduced biases in the results obtained (Dong et al., 2021; Nottmeyer et al., 2023; Villeneuve and Goldberg, 2020; Weaver et al., 2022) and iii) the omission of relevant variables that may significantly impact transmission, such as containment measures adopted by governments (Mecenas et al., 2020; Sera et al., 2021; Smit et al., 2020), among others.

Moreover, initial lack of population immunity is a critical factor in virus spread (Baker et al., 2020; Carlson et al., 2020) that has not been considered in previous works. In two previous studies, Baker et al. developed a climate-dependent epidemic model to simulate the SARS-CoV-2 pandemic using data from other human coronaviruses (HKU1 and HCoV-OC43) (Baker et al., 2021; Baker et al., 2020). They found that, while weather fluctuations may to some extent contribute to transmission, high levels of susceptibility (low population immunity) is the main driving factor for the pandemic and will mitigate the effect of environmental variables such as obstruction of spread of infection by high temperature. A limitation of these important studies is that they did not directly estimate the sensitivity of SARS-CoV-2 to climate, despite offering valuable insights into the possible role of weather in the pandemic. In this context, modeling the impact of climate factors in the scenario of population immunity could provide significant clues about the impact of temperature and humidity on virus transmission.

Nevertheless, after more than three years of pandemic, over 4 billion people have been vaccinated with at least two doses worldwide, according to Our World in Data (Mathieu et al., 2021). This available immunity data, together with larger epidemiological records, is an invaluable source for evaluating the effect of climate on the evolution of COVID-19 transmission and obtaining further insights into the potential seasonality pattern.

In this study, we investigated the association between SARS-CoV-2 transmission, temperature, and specific humidity (SH), considering the effect of population immunity. We analyzed data from two periods of the same duration: June to December 2020 (P1) and June to December 2021 (P2). During P1 there was a near absence of population immunity, whereas in P2, a notable level was achieved due to vaccination (approximately 80 % of the population having received two or more doses at the end of the period).

In our analyses, we considered temperature and specific humidity as the environmental variables. In addition, to take into account potential confounding factors that could have an impact on our results, we also considered other variables, such as the dominant virus variants and the Stringency Index (SI), which measures the different government restrictions. Results from the analysis of data in Spain revealed that temperature and specific humidity only slightly influence transmission in the analyzed period with vaccination, which was also validated by modeling the meteorological effects in different European countries and Italian regions.

2. Methods

2.1. Data collection

We considered two periods for data collection: the first period (P1) ran from June 1, 2020 to December 31, 2020, and was characterized by a low level of population immunity. The second period (P2) ran from June 1, 2021 to December 31, 2021, during which a certain degree of population immunity was achieved due to vaccination efforts. We selected these specific time periods due to their equal duration and identical dates across two different years, making them more affordable. All the code and data and are available at Github: https://github.com/GENyO-BioInformatics/Covid19_Seasonality.

2.1.1. Data for Spanish autonomous communities

The study focused on 16 autonomous communities (regions) in Spain, excluding the Canary Islands due to their subtropical climate and narrower temperature range, which makes it difficult to compare with other communities.

Data of the evolution of COVID-19 pandemic from the 16 autonomous communities of Spain were extracted from the DataC project (Martorell-Marugán et al., 2021), a web application that contains data from the national COVID-19 pandemic that were collected from the Spanish Ministry of Health (Spanish Ministry of Health [WWW Document], 2023) and the Datatista repository (Datatista [WWW Document], 2022) from the beginning of the pandemic up to mid-2022, when the health authorities stopped publishing detailed data. Specifically, the number of daily COVID-19 cases, the number of daily COVID-19 deaths and the daily percentage of fully COVID-19 vaccinated individuals from the two different periods were considered. Moreover, from the daily COVID-19 cases, the effective reproductive number (R_e) was estimated by applying the EpiEstim R package (Cori et al., 2013), assuming an uncertain serial interval with a mean of 4.7 and a standard deviation of 2.9 days, respectively (Baker et al., 2021). The effective reproductive number measures the number of secondary cases generated by a single infected individual. If R_e is >1 , the disease is spreading rapidly, but if R_e is <1 , the spread of the disease is decreasing.

The daily mean of temperature for each region was also extracted from the DataC application, which took the data from the Spanish State Meteorological Agency (AEMET, 2023). Subsequently, the variable hourly 2-m specific humidity (kg/kg) was extracted from the European Centre for Medium-Range Weather Forecast ERA5 climate reanalysis (Hersbach et al., 2020). This variable refers to the specific humidity (SH) at two meters above the surface of the land. This information was then used to calculate the daily mean of SH for each region.

Finally, to take into account the effects of the different measures adopted by the governments during the course of the pandemic, the Stringency Index (SI) for Spain was obtained from the Oxford COVID-19 Government Response Tracker (OxCGRT) (Hale et al., 2021). The SI consists of a composite measure based on nine response indicators: workplace closures, cancellation of public events, restrictions on public gatherings, closures of public transport, stay-at-home requirements, public information campaigns, restrictions on internal movements and international travel controls.

2.1.2. Data for European countries and Italian regions

The European countries chosen for the study are countries on a similar latitude to Spain and mainly close to the Mediterranean Sea. Specifically, those considered were: France, Portugal, Italy, Greece, Slovenia, Croatia, Serbia and Montenegro. Other countries with similar latitudes to others, such as Albania and North Macedonia, were not chosen due to their inferior reported data quality. This is exemplified by the presence of daily cases equal to 0, which does not correspond to the reality of other countries.

The data for Italy were also analyzed in this study, where 19 out of the 20 regions were considered. Valle d'Aosta was excluded due to its significantly colder climate compared to the remaining regions, with an average temperature below 20 °C.

COVID-19 pandemic data were extracted from the John Hopkins University Coronavirus Resource Centre (Dong et al., 2020) and Our World in Data (Hannah Ritchie et al., 2020; Mathieu et al., 2021). As in the case of the communities of Spain, the number of daily COVID-19 cases, the number of daily COVID-19 deaths, the daily percentage of fully COVID-19 vaccinated individuals and the effective reproductive (R_e) from the two different periods were obtained.

Climatological data were downloaded from the European Centre for Medium-Range Weather Forecast ERA5 climate reanalysis (Hersbach et al., 2020). The same meteorological variables were obtained as in the case of Spanish communities.

Finally, again as in the case of Spanish communities, the SI of Italy and the different European countries was obtained from the OxCGRT (Hale et al., 2021).

2.2. Influence of meteorological factor in COVID-19 transmission

The study of the influence of meteorological factors' on COVID-19 transmission involved two distinct stages. Firstly, the potential relationship

between these factors and the reproduction number (R_e) was tested. Secondly, the significant relationships identified in the first step were quantified. These analyses were performed on the two different periods, P1 and P2.

2.2.1. Relationship between meteorological factors and evolution of R_e

The complex relationship between temperature and R_e was estimated using generalized additive mixed models (GAMs), applied independently for each Spanish region and European country included in the study.

This GAM model can be represented as:

$$Re_{i,t} = \alpha + s(MV_{i,t}) + \beta_1(VR_{i,t}) + \beta_2(SI_{i,t}) + f(V_t)$$

where: $Re_{i,t}$ is the effective reproductive number (R_e) on a day t in the region i .

$MV_{i,t}$ is the meteorological variable on a day t in the region i .

$VR_{i,t}$ is the vaccination rate on a day t in the region i .

$SI_{i,t}$ is the stringency index on a day t in the region i .

And $f(V_t)$ the dominant variant on a day t .

In this model, the meteorological variable (temperature or specific humidity) is incorporated as a natural cubic spline (s). To account for the potential effect of variants on transmission, a factor representing the

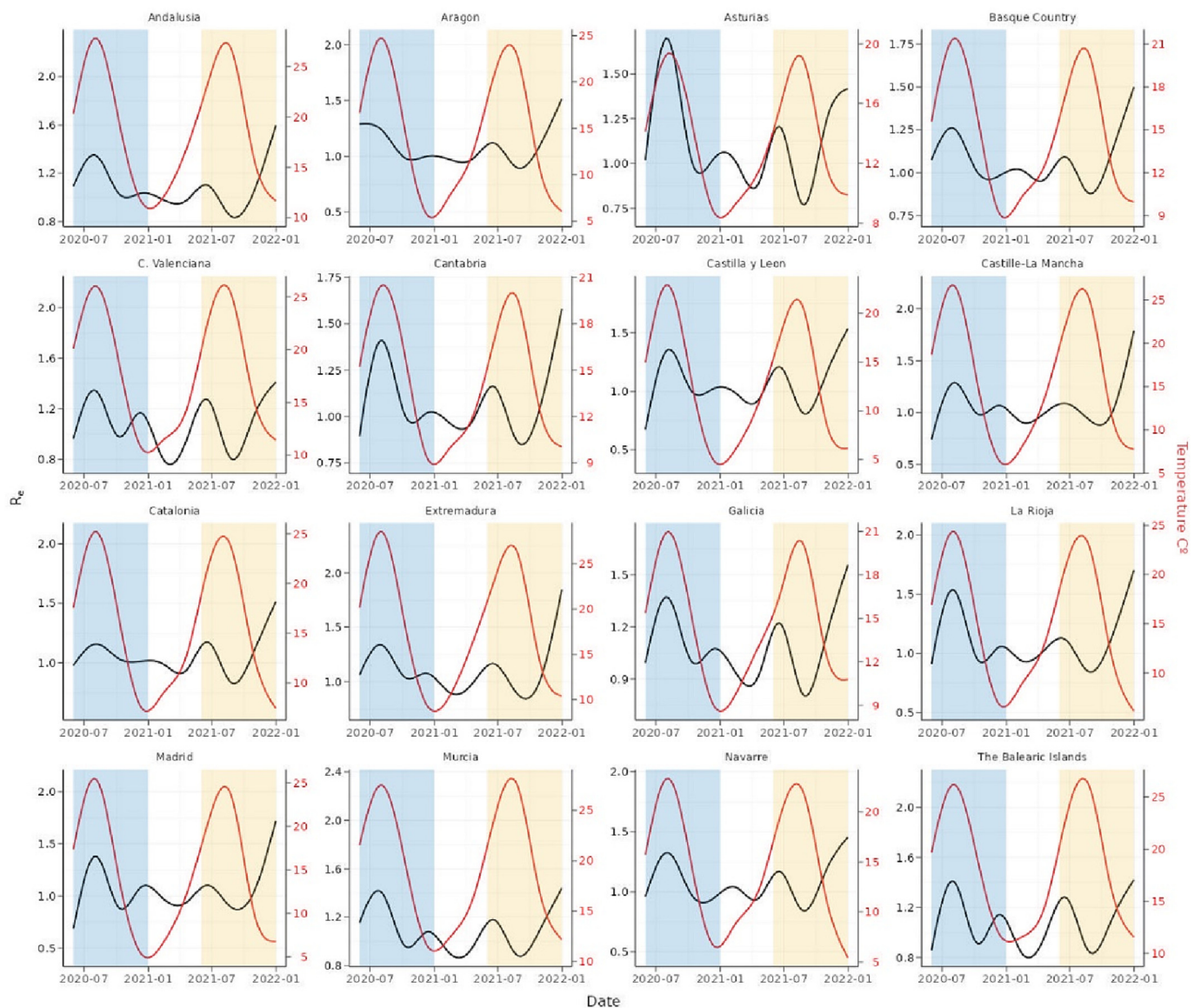


Fig. 1. Distribution of COVID-19 R_e and temperature ($^{\circ}$ C). Longitudinal plot representing the daily COVID-19 R_e in black and the daily temperature in red line from June 1, 2020 and December 31, 2021 in the different Spanish communities. The following periods considered in the study are represented with blue and yellow backgrounds respectively: a first period with a low level of population immunity (P1) and a second period with a high level of population immunity thanks to vaccination (P2). Smoothing has been applied to the R_e and temperature to facilitate visualization.

dominant variant at each time period is also included in the model. The analysis was performed using the mgcv R package (Wood, 2022; Wood, 2017). The p-values obtained were corrected by the Benjamini & Hochberg method (Benjamini and Hochberg, 1995).

To control for the time interval between infection and detection, a lag was applied to the independent variables (lagged variables) included in the model. To account for the distinct characteristics of the two periods under study, distinct lag days were considered for each period. In P1, the delay between infection and detection was substantial, as indicated by previous studies examining the seasonality of COVID-19 that reported a lag range from 10 to 15 days (Ma et al., 2021; Nottmeyer et al., 2023; Sera et al., 2021). As a result, a lag of 14 days (corresponding to 2 weeks) was employed for P1. In contrast, P2 saw a significant improvement in detection methods, leading to a reduced lag. Thus, a lag of 7 days (equivalent to 1 week) was applied for P2.

2.2.2. Quantification of effect of meteorological factors on risk of contagion

In addition to examining the influence of factors on the evolution of disease transmission, it is crucial to understand the magnitude of this influence. To quantify the evolution of the effect of environmental factors on the risk of infection, a two-stage analysis was conducted, encompassing individual analyses by region followed by an estimation of the global effect.

The first step involved the implementation of a distributed lag non-linear model (DLNM) (Gasparrini et al., 2010) for each region during the two distinct periods (P1 and P2). This models can be represented as:

$$R_{e,it} = CB(MV_{i,t}) + CB(SI_{i,t}) + f(V_t) + Ind(Vac) + int + NS(date, df = 2)$$

where:

$CB(MV_{i,t})$ is the cross-basis term for the meteorological variable on a day t in the region i . It incorporates a lag ranging from 7 to 14 days, allowing for consistent considerations comparable to previous (GAMs).

$CB(SI_{i,t})$ is the cross-basis term for the SI on a day t in the region i . Similar to $CB(MV_{i,t})$, it considers a lag between 7 and 14 days to ensure consistency with the previous GAMs.

$f(V_t)$ is the dominant variant on a day t .

$Ind(Vac)$ is a binary variable that represents the lack or presence of vaccination.

int is an interaction term for the pre and post vaccination period.

$NS(date, df = 2)$ is a term that modulates the intra-period trend of COVID-19 evolution. In this case a natural spline function of the date with 2 degrees of freedom (dfs) is considered, which equals approximately 1 df per three months.

The model was built using the *dlm* R package (Gasparrini, 2011) and the residual variation of the $R_{e,it}$ was assumed to follow a quasi-Poisson distribution. For each region and period, the evolution of the effect of R_e was obtained (association curve), measured by the relative risk (RR) and taking as reference the mean of the meteorological variable.

Secondly, a meta-analysis of the different association curves was applied to obtain the evolution of the global effect by using the *mvmeta* R package with the estimation method of restricted maximum likelihood (REML) (Gasparrini et al., 2012). This enabled us to obtain the global association curve for each meteorological factor,

3. Results

3.1. Evolution of R_e and meteorological factors in Spain during analyzed periods

Throughout the pandemic, the Spanish government reported epidemiological data for various autonomous communities. Fig. 1 illustrates the evolution of the effective reproduction number (R_e) across these communities from June 1, 2020 to December 31, 2021. This evolution remained consistent across the different communities. Furthermore, this consistency can also be observed in the distribution of temperature and specific humidity (SH). (Fig. 1 and Supplementary Fig. S1). Moreover, the distribution of meteorological factors remained homogeneous between the two periods under

study, exhibiting similar patterns between the first period with low population immunity (P1) and the second period with higher population immunity due to vaccination (P2). However, no clear correlation can be observed between the evolution of these environmental factors and the evolution of R_e .

On the other hand, a certain relationship can be observed between the distribution of the vaccination rate and the measures adopted by the government. An increase in the vaccination rates concur with a decrease in the Stringency Index (SI) (Supplementary Fig. S2). Furthermore, similar to the evolution of R_e and meteorological variables, a comparable distribution of vaccination rates can be observed among the different communities.

3.2. Influence of temperature and specific humidity varies depending on population immunity

To assess the impact of meteorological factors on the progression of disease transmission, two types of model were employed.

Table 1

Results of the GAM models with temperature as meteorological factor for Spanish communities.

P1 (1 June 2020 to 31 December 2020)						
Autonomous community	Deviance explained	R ²	Corrected p-values			
			Temperature	SI	Vaccination rate	Variants
Andalusia	38.54	0.36	<0.0001	<0.0001	NA	0.0731
Aragon	43.72	0.42	0.0050	<0.0001	NA	0.0413
Cantabria	13.32	0.12	0.0171	0.0002	NA	0.3109
Castilla y Leon	36.98	0.35	<0.0001	0.1917	NA	0.0731
Castille-La Mancha	47.41	0.45	<0.0001	0.7907	NA	0.0614
Catalonia	62.55	0.61	<0.0001	<0.0001	NA	0.1952
Madrid	61.21	0.60	<0.0001	0.3729	NA	0.9196
Navarre	46.07	0.45	0.6030	<0.0001	NA	0.0413
C. Valenciana	29.67	0.28	0.0095	<0.0001	NA	0.2570
Extremadura	23.42	0.21	0.0009	<0.0001	NA	0.0824
Galicia	20.24	0.17	0.0030	<0.0001	NA	0.9196
Balearic Islands	11.44	0.09	0.0046	0.6126	NA	0.0731
La Rioja	38.83	0.37	0.0001	<0.0001	NA	0.0739
Basque Country	35.95	0.35	0.1301	<0.0001	NA	0.9196
Asturias	27.32	0.26	0.5348	<0.0001	NA	0.5804
Murcia	40.01	0.38	0.0001	<0.0001	NA	0.0001
Median	37.76	0.36	0.0019	<0.0001	NA	0.0782
P2 (1 June 2021 to 31 December 2021)						
Autonomous community	Deviance explained	R ²	Corrected p-values			
			Temperature	SI	Vaccination rate	Variants
Andalusia	81.79	0.81	<0.0001	<0.0001	<0.0001	<0.0001
Aragon	56.17	0.55	<0.0001	<0.0001	<0.0001	<0.0001
Cantabria	59.54	0.58	<0.0001	<0.0001	<0.0001	<0.0001
Castilla y Leon	60.01	0.59	<0.0001	<0.0001	<0.0001	0.0007
Castille-La Mancha	85.91	0.85	<0.0001	<0.0001	<0.0001	<0.0001
Catalonia	53.58	0.52	<0.0001	<0.0001	<0.0001	0.7814
Madrid	74.87	0.74	<0.0001	<0.0001	<0.0001	0.0001
Navarre	44.45	0.43	<0.0001	<0.0001	<0.0001	0.0011
C. Valenciana	68.00	0.67	<0.0001	<0.0001	<0.0001	<0.0001
Extremadura	76.66	0.76	<0.0001	<0.0001	<0.0001	0.0011
Galicia	72.83	0.72	<0.0001	<0.0001	<0.0001	0.7813
Balearic Islands	70.69	0.70	<0.0001	<0.0001	<0.0001	0.8998
La Rioja	66.19	0.65	<0.0001	<0.0001	<0.0001	0.0023
Basque Country	69.08	0.68	<0.0001	<0.0001	<0.0001	0.0873
Asturias	49.90	0.48	<0.0001	<0.0001	<0.0001	0.7848
Murcia	65.62	0.65	<0.0001	<0.0001	<0.0001	<0.0001
Median	67.09	0.66	<0.0001	<0.0001	<0.0001	0.0009

Note: Results of the GAM models with temperature as meteorological variable for the different Spanish autonomous communities. The first and the second columns represent the deviance explained and the adjusted R² of the different models. The remaining columns represent the corrected p-values for the different variables included in the models. The values in bold represent the median of the different communities.

Firstly, GAMs were utilized to examine whether meteorological factors had any influence on the disease's evolution, differentiating between the two periods. Once the influence of these factors was confirmed based on the vaccinated population, DLNMs were employed to quantitatively determine their effect on the risk of contagion.

3.2.1. Relationship between meteorological factors and transmission of disease in different periods

The relationship between temperature and R_e was estimated using non-generalized additive mixed models (GAMs), applied for each Spanish region included in the study in two different time periods: P1, with a low level of population immunity (1 June 2020 to 31 December 2020) and P2 (1 June 2021 to 31 December 2021), with a substantial level of immunization due to the vaccination of the population. The results of the models can be observed in Table 1.

The results of the models for P1 suggest an association between temperature and transmission in most communities, with the majority of corrected p-values below 0.05 (median of p-values 0.002, as shown in Table 1). However, analyzing the distribution of temperature and transmission for the

GAMs. by isolating the influence of other variables, no clear association was observed before vaccination, with a large increase in R_e around 17–20 °C (Fig. 2).

During P2, results from GAM showed that temperature is also associated with transmission in the majority of communities, with a median of corrected p-values of <0.001 (Table 1). Unlike the previous period, in most communities, a general decrease in R_e was observed with increasing temperature (Fig. 2). However, some northern regions (Cantabria, Basque Country, and Galicia) experienced an increase in transmission above 20 °C, likely due to their milder summers. Overall, virus transmission was lower at warmer temperatures compared to cooler temperatures (Fig. 2).

Furthermore, the adjusted R^2 and percentage of explained deviance were considerably higher for P2 than for P1 in most communities (Table 1). This was also reflected in the read data estimation of the modes, which showed a better fit for P2 (Supplementary Fig. S3) than for P1 (Supplementary Fig. S4). However, for both periods, the percentage of variability explained was moderate, with most adjusted R^2 not exceeding 0.75, indicating the presence of other factors beyond those included in the models that could affect virus transmission, such as population behavior. Nevertheless, these findings

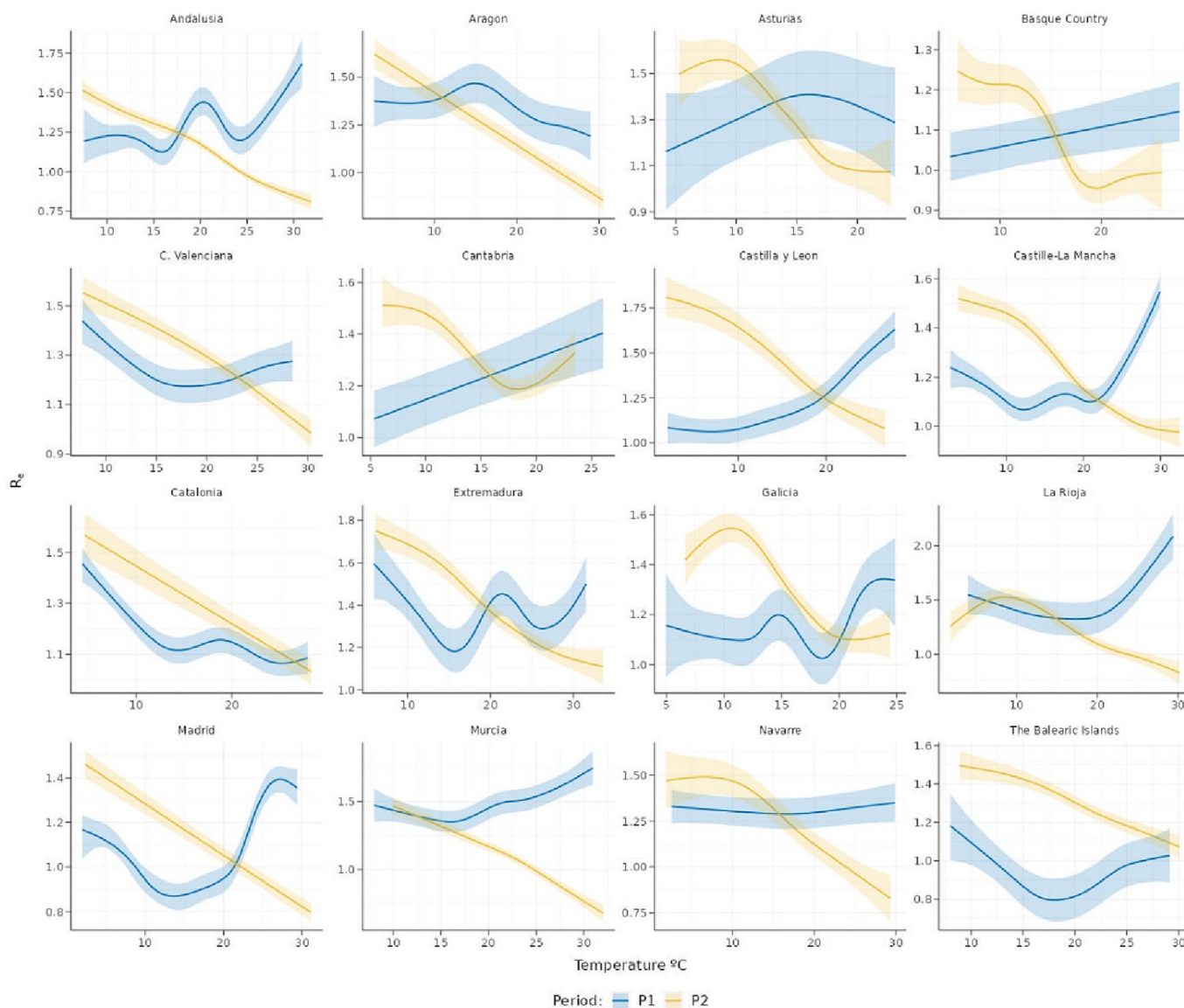


Fig. 2. Estimation of evolution R_e from influence of temperature (°C) predicted by GAMs insulating rest of variables. Graphic representation of the R_e predicted by the GAMs with temperature as meteorological variable and considering the rest of variables remain constant for the different Spanish communities. The blue color represents the period without vaccination (P1) and the yellow color represents the period with vaccination (P2).

suggest that when a significant portion of the population is vaccinated, higher temperatures may lead to a slight reduction in the transmission of COVID-19.

The analysis of specific humidity (SH) revealed that it was a significant factor for most communities for P1 (Table 2). However, deviance explained and adjusted R² values were relatively low for most communities during this time period, with median deviance explained of 24.807 and a median adjusted R² of 0.2335. As a result, the explained variability in most communities is <25 % in P1, and the Stringency Index (SI) was the most significant variable among all the communities.

Further investigation into the evolution of R_e from SH after eliminating the influence of other variables revealed no common pattern among communities, as in the case of temperature (Fig. 3). Some communities exhibited greater transmission during dry periods, while others showed the opposite. Therefore, we did not observe a consistent relationship between SH and COVID-19 transmission during P1.

During P2, SH was also a significant factor for all communities (Table 2). Nevertheless, the explained deviance and adjusted R² showed a significant increase, with median values of 62.687 and 0.613, respectively.

Table 2
Results of GAMs with SH as meteorological factor for Spanish autonomous communities.

P1 (1 June 2020 to 31 December 2020)						
Autonomous community	Deviance explained	R ²	Corrected p-values			
			SH	SI	Vaccination rate	Variants
Andalusia	21.84	0.20	0.0502	<0.0001	NA	0.2942
Aragon	39.45	0.39	0.0308	<0.0001	NA	0.0669
Cantabria	14.49	0.13	0.0065	0.0008	NA	0.3418
Castilla y Leon	13.87	0.13	0.0011	0.0022	NA	0.2942
Castille-La Mancha	11.79	0.09	0.0400	0.0039	NA	0.0715
Catalonia	58.92	0.58	0.0001	<0.0001	NA	0.0057
Madrid	5.69	0.04	0.4886	0.0053	NA	0.5953
Navarre	48.54	0.47	0.0502	<0.0001	NA	0.0203
C. Valenciana	34.93	0.33	0.0005	<0.0001	NA	0.2229
Extremadura	11.53	0.10	0.3783	<0.0001	NA	0.0669
Galicia	9.41	0.08	0.3783	0.0003	NA	0.9958
Balearic Islands	13.61	0.11	0.0048	0.6563	NA	0.1716
La Rioja	39.98	0.39	<0.0001	<0.0001	NA	0.0376
Basque Country	38.04	0.37	0.0056	<0.0001	NA	0.8169
Asturias	27.78	0.26	0.4017	<0.0001	NA	0.5953
Murcia	31.64	0.31	0.0502	<0.0001	NA	0.0004
Median	24.81	0.23	0.0354	<0.0001	NA	0.1972
P2 (1 June 2021 to 31 December 2021)						
Autonomous community	Deviance explained	R ²	Corrected p-values			
			SH	SI	Vaccination rate	Variants
Andalusia	67.47	0.66	<0.0001	<0.0001	<0.0001	0.7620
Aragon	49.26	0.48	<0.0001	<0.0001	<0.0001	0.0146
Cantabria	56.28	0.55	<0.0001	<0.0001	<0.0001	<0.0001
Castilla y Leon	55.56	0.54	<0.0001	<0.0001	<0.0001	0.2524
Castille-La Mancha	75.46	0.75	<0.0001	<0.0001	<0.0001	0.0148
Catalonia	51.73	0.50	0.0003	<0.0001	<0.0001	0.2524
Madrid	64.85	0.64	0.02	<0.0001	<0.0001	0.7620
Navarre	41.92	0.40	<0.0001	<0.0001	<0.0001	0.0217
C. Valenciana	64.65	0.64	<0.0001	<0.0001	<0.0001	<0.0001
Extremadura	64.15	0.63	0.0145	<0.0001	<0.0001	0.7620
Galicia	68.56	0.67	<0.0001	<0.0001	<0.0001	0.7620
Balearic Islands	68.70	0.68	<0.0001	<0.0001	<0.0001	0.5464
La Rioja	61.22	0.60	<0.0001	<0.0001	<0.0001	0.3484
Basque Country	69.30	0.68	<0.0001	<0.0001	<0.0001	0.2037
Asturias	43.87	0.42	<0.0001	<0.0001	<0.0001	0.7620
Murcia	53.37	0.52	<0.0001	<0.0001	<0.0001	0.7620
Median	62.69	0.61	<0.0001	<0.0001	<0.0001	0.3004

Note: Results of the GAM models with SH as meteorological variable for the different Spanish autonomous communities. The first and the second columns represent the deviance explained and the adjusted R² of the different models. The remaining columns represent the corrected p-values for the different variables included in the models. The values in bold represent the median of the different communities.

This suggested that, for this period, the model is able to explain over 60 % of the variability for most communities. The predictions of the model also showed a better fit for this period (as seen in Supplementary Fig. S5) than for the previous one (as seen in Supplementary Fig. S6).

Furthermore, after removing the influence of other variables, a general decrease in transmission is observed in most communities as the humidity level increases. Therefore, when a certain level of population immunity exists, a slight increase in COVID-19 transmission is observed during drier periods.

3.2.2. Quantification of effect of environmental factors on risk of contagion in different periods

In the preceding section, we noted contrasting influences of temperature and humidity during the period with and without vaccination. Nonetheless, the true impact of these variables on the risk of contagion in the different periods remains uncertain. Therefore, to quantify the evolution of the effect of the different environmental factors on the risk of contagion, DLNMs were applied. to each region and period for each of the environmental factors.

Fig. 4 shows the overall pooled association curve representing the relative risk (RR) of COVID-19 infection in relation to temperature. This curve was derived from a meta-analysis of the models across different regions. The analysis reveals significant disparities between the two periods examined. During P1, the risk of infection decreases at lower temperatures and increases as the temperature rises. Conversely, in P2, the opposite pattern emerges, with a higher risk of contagion at lower temperatures, which diminishes as temperatures increase. In the case of P2, the probability of contagion during lower temperatures, around 5 °C, is approximately 1.75 times higher (RR = 1.75, CI = [1.63,1.87]) than with respect to the mean global temperature used as a reference, 17.5 °C. Likewise, at higher temperatures, around 28 °C, during P2, the probability of contagion is 1.61 times lower than with respect to the reference temperature (RR = 0.62, CI = [0.59,0.66]). This consistent trend is observable in the specific association curves for each Spanish region (Supplementary Fig. S7).

In the case of SH, a similar trend is observed as with temperature (Supplementary Fig. S8 and S9). The overall pooled association curve (Supplementary Fig. S8) shows that during P1 the risk of contagion is greater in more humid environments. However, in accordance with the GAMs, in the period with vaccination (P2), it is observed that risk of contagion drops as humidity increases. Specifically, during P2, the probability of contagion during drier environments, around 3.3 g/kg, is approximately 1.72 times higher (RR = 1.72, CI = [1.62, 1.81]) than that in respect to the mean global SH used as a reference, 8.12 g/kg. Likewise, in humid environments, around 12 g/kg, during P2, the probability of contagion is 1.54 times lower than that regards to the reference SH (RR = 0.65, CI = [0.99, 1.31]). This same evolution is observed in the specific association curves of each autonomous community, in which for P1 the RR increases or does not vary in P1 as a function of humidity, while in P2, in a general way, this risk decreases. to higher humidity.

These findings align with the results obtained from our previous GAM models, affirming that higher temperatures and humid conditions contribute to a marginal reduction in the risk of contagion when considerable percentage of people are immunized.

3.3. Association of temperature and specific humidity with R_e in other countries

To validate our findings on the association of temperature and relative humidity with R_e we tested our models on countries with similar latitudes to Spain (Supplementary Tables S1 and S2, finding significant heterogeneity in the results (Supplementary Figs. S10 and S11)). When examining the influence of temperature and SH on R_e while controlling for other variables, we observed similar patterns to Spain in some countries, such as France, Portugal, Greece, and Italy. In contrast, in countries with lower vaccination rates in P2, such as Macedonia and Serbia, the observed patterns were almost the opposite. This difference may be mainly attributed to the much

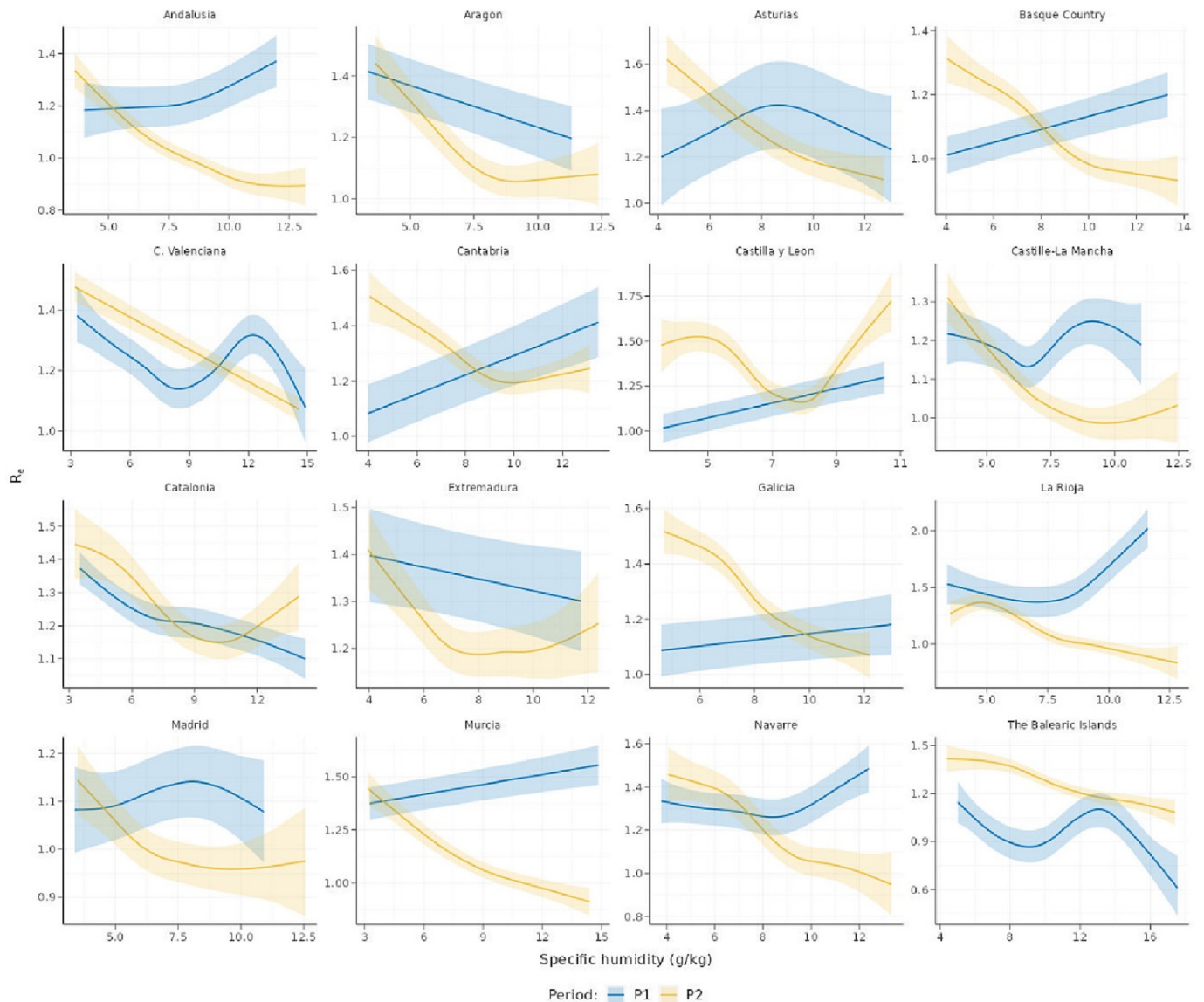


Fig. 3. Estimation of evolution R_e from influence of specific humidity (SH) predicted by GAMs insulating rest of variables. Graphic representation of the R_e predicted by the GAMs with SH as meteorological variable and considering the rest of variables remain constant for the different Spanish communities. The blue color represents the period without vaccination (P1) and the yellow color represents the period with vaccination (P2).

lower vaccination rate in P2 in these countries than in Spain, France, Portugal, Greece, and Italy, where vaccination rates were similar (Supplementary Fig. S12). These trends are also observed when we quantify the effect of the meteorological factors, finding that the specific association curves (Supplementary S13 and S14) for France, Portugal, Greece and Italy show similar tendency to the regions of Spain.

As Italy globally shows a similar pattern to that of Spain, to further validate our findings, we applied the same models to different regions in Italy, which have a similar climate and latitude to their Spanish counterpart. For temperature, we found comparable results in the GAMs between Italian and Spanish regions (Supplementary Table S3 and Supplementary Fig. S15). While temperature is significant in the model for P1, we observed an increase in transmission as the temperature rose in several regions, with a relatively low percentage of variability explained during this time. However, for the period with vaccination, the temperature is significant in almost all regions, except for Molise. We also observed a decrease in transmission with increasing temperature for most regions in the model. In a similar way to Spain, the explained deviance and adjusted R^2 also increased considerably, with over 50 % of the variability being explained for the majority of the regions. A similar pattern emerges from the DLNMs applied for each

of the regions of Italy [Supplementary Fig. S16]. Only in P2is a reduction in the risk of contagion observed as the temperature increases.

Regarding SH, we observed similar patterns compared to temperature (Supplementary Fig. S17, S18 and Supplementary Table S4). SH is only significant for P2, and greater transmission of the disease is observed during drier periods.

Overall, the results for Italian regions confirmed our findings for Spain. To observe the potential seasonality of the disease, a certain population must be vaccinated. In this scenario, more risk of contagion is seen in cold and dry periods.

4. Discussion and conclusions

The impact of environmental factors on COVID-19 transmission has received significant attention among researchers due to its medical, political, and social implications. However, the findings of various studies exploring the relationship between the transmission of the virus and different environmental factors have been conflicting. Such changeability in results may stem from differences in methodology and variables considered, the presence of confounding factors, period studied, or insufficient data (Nottmeyer et al., 2023).

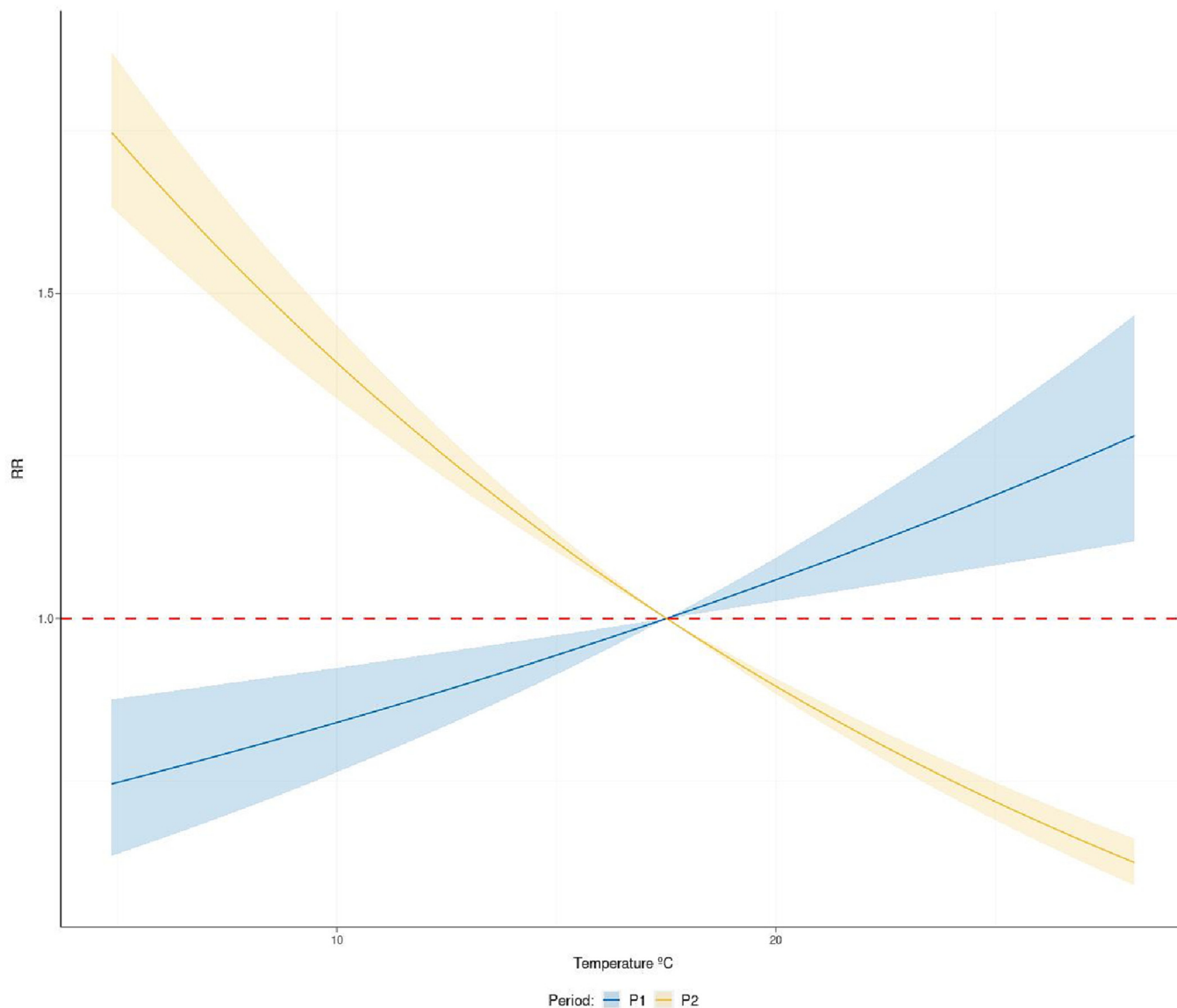


Fig. 4. Global pooled association curve for temperature. Graphic representation of the evolution of Relative Risk (RR) of COVID-19 infection depending on the temperature obtained by the meta-analysis of the different region's models. The global mean temperature (17.5 °C) is used as a reference. The blue color represents the period without vaccination (P1) and the yellow color represents the period with vaccination (P2).

Being a respiratory disease, transmission of COVID-19 may increase in cool and dry conditions, similar to other respiratory diseases like influenza (Baker et al., 2018; Lowen et al., 2007; Lowen and Steel, 2014). Previous studies have suggested that population immunity is a significant confounding factor that may influence the impact of seasonality in SARS-CoV-2 transmission (Baker et al., 2020; Telenti et al., 2021). The initial absence of population immunity during the start of the pandemic may have resulted in unreliable data and findings in non-immunized populations, making it challenging to determine the seasonal patterns of the virus accurately. Thus, the time frame selected for studying the effect of environmental factors on the transmission of SARS-CoV-2 is crucial for the accuracy of results and the reliability of the conclusions.

To consider the impact of population immunity on the association between weather and virus transmission we analyzed two separate time periods. The first period, from June to December 2020, saw a low proportion of the population being vaccinated and hence, low population immunity. In contrast, the second period from June to December 2021 had a high proportion of the population vaccinated with two or more doses, resulting in a high level of population immunity. Additionally, the two periods were selected to include the same months of the year, allowing

for a more accurate comparison of the weather conditions. Furthermore, to control other potential confounding factors that could impact the outcomes, the models incorporated variables that took into account population mobility and severity of measures implemented by governments.

Our analysis revealed that population immunity influences the relationships between temperature, SH and COVID-19 transmission. During the period of low population immunity (June–December 2020), our results indicate that an increase in temperature does not lead to a decrease in virus transmission and may even be associated with increased transmission. These findings are consistent with previous studies conducted early in the pandemic, which reported either a lack of correlation or a positive correlation between temperature and transmission of COVID-19 (Bashir et al., 2020; Briz-Redón and Serrano-Aroca, 2020, p.; Meyer et al., 2020).

However, during the period when a high proportion of the population were vaccinated, the results suggest a different trend, indicating that temperature and specific humidity do have an impact on SARS-CoV-2 transmission in accordance with prior studies (Baker et al., 2020; Telenti et al., 2021). Specifically, a slight reduction in the risk of contagion was noted with higher temperatures and less dry environment.

We wish to point out some limitations of this study. Firstly, the scope of our analysis is restricted to individuals who received a minimum of two doses of the COVID-19 vaccine, thereby disregarding those who may have acquired immunity from contracting the virus. Additionally, we have not accounted for the variable duration of vaccine-induced immunity, which may influence the definition of what constitutes effective immunization (Lopman et al., 2021). Nevertheless, it is notable that a decline in COVID-19 immunity has been reported starting from the first month after vaccination (Addo et al., 2022), with immunity largely diminishing by the sixth month, a timeframe which corresponds to the duration of our study periods.

Secondly, another limitation of our study is that it primarily concentrates on Spain, Italy, and other Mediterranean European countries, which are generally known for having warm summers and mild winters. Weather conditions, however, may have varying impacts on the transmission of the virus in other regions, such as tropical or colder areas, as occurs with other viruses such as influenza (Baker et al., 2019; Tamerius et al., 2013). Therefore, to gain a comprehensive understanding of how different climates affect the transmission of the disease, it is necessary to conduct a more extensive analysis in different climatic regions, in which the temperature and humidity do not follow seasonal patterns.

Thirdly, an additional potential limitation of our study is that it only considers SH and temperature, while there are other environmental factors that may affect the seasonality of the virus and that better explain the seasonal patterns in other climatic zones (Tamerius et al., 2013). For instance, certain factors like allergens or daily sunlight duration have been explored in previous studies as potential explanations for this seasonal pattern (Abraham et al., 2021; Hoogeveen et al., 2022; Shah et al., 2021). In future investigations, it would be valuable to incorporate these variables for a more comprehensive analysis and to account for other potentially relevant factors associated with the seasonality of the disease.

Finally, it is important to note that in the case of our study it was not possible to analyze other variables due to the unavailability of comprehensive pandemic-related information in some countries. For instance, in Spain, the collection of pandemic-related data was halted in 2022, which limits the completeness of our analysis. Furthermore, due to the lack of these data, the periods analyzed do not include complete annual cycles, which may have influence on our results. To perform a more compressive analysis of the impact of environmental factors on the disease, it is critical that countries provide complete and up-to-date information on the progression of the pandemic.

Our results suggest that meteorological factors might affect COVID-19 transmission, which may be slightly reduced during warmer periods when there is a substantial proportion of the population immunized. Despite some limitations, this study represents a novel approach in exploring the relationship between COVID-19 seasonality and population immunity. Our results suggest that temperature and specific humidity have a differential effect on virus transmission, with the effects observed being a result of population immunity. Future studies incorporating more data and longer periods of immunity are expected to further clarify the relationship between seasonality and COVID-19 transmission. The insights gained from this study provide valuable information for public health and disease management strategies.

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Additional information

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Code availability

Code for recreating the results is available at: https://github.com/GENyO-BioInformatics/Covid19_Seasonality.

CRediT authorship contribution statement

Juan Antonio Villatoro-García: Methodology, Formal analysis, Data Curation, Writing - Review & Editing. **Jordi Martorell-Marugán:** Validation, Writing - Review & Editing. **Raúl López Domínguez:** Data curation, Writing - Review & Editing. **Juan de Dios Luna:** Methodology, Writing - Review & Editing, **Jose Antonio Lorente:** Results interpretation, Writing - Review & Editing, **Pedro Carmona-Sáez:** Conceptualization, Supervision, Methodology, Funding acquisition, Original Draft, Writing - Review & Editing.

Data availability

The data employed in this article is available at: https://github.com/GENyO-BioInformatics/Covid19_Seasonality.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pedro Carmona-Saez reports financial support was provided by Government of Andalusia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:<https://doi.org/10.1016/j.scitotenv.2023.165487>.

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