# The impact of ambient temperature and air pollution on SARS-CoV2 infection and Post COVID-19 condition in Belgium (2021–2022)

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# Title: The Impact of Ambient Temperature and Air pollution on SARS-CoV2 Infection and Post COVID-19 condition in Belgium (2021-2022)”

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## Abstract

**Introduction:** The associations between non-optimal ambient temperature, air pollution and SARS-CoV-2 infection and post COVID-19 condition (PCC) remain constrained in current understanding. We conducted a retrospective analysis to explore how ambient temperature affected SARS-CoV-2 infection in individuals who later developed PCC compared to those who did not. We investigated if these associations were modified by air pollution.

**Methods:** We conducted a bidirectional time-stratified case-crossover study among individuals who tested positive for SARS-CoV-2 between May 2021 and June 2022. We included 6,302 infections, with 2,850 PCC cases. We used conditional logistic regression and distributed lag non-linear models to obtain odds ratios (OR) and 95% confidence intervals (CI) for non-optimal temperatures relative to the period median temperature (10.6°C) on lags 0 to 5. For effect modification, daily average $PM_{2.5}$ concentrations were categorized using the period median concentration (8.8μg/m$^3$). Z-tests were used to compare the results by PCC status and $PM_{2.5}$.

**Results:** Non-optimal cold temperatures increased the cumulative odds of infection (OR=1.93; 95%CI:1.67–2.23, OR=3.53; 95%CI:2.72–4.58, for moderate and extreme cold, respectively), with the strongest associations observed for non-PCC cases. Non-optimal heat temperatures decreased the odds of infection except for moderate heat among PCC cases (OR=1.32; 95%CI:0.89–1.96). When $PM_{2.5}$ was >8.8μg/m$^3$, the associations with cold were stronger, and moderate heat doubled the odds of infection with later development of PCC (OR=2.18; 95%CI:1.01–4.69). When $PM_{2.5}$ was ≤8.8μg/m$^3$, exposure to non-optimal temperatures reduced the odds of infection.

**Conclusion:** Exposure to cold increases SARS-CoV2 risk, especially on days with moderate to high air pollution. Heated temperatures and moderate to high air pollution during infection may cause PCC. These findings stress the need for mitigation and adaptation strategies for climate change to reduce increasing trends in the frequency of weather extremes that have consequences on air pollution concentrations.



**Keywords:** post COVID-19 conditions, SARS-CoV2 infection, ambient temperature(s), air pollution, climate change

# 1 Introduction

Despite the World Health Organization (WHO) declaring the conclusion of the global health emergency status for Coronavirus Disease 2019 (COVID-19) in May 2023, the world continues to witness millions of new infections and thousands of associated deaths each month (1). In August 2023, WHO's six regions reported over 1.4 million new cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and more than 2300 deaths, marking a 63% increase in cases and a 56% decrease in deaths compared to the preceding 28 days (2). In addition, the symptoms of COVID-19 may persist for months after the infection. Following acute SARS-CoV-2 infection, organ damage and a prolonged pro-inflammatory response can lead to persistent symptoms of SARS-CoV-2 infection (3, 4). These persistent symptoms are defined as post COVID-19 conditions (PCC) that emerge in COVID-19 patients three months after onset, last at least 2 months, and have no alternative explanation (5). The prevalence of PCC was high (45.7% of hospitalized COVID-19 patients, and 36.9% of non-hospitalized COVID-19 patients) in a population-based cohort study in Switzerland (6). Another cohort study in Faroe Islands found that 53% of people infected with SARS-CoV-2 showed persistence of at least one symptom, and 33% reported persistence of one or two symptoms (7).

Climate factors such as ambient temperature and humidity, alongside elements like air pollution (8-19), wind speed (20), and population density (21) significantly contribute to the transmission, persistence, and infectivity of SARS-CoV-2 infection and might contribute to the risk of further development of PCC. According to a systematic review in 166 countries, each 1% increase in relative humidity was linked to 0.5% decrease in daily new COVID-19 deaths and a 1 degree Celsius (°C) increase in temperature was linked to a 3% reduction in the number of SARS-CoV-2 infection (22). Another report from 122 cities in China also confirmed that the correlation between average temperature and COVID-19 cases followed a linear trend below 3°C but leveled off above this point (23). Under 3°C, every 1°C increase was associated with a 4.861% rise (95% CI: 3.209-6.513) in daily confirmed COVID-19 cases (23). An escalation of 10 μg/m$^3$ in ambient particulate matter with a diameter of ≤2.5 mm ($PM_{2.5}$) was linked to a 66% higher likelihood of SARS-CoV-2 infection (24). However, the majority of studies have only examined the impacts of ambient temperatures, relative humidity, and air pollution independently, failing to account for their potential to function as confounding factors or effect modification for one another. Regarding the impact on the development of PCC, environmental factors that cause chronic inflammation and stress responses could potentially increase the risk of persistence of symptoms and influence the severity of COVID-19, contributing to increase the risk of developing PCC (25). However, the scientific evidence about the environmental factors-PCC relationship is limited. To date, only one study conducted in China has investigated the associations between medium-term exposure to non-optimal temperatures and PCC. The results of this study suggest that prolonged exposure to higher temperatures over a three-month period may double the odds of long recovery duration in COVID-19 patients (26). The existing evidence suggests a potential influence of long-term exposure to high temperatures on the development of PCC, although it is important to acknowledge that this conclusion is derived from a single study. In addition, a cohort study conducted in Sweden demonstrated that long-term exposure to air pollution was associated with an increased risk of PCC (27). Air pollution can act as a modifier for the relationship between ambient temperature and health (28, 29). However, our understanding of the association between short-term exposure to both low and high temperatures and PCC, as well as the role of air pollution in these associations, remains limited. Therefore, in this study, we aimed to investigate the relationship between ambient temperature and SARS-CoV-2 infection, both overall and by PCC status, and the effect modification by air pollution. Specifically, we conducted a retrospective analysis to explore how ambient temperature affected SARS-CoV-2 infection in individuals who later developed PCC compared to those who did not. Secondly, we investigated if these associations were modified by air pollution.

## 2 Materials and methods

### *Study population and study design*

This study used data from the COVIMPACT study, a cohort study in Sciensano (Belgian Institute for Health), which investigated risk factors of PCC among SARS-CoV-2 infection infected people in Belgium from May 2021 to April 2023 (30). All Belgian people aged 18 years and older, living in Belgium, with a recent SARS-CoV-2 positive test result (a molecular or an antigen test) from May 1st, 2021, to June 30th, 2022, were eligible to participate. The contact tracing call centers in Belgium contacted them on the date of their SARS-CoV-2 infection test results and introduced them about the COVIMPACT study (31). If the participants agreed to participate in the COVIMPACT study, a consent form and two online questionnaires were sent to them: (1) a baseline questionnaire sent at the time of their infection, and (2) a follow-up questionnaire sent three months later to assess the presence of PCC. Overall, 5% of all Belgian adults infected with SARS-CoV-2 during the study period completed the baseline questionnaire, and the follow-up participation rate was 79% (32). In total, 6,302 SARS-CoV-2 infection cases completed two questionnaires and 2,850 PCC cases (45.2%) were identified in this study from May 1st, 2021, to June 30th, 2022.

We used a bidirectional, time-stratified case-crossover design. This design is efficient and robust in investigating associations between transient exposures such as ambient temperatures and the onset of acute events (33). This design combines the features of case-control studies with those of crossover trials. In this design, cases (or events) are compared with control days on the same individual, therefore, each case (or event) acts as its own control, thus controlling for time-invariant confounding (such as age, sex or socioeconomic status) by design (33). In addition, the time-stratified feature of this design allows for controlling by seasonality and time-trends because control moments for each participant are selected within the same month and year as the date of the event (34).

In our study, the events were defined as the dates when a positive test result for SARS-CoV-2 infection was obtained. Events were matched with control days on the same year, month, and day of week (time stratified approach). This matching approach allows to reduce temporal autocorrelation due to day-to-day correlation of the environmental exposures (34). Therefore, the number of control days per event ranged from 4 to 5. To assess the impact of ambient temperatures on the outcome, we compared the distribution of ambient temperature on the days when the event occurred with the distribution on control days.

### *Measurement of variables*

#### *Assessment of SARS-CoV-2 infection and PCC*

We defined an event of SARS-CoV-2 infection as a confirmed SARS-CoV-2 infection via molecular or antigen testing. These cases were obtained from the central database "COVID-19 DATABASE" at Healthdata.be, which stores all laboratory test results in Belgium (35).

A PCC case was defined on the basis of the guidelines of the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE) (5, 36) as having at least one symptom related to SARS-CoV-2 infection three months after it. This information was collected through questionnaires administered three months after the infection date (event day). Participants were asked *"Within the last seven days have you had any of these symptoms? (That you did not experience before onset of your COVID-19 illness)".* To be classified as having PCC, a participant must have exhibited at least one symptom from a list of 30 potential symptoms associated with PCC (**Table S1 in supplementary materials**). Participants were grouped into seven groups based on their self-reported PCC symptoms: neurocognitive, autonomic, gastrointestinal, respiratory, musculoskeletal, anosmia and/or dysgeusia, other manifestations (5, 36).

*Exposure measurement*

We obtained daily mean ambient temperatures per postcode in Belgium during the study period from the Royal Meteorological Institute (RMI) (37). RMI gathered data from land-based weather stations, radars, and LIDAR observations. After conducting thorough quality control checks, monthly time series for temperatures were standardized using the HOMER software with available metadata (38).

Participants' municipal postcodes were merged with daily average temperature records. In this study, we defined non-optimal temperature as moderate and extreme heat and cold. These were defined with the $1^{st}$, $5^{th}$ percentiles (extreme and moderate cold, respectively) and $95^{th}$ and $99^{th}$ percentiles (moderate and extreme heat, respectively) of daily average temperatures throughout the study period. A description of the average daily temperature recorded within the study period is provided in **table S2 in the supplementary materials**. In brief, the period temperature ranged from -0.4 to 27.3 °C. Extreme and moderate cold were 2.5 °C and 4.6°C, respectively. The median temperature was 10.6°C, and moderate and extreme heat were 19.1°C and 20.9°C, respectively.

*Potential confounders and effect modifiers*

In this study, we considered relative humidity as confounder because it can influence both ambient temperature (28) and SARS-CoV-2 infection (39). Relative humidity was collected by RMI using the same measurement methodology as described in the previous section for ambient temperature.

We considered air pollution as a potential effect modifier in the associations between temperature and infection with and without later development of PCC. Modelled daily mean concentrations of particulate matter ($PM_{2.5}$, $PM_{10}$), black carbon (BC) and nitrogen dioxide ($NO_2$) at postcode level were provided by Irceline - Belgian Interregional Environment Agency (RIO-IFDM model, 100m spatial resolution) (40). Air pollutants are employed within spatial-temporal interpolation models, which are integrated with a Gaussian dispersion model utilizing emissions from industrial and traffic origins, alongside meteorological data. The model has been previously validated (41). We used the median concentrations of each pollutant during the study period as a cut-off point, which was obtained from the pollutant distribution (lag 0-1 moving average). The median value of $PM_{2.5}$, $NO_2$, $PM_{10}$, and black carbon was 8.8 µg/m$^3$, 12.25 µg/m$^3$, 15.95 µg/m$^3$ and 0.7 µg/m$^3$, respectively. For simplicity, we present the results for $PM_{2.5}$ (above 8.8µg/m$^3$ vs equal or below 8.8µg/m$^3$) in the main text and the results for the other pollutants in the supplement.

## Data analysis procedure

In the descriptive analysis, we compared the daily average temperature, relative humidity, and $PM_{2.5}$ levels on event days with the daily averages on control days (42), by calculating the absolute difference.

Conditional logistic regression models combined with distributed lag non-linear models (DLNM) were applied to assess the associations between recent exposure to ambient temperatures and the SARS-CoV-2 infection (43). We used natural cubic splines with three knots, covering lags 0 to 5 to model the relationships between ambient temperature and SARS-CoV-2 infection. This allowed us to examine the association up to the previous five days prior to the case/control day (lags 1 to 5) accounting for the potentially delayed effects of temperature on the outcome. The conditional logistic regression models were adjusted for relative humidity (natural cubic spline function with 3 degrees of freedom). The number of lags chosen for analysis was based on previous research that reported the mean incubation period of SARS-CoV-2 infection for different variants of the virus. Specifically, the mean incubation periods was between 4 and 5 days for the different variants (44). Furthermore, this number of lags enables a one-day washout period between case and control days within an event, ensuring that any lingering effects from the previous exposure have dissipated. In addition, we tested cubic natural splines with 4-5 knots and quadratic B-splines with 2-3 internal knots placed at specific percentiles of the temperature distribution to model the relationship between temperature and the outcome. The selected model was the one with the minimal AIC (45). The models were utilized on the entire population to calculate association estimates for the short-term effect of temperature on SARS-CoV-2 infection. Estimates are presented as odds ratios (OR) and their 95% confidence intervals (CI) for moderate, extreme cold and heat relative to the median of the mean daily temperature of the study period.

To examine the potential differential association according to later development of PCC, we conducted stratified analyses by PCC status. In addition, to evaluate the potential effect modification of air pollution, we conducted stratified analyses based on air pollutant concentrations. We used the Z-test to compare effect estimates between the two subgroups and evaluated effect modification by comparing the Z-test statistic to the standard normal distribution (46).

In our sensitivity analyses, we incorporated lags of 3-5 days preceding the date of a positive SARS-CoV-2 infection PCR test, instead of 0-5 days, considering potential delays in test result reporting. Consequently, the period of 3-5 days before a positive SARS-CoV-2 infection PCR test may align with the onset of SARS-CoV-2 infection. By adopting this approach, we aimed to minimize misclassification since the precise date of SARS-CoV-2 infection is unknown. In addition, we conducted stratified analyses by air pollution based on air pollutant concentrations of BC, $PM_{10}$, and $NO_2$.

Statistical analyses were performed with the statistical software R, using the ‘dlnm’ and ‘survival’ packages (47).

## 3 Results

### *Descriptive analysis*

**Table 1** displays the distribution of daily events, including SARS-CoV-2 infection event, SARS-CoV-2 infection event with subsequent PCC, and SARS-CoV-2 infection event without subsequent PCC, along with ambient temperature, humidity, and $PM_{2.5}$ concentrations on event days. The table also shows the absolute differences between event and control days for these outcomes. The median daily number of positive SARS-CoV-2 infection tests who participated in the study was 17.0 (Interquartile range (IQR) = 8-35). The daily median of infections with subsequent development of PCC was similar to that without subsequent PCC development (i.e. 9 cases/day in both groups). The median temperature and relative humidity for the event days was 10.3°C (IQR = 7.3-13.2°C) and 79.0% (IQR = 71-86%), respectively. The median temperature and relative humidity were slightly higher for PCC cases compared to non-PCC cases, while both groups had similar median concentrations of $PM_{2.5}$. The difference in exposure between event days and control days, regarding the median of average temperature, relative humidity, and daily concentrations of $PM_{2.5}$, was slightly lower for PCC cases than for non-PCC cases. The distribution of $PM_{10}$, $NO_2$, and black carbon on event days, as well as the difference in their exposure between event days and the average of control days, are presented in **Table S.3 of the supplementary materials.**

| | Mean | SD | Min | p25 | Median | p75 | Max |
|---|---|---|---|---|---|---|---|
| **Daily number of positive tests (SARS-CoV-2 infections)** | | | | | | | |
| *total* | 24.8 | 22 | 1 | 8 | 17 | 35 | 102 |
| *PCC cases* | 11.6 | 10.2 | 1 | 4 | 9 | 16 | 54 |
| *non-PCC cases* | 14.1 | 12.8 | 1 | 5 | 9 | 19 | 56 |
| **Exposure on event days** | | | | | | | |
| Average Temperature (°C) | | | | | | | |
| *total* | 10.8 | 4.5 | 1.4 | 7.3 | 10.3 | 13.2 | 25 |
| *PCC cases* | 11.1 | 4.5 | 1.5 | 7.6 | 10.8 | 13.6 | 25 |
| *non-PCC cases* | 10.5 | 4.5 | 1.4 | 7 | 10 | 13 | 24.9 |
| Relative humidity (%) | | | | | | | |
| *total* | 77 | 11 | 40 | 71 | 79 | 86 | 98 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *PCC cases* | 78 | 10 | 41 | 72 | 80 | 86 | 98 |
| *non-PCC cases* | 77 | 11 | 40 | 70 | 79 | 86 | 98 |
| PM2.5 (µg/m$^3$) | | | | | | | |
| *total* | 10 | 7 | 1 | 6 | 8 | 12 | 46 |
| *PCC cases* | 9 | 5.1 | 1 | 5.6 | 8 | 11.3 | 32.5 |
| *non-PCC cases* | 10 | 7 | 1 | 6 | 8 | 13 | 45 |
| **Exposure difference between event days and average of control days*** | | | | | | | |
| Average Temperature (°C) | | | | | | | |
| *total* | 2.2 | 1.7 | 0 | 0.9 | 1.8 | 3 | 9.1 |
| *PCC cases* | 2.1 | 1.7 | 0 | 0.8 | 1.7 | 3 | 8.6 |
| *non-PCC cases* | 2.2 | 1.7 | 0 | 0.9 | 1.8 | 3 | 9.1 |
| Relative humidity (%) | | | | | | | |
| *total* | 6.4 | 5.2 | 0 | 2.3 | 5 | 9.2 | 34.4 |
| *PCC cases* | 6.3 | 5.2 | 0 | 2.2 | 4.9 | 8.9 | 34.4 |
| *non-PCC cases* | 6.5 | 5.2 | 0 | 2.4 | 5.3 | 9.3 | 33.2 |
| PM2.5 (µg/m$^3$) | | | | | | | |
| *total* | 4.4 | 4.1 | 0 | 1.4 | 3.2 | 6.2 | 26.1 |
| *PCC cases* | 4.1 | 3.7 | 0 | 1.3 | 3 | 6.4 | 25.6 |
| *non-PCC cases* | 4.5 | 4.2 | 0 | 1.5 | 3.3 | 6.3 | 26.1 |

*Table 1. Description of daily numbers of SARS-CoV-2 infections, and environmental factors (daily average ambient temperature, humidity, and air pollution), and exposure difference between event and control days for the study period (May 2021 to June 2022).*

*PCC cases: cases of Post covid condition (PCC) reported 3 months after the date of the date of the positive test; SD: standard deviation; Min: minimum; p25: 25th percentile; p75: 75th percentile; Max: maximum. * absolute differences between the daily average temperature, relative humidity and* pollutant concentrations *on event days and the average exposure on control days, Belgium 2021–2022.*

### *Associations between recent ambient temperature exposure and SARS-CoV-2 infection*

We observed a non-linear relationship between all events and temperature up to 5 days before the event (**Figure 1**). The associations were most pronounced on days 3, 4, 5 before the events, the odds of infection were significantly higher on extreme and moderate cold temperature days compared to median temperature days, whereas a protective effect of extreme and moderate cold was observed on days 1 and 2 before the event days.

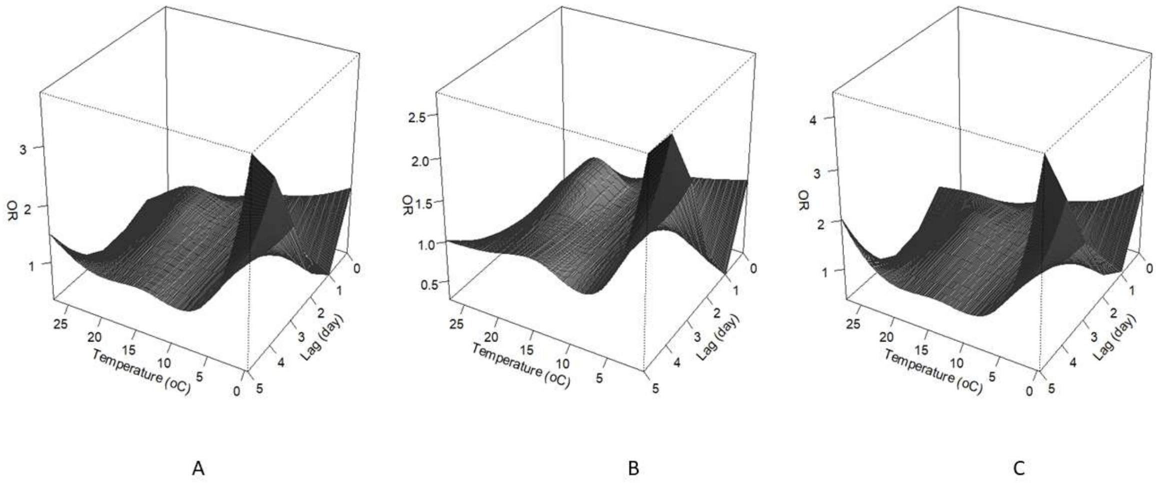


*Figure 1. Exposure-lag-response surface for the association of daily mean temperature with (A) SARS-CoV-2 infections, (B) SARS-CoV-2 infections with PCC, and (C) SARS-CoV-2 infections without PCC.*

*All models were adjusted for relative humidity. ORs are relative to the median temperature of (10.57°C); OR: odds ratios; PCC: Post covid condition (PCC)*

The dose-response relationships of cumulative OR for lags 0-5 between ambient temperatures and infections, for all events (A) and stratified by PCC status (B), are presented in **Figure 2**. The odds of infection were higher on days with temperatures below extreme heat (20.9°C) compared to median temperature days (10.57°C), overall and by PCC status. Conversely, the odds of infection were lower on days with temperatures above 20.9°C compared to median temperature days. Notably, on moderate heat days, the cumulative effects of ambient temperature were stronger in PCC cases than in non-PCC cases.

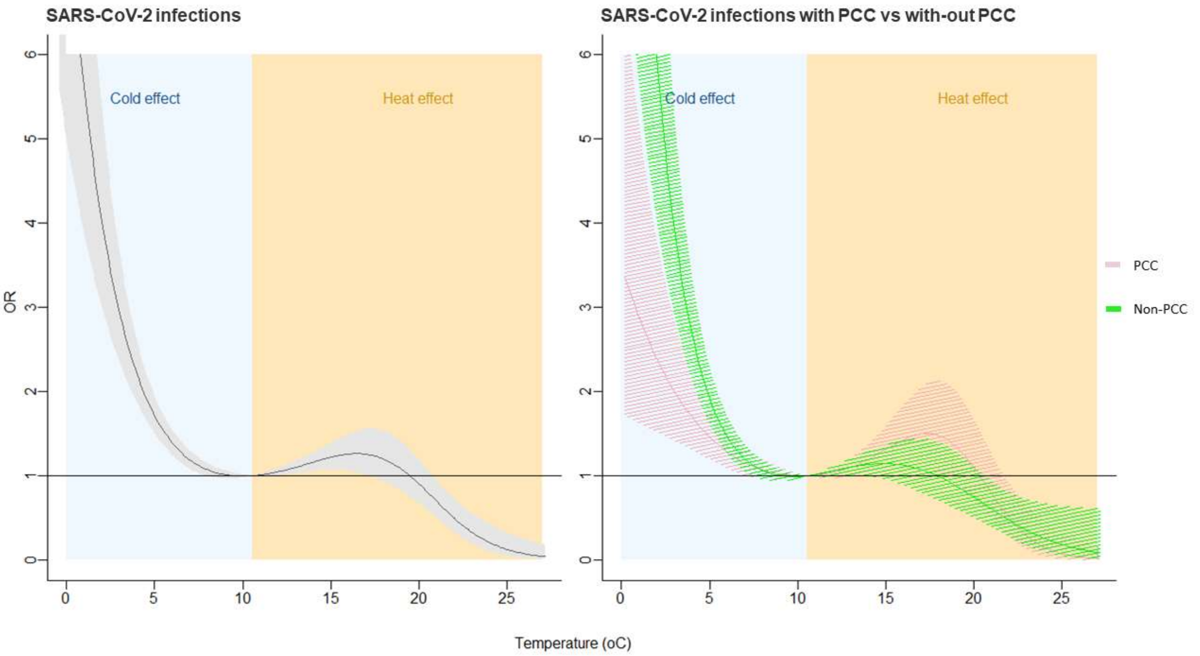


*Figure 2. Associations (Odds Ratios) between temperature and SARS-CoV-2 infections, cumulated over lags 0-5 (overall and by PCC status)*

*All models were adjusted for relative humidity. OR: odds ratios. ORs are relative to the median temperature of (10.57°C), the shaded area represents the 95% confidence interval of the OR. PCC: Post covid condition (PCC)*

**Table 2** shows the cumulative ORs and 95% CI for the associations of infection with moderate and extreme heat and cold, in total and by PCC status. For moderate and extreme cold temperatures, the cumulative associations were generally inverse and statistically significant for lags 0-1. On the contrary, when including lags 0 to 5, the cumulative ORs were consistently above 1 for SARS-CoV-2 infections, in total and stratified by PCC development, and stronger for extreme cold than for moderate cold. For example, for moderate cold, the ORs were 1.93 (95% CI: 1.67 – 2.23), being 1.57 (95% CI: 1.25 – 1.96) among cases with further development of PCC, and 2.25 (95% CI: 1.86 – 2.72) among those who do not develop PCC. For heat, the associations were generally below 1. However, for SARS-CoV-2 infections with PCC, the cumulative ORs (lags 0-5) for moderate hot temperatures was 1.32, but not statistically significant (95%CI: 0.89 - 1.96).

| | SARS-CoV-2 infections n=6302 | SARS-CoV-2 infections with PCC n=2850 | SARS-CoV-2 infections without PCC n=3452 |
|---|---|---|---|
| **Cold** | | | |
| **Moderate (=4.6°C)** | | | |
| Lag 0-1 | 0.87 (0.76 - 1.00) | **0.74 (0.60 - 0.91)** | 0.98 (0.82 - 1.17) |
| Lag 0-3 | 1.02 (0.88 - 1.17) | 0.92 (0.74 - 1.14) | 1.08 (0.90 - 1.29) |
| Lag 0-5 | **1.93 (1.67 - 2.23)** | **1.57 (1.25 - 1.96)** | **2.25 (1.86 - 2.72)** |
| **Extreme (=2.5°C)** | | | |
| Lag 0-1 | **0.70 (0.56 - 0.87)** | **0.51 (0.36 - 0.72)** | 0.89 (0.68 - 1.18) |

| | | | |
|---|---|---|---|
| Lag 0-3 | 0.91 (0.73 - 1.14) | **0.67 (0.47 - 0.95)** | 1.14 (0.85 - 1.53) |
| Lag 0-5 | **3.53 (2.72 - 4.58)** | **2.22 (1.48 - 3.34)** | **5.02 (3.56 - 7.08)** |
| **Heat** | | | |
| **Moderate (=19.1°C)** | | | |
| Lag 0-1 | **0.69 (0.56 - 0.84)** | 0.80 (0.60 - 1.07) | **0.60 (0.45 - 0.80)** |
| Lag 0-3 | 0.93 (0.74 - 1.18) | 1.11 (0.78 - 1.58) | 0.79 (0.57 - 1.10) |
| Lag 0-5 | 1.06 (0.81 - 1.39) | 1.32 (0.89 - 1.96) | 0.86 (0.59 - 1.26) |
| **Extreme (=20.9°C)** | | | |
| Lag 0-1 | **0.58 (0.46 - 0.74)** | **0.64 (0.45 - 0.90)** | **0.54 (0.38 - 0.74)** |
| Lag 0-3 | **0.67 (0.51 - 0.88)** | 0.77 (0.52 - 1.16) | **0.58 (0.40 - 0.84)** |
| Lag 0-5 | 0.73 (0.54 - 1.00) | 0.85 (0.54 - 1.32) | **0.63 (0.42 - 0.96)** |

*Table 2. Adjusted cumulative odds ratios (OR) and their 95% confidence intervals (CI) for the association between non-optimal temperatures (cold and heat) and SARS-CoV-2 infections, in total and stratified by PCC development.*

*Bold indicates p-value <0.05, All models were adjusted for relative humidity. ORs are relative to the median temperature of (10.57°C); OR: odds ratios; PCC: Post covid condition (PCC)*

The dose-response relationships of cumulative OR for lags 0-5 between ambient temperatures and SARS-CoV-2 infections by daily average PM2.5 concentrations (in the total population and by PCC status) are presented in **Figure 3**. On days with $PM_{2.5}$ concentrations greater than 8.8 µg/m$^3$, we observe that non-optimal temperatures (both, cold and hot) increase the odds of infection with stronger effects of heat observed among SARS-CoV-2 infections with PCC than among those without PCC. On the contrary, on days with $PM_{2.5}$ concentrations lower or equal to 8.8 µg/m$^3$, the direction of the associations is the opposite. Both, heat and cold decrease the odds of infection relative to the period median temperature.

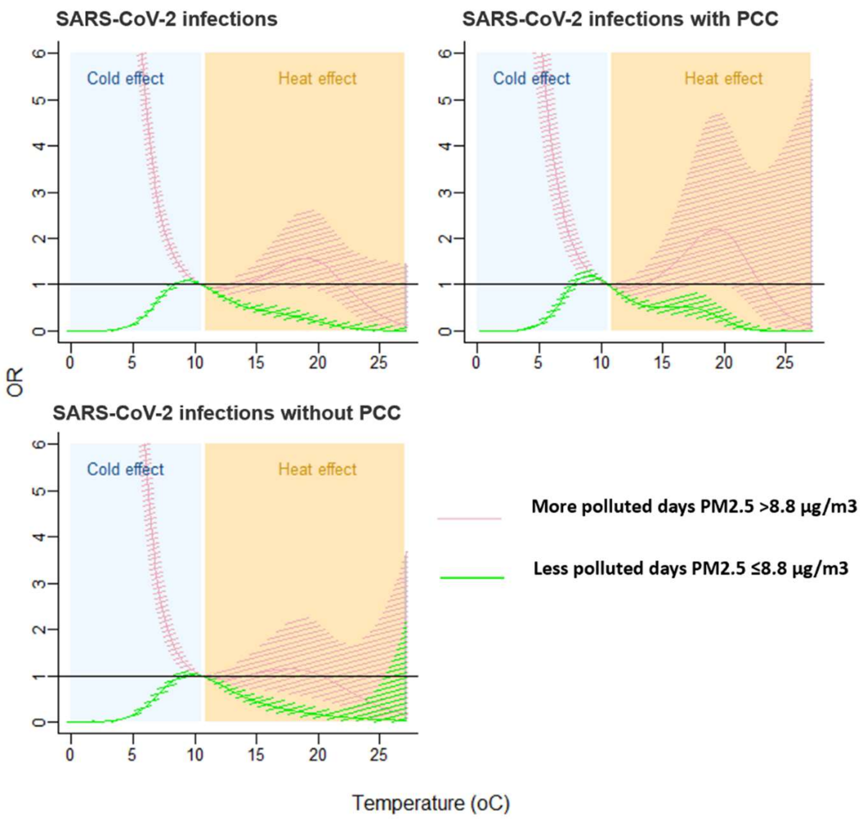


*Figure 3. Associations (odds ratios) between temperature and SARS-CoV-2 infections by daily average PM2.5 concentrations, cumulated over lags 0 to 5 (overall and by PCC status)*

*All models were adjusted for relative humidity. ORs are relative to the median temperature of (10.57°C); OR: odds ratios; PCC: Post covid condition (PCC)*

The cumulative ORs for moderate cold and heat on lags 0 to 5 after stratification by $PM_{2.5}$ concentrations, and the p-values for the differences between $PM_{2.5}$ concentration groups are presented in **Table 3**. Except for moderate heat among non-PCC cases, all p-values for between group differences were statistically significant. As shown in Figure 3, the direction of the associations changed according to the concentrations of $PM_{2.5}$, with direct effects observed for non-optimal temperatures when the concentrations were high (>8.8 μg/m$^3$), and indirect when they were low. This was particularly noticeable for moderate cold in all cases, and moderate heat only among the participants with further development of PCC. Among cases with further PCC development, the odds of infection on high air pollution days after exposure to moderate heat was more than twice the odds of infection on days with median temperature (10.57°C). Contrarily, their odds of infection on low air pollution days after exposure to moderate heat was 65% lower as compared to the exposure to the period median temperature.

| Factors | n | Moderate cold effect (=4.6°C) | | Moderate heat effect (=19.1°C) | |
|---|---|---|---|---|---|
| | | OR | p-value* | OR | p-value* |
| *SARS-CoV-2 infections (n=6302)* | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| $PM_{2.5}$ >8.8 μg/m³ | 2921 | **13.6 (10.33 – 17.95)** | **<0.001** | 1.57 (0.93 – 2.62) | **0.002** |
| $PM_{2.5}$ ≤8.8 μg/m³ | 3381 | **0.09 (0.06- 0.14)** | | **0.26 (0.17 – 0.39)** | |
| ***SARS-CoV-2 infections with PCC (n=2850)*** | | | | | |
| $PM_{2.5}$ >8.8 μg/m³ | 1261 | **9.19 (6.06 – 13.98)** | **<0.001** | **2.18 (1.01 - 4.69)** | **0.03** |
| $PM_{2.5}$ ≤8.8 μg/m³ | 1589 | **0.08 (0.04 – 0.15)** | | **0.35 (0.19 – 0.65)** | |
| ***SARS-CoV-2 infections without PCC (n=3452)*** | | | | | |
| $PM_{2.5}$ >8.8 μg/m³ | 1660 | **18.25 (12.56 – 26.49)** | **<0.001** | 1.01 (0.05 – 2.25) | 0.47 |
| $PM_{2.5}$ ≤8.8 μg/m³ | 1792 | 0.10 (0.05-1.17) | | **0.19 (0.10 – 0.35)** | |

*Table 3. Cumulative lag 0-5 effects of moderate cold and heat temperature by daily average PM2.5 concentration.*

*Bold indicates p-value <0.05; *p-value for Z-test which examined the statistical significance of the effect differences between different subgroups; OR: odds ratios; PCC: Post covid condition (PCC);* $PM_{2.5}$: particles that are 2.5 microns or less in diameter.

### *Sensitivity analysis*

The cumulative effects of lags 3 to 5 on the association between moderate/extreme heat, cold ambient temperature, and SARS-CoV-2 infection are presented in **Table S4 of the supplementary materials**. Overall, we did not observe relevant differences for cold temperatures when comparing the cumulative ORs for lags 3 to 5 with those for lags 0 to 5. However, for heat, excluding lags 0 to 2 resulted in statistically significant direct associations for moderate heat with infections, and with infections without further development of PCC. Exposure to moderate heat on lags 3 to 5 increased the odds of infection in 34% relative to the exposure to the period median temperature. The ORs for infections with PCC for moderate heat remained similar after excluding lags 0 to 2 (OR=1.27; 95% CI: 0.97 - 1.66).

Last, the results of the effect modification by other air pollutants (i.e. $NO_2$, $PM_{10}$, and black carbon) are presented in **tables S5, S6 and S7.** Effect modification by other pollutants resulted in very similar results to those presented in Table 3 and Figure 3 for $PM_{2.5}$.

## 4 Discussion

Overall, our study provides first insights into the complex relationship between recent exposure to non-optimal ambient temperatures and SARS-CoV2 infection, and the further development of PCC. We found that recent exposure to non-optimal cold temperatures during 5 days prior to the SARS-CoV2 positive test doubles the odds of infection. This association is stronger for non-PCC cases compared to PCC cases. Recent exposure to moderate heat temperatures may increase the risk of infection with further development only among PCC cases, but this was not statistically significant. In addition, we observe a significant effect modification by air pollution, with direct effects on days when the concentrations of air pollutants are above the period median and indirect effects on days when the concentrations of air pollutants are below the period median.

Regarding the impact of non-optimal cold temperature, we found that recent exposures to 4.6°C nearly doubled the odds of SARS-CoV2 infection. Our results are in line with the conclusions of a systematic review including 23 scientific articles studying the association between short-term exposure to temperatures and COVID-19 incidence. They found that the incidence of COVID-19 increases as temperature decreases, with the highest incidence of COVID-19 reported in the temperature range of 0–17 °C (48). In addition, our findings align with a study conducted in Korea which indicated that temperatures below 8°C were correlated with an increase in confirmed COVID-19 cases (49). SARS-CoV-2 viruses have a higher survival rate and are more easily transmitted in cold, dry air (50). The combination of low humidity and lower temperatures provides an environment that allows the virus to persist for longer periods and enhances its ability to spread between individuals (51).

In addition, our study adds to the evidence about the potential impact of recent exposure to non-optimal ambient temperatures on the SARS-CoV-2 infection with further development of PCC. To the best of our knowledge, this is the first study indicating a link between individual-level short-term exposure to non-optimal ambient temperatures and PCC. We found that recent exposure to non-optimal cold temperatures exhibits a greater impact on non-PCC cases compared to PCC cases, whereas exposure to non-optimal heat temperatures shows an effect only in PCC cases. However, after excluding the day of the SARS-CoV-2 positive test (in this study considered as day of the infection) and the two days prior to the positive test, the odds of infection after exposure to moderate heat was also increased in non-PCC cases. These contradictory results may be due to either a harvesting effect or to exposure misclassification as the date of the test is most likely 2 to 3 days after the actual date of infection (52). The time frame of 3-5 days before the event may be explained by the delays in the testing of SARS-CoV-2 infection PCR test results. Individuals receive a positive SARS-CoV-2 infection test result at least two days after registering for a test near their address and undergoing the testing process (53). This implies that the period of 3-5 days prior to the date of a positive SARS-CoV-2 infection PCR test result may coincide with the onset of SARS-CoV-2 infection and is particularly sensitive to exposure to cold temperatures. Unfortunately, with the information available for this study, it is not possible to know the exact date of infection. Previously, only one study has investigated the associations between temperature and PCC, however this study was focusing on long term effects of temperatures (26). This study suggests that COVID-19 patients who had encountered elevated temperatures within the three months prior to infection were more likely to experience extended recovery periods. Our results on the potential hazards of heat temperatures on PCC align with the results presented in this paper.

The mechanism underlying the association between ambient temperature at the time of infection and the onset of PCC could be explained by organ damage and inflammation during acute SARS-CoV-2 infection. Tissue injury severity increases with prolonged exposure to non-optimal temperatures, which impairs the regulation of inflammatory and stress responses (54). Staying in non-optimal temperatures for at least 15 minutes, can cause stress shock in the cells and gene expression of Heat Shock Protein 72, which increases the receptor of SARS-COV-2 virus (ACE2), inflammation, cell death and finally pneumonia (55). These findings may support the hypothesis that the PCC window period occurs during the acute phase of SARS-CoV-2 infection. Previous research suggests that individuals with PCC may not show symptoms during acute SARS-CoV-2 infection, but the disease may have already started during that phase (56). COVID-19 is often asymptomatic, and cell damage can be insidious (57). As damage accumulates, PCC symptoms may occur after three months. This is consistent with a previous study that identified frequent and specific clinical features of PCC (58). Alongside biological mechanisms, social factors such as indoor crowding during temperature extremes, prevention policies such as lockdown and wearing masks were reported to significantly increase SARS-CoV-2 infection (59). From 2021 to 2022, Belgium didn't implement lockdown measures, and as of May 2022, face masks was no longer be mandatory except in health-care settings, pharmacies and public transport (60). With the increasing of the frequency and intensity of extreme temperature events worldwide (61, 62), further studies should be conducted to investigate the underlying mechanism of PCC at the time of infection, in order to better understand its potential role in the immune response and identify potential therapeutic targets.

Regarding the influence of air pollution on the associations between ambient temperature and SARS-CoV-2 infection, we observe that exposure to air pollution significantly potentiates the adverse effect of non-optimal temperatures on the risk of SARS-CoV-2 infection. To the best of our knowledge, there are no published studies specifically looking at the effect modification of air pollution in these associations. Previous studies have solely focused on considering air pollution as the primary exposure factor. An analysis of 116 studies conducted in a systematic review indicated that prolonged exposure to $PM_{2.5}$, $PM_{10}$, $O_3$, $NO_2$, and CO showed a higher likelihood (63.8%) of being positively linked to COVID-19 incidence (63). Zhebin Yu et al. found that for an IQR increase in long term exposure to $PM_{2.5}$, the odds of having PCC increased by approximately 30% (27). Previous studies ambient levels of $PM_{2.5}$ were associated with persistent dyspnea, increased fatigue, and lower functional status at follow-up (64, 65). In fact, certain air pollutants can interact with temperature to create unfavorable conditions for human health (66). Air pollution can alter temperature patterns by affecting the atmosphere's thermal properties. For instance, pollutants like black carbon absorb sunlight, leading to localized warming effects and the formation of microclimates with higher temperatures. These temperature variations can have distinct implications for human health compared to ambient temperature alone (67).

Conversely, when the levels of air pollution are low, our study found that non-optimal temperatures decreased the likelihood of infection and subsequent development of PCC. This implies that air pollution could be a significant contributing factor in the development of PCC. Furthermore, our pollution levels are below the recommended thresholds established by the World Health Organization (WHO). However, we identified a modification effect at PM2.5 concentrations of 8.8μg/m3, which is lower than the current WHO-recommended threshold of 15μg/m3 for exceedances (68). This suggests that the adverse effects of air pollution at the WHO-recommended threshold could potentially be more severe than indicated by our findings. As a result, it is essential to consider both temperature and air pollution levels when assessing the potential health risks associated with PCC.

It is important to note that our study has some limitations that must be considered when interpreting the results. Firstly, as previously mentioned, the date of SARS-CoV-2 infection was proxy measured by the date of positive PCR test result. It is likely that there is a delay of 1 to 3 days between the time of infection and the test. For this reason, we conducted sensitivity analyses including only exposures on lags 3 to 5 with the hypothesis that the infection would have happened on lag 3. The results for cold temperatures were robust to this sensitivity analysis, however for heat we observed an increased odd of infection, not only with subsequent development of PCC but also without PCC. Unfortunately, it is not possible within our study to know the exact date of infection and therefore, we have to interpret the results for heat among non-PCC cases with caution. Second, for PCC cases, it is possible that we face some misclassification due to the fact that PCC symptoms were self-reported. PCC symptoms often overlap with those of common illnesses like colds and flu, making it challenging for participants to differentiate between them. Consequently, it may be that some non-PCC cases were misclassified as PCC. Third, we measured ambient temperature based on the participant's postcode, which is less accurate than using their home address. The size of the area for each postcode varies based on the geographic area it covers and the population density of the region, the largest being more than 200km$^2$ and the smallest less than 5km$^2$ (69). However, we believe that this will have a marginal impact on our findings because our study focuses on temporal variations, not on spatial variations (32). Finally, we did not consider other information which could impact the risk of infection be correlated with temperature (e.g. wind speed, lockdowns and other prevention measures or COVID-19 vaccination). Nevertheless, in our design, we selected control days within the same month and day of the week as the infection day. Therefore, the bias introduced by the aforementioned measures would only apply to cases within months when the changes happened.

Despite the aforementioned limitations, our study has some strengths that are worth acknowledged. We used a case-crossover study design that controls time-invariant confounders by design, because each case acts as its own control. Therefore, the number of potential confounders is limited. In addition, the time-stratified method for control selection allows to also control for seasonality and time trends by design. Furthermore, we had accurate information of infection because we used the results of PCR tests from Belgium from May 1st, 2021, to June 30th, 2022, thereby encompassing the majority of SARS-CoV2 infection waves in the country (70).

## 5 Conclusion

This study is the first to comprehensively consider the effects of recent exposure to ambient temperatures on SARS-CoV-2 infection and further development of PCC. Our findings show that exposure to cold temperatures increases the risk of SARS-CoV2 infection, especially on days when air pollution levels are moderate to high. Furthermore, heat temperatures combined with moderate to high levels of air pollution during the infection days may contribute to the development of PCC after infection. We also found that when air pollution concentration is low, non-optimal temperatures decrease infection and PCC risk, which emphasizes air pollution's potential role in PCC development. Although our pollution levels in our study are below European and WHO recommendation thresholds, a modification effect was observed at lower PM2.5 concentrations. In the current climate change scenario, weather extremes such as non-optimal temperatures are increasing in frequency. In addition, they contribute to increased concentrations of air pollutants in the outdoor environment. Our findings emphasize the necessity for more stringent regulations for governing air quality standards and proactive policies to tackle the implications of climate change. Given the limitations the present study, future studies should assess the effect of ambient temperatures on SARS-CoV-2 infection and subsequent PCC also taking into account other factors such as wind speed, lockdowns and other protective measures, and vaccination status.

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