Accepted Manuscript

A time series analysis of the relationship between apparent temperature, air pollutants and ischemic stroke in Madrid, Spain

Dominic Royé, María T. Zarrabeitia, Javier Riancho, Ana Santurtún

PII: S0013-9351(19)30199-9

DOI: https://doi.org/10.1016/j.envres.2019.03.065

Reference: YENRS 8427

To appear in: *Environmental Research*

Received Date: 13 January 2019

Revised Date: 23 March 2019

Accepted Date: 25 March 2019

Please cite this article as: Royé, D., Zarrabeitia, Marí.T., Riancho, J., Santurtún, A., A time series analysis of the relationship between apparent temperature, air pollutants and ischemic stroke in Madrid, Spain, *Environmental Research* (2019), doi: https://doi.org/10.1016/j.envres.2019.03.065.

A time series analysis of the relationship between Apparent Temperature, Air Pollutants and Ischemic Stroke in Madrid, Spain.

Dominic Royé[a], María T. Zarrabeitia[b], Javier Riancho[c], Ana Santurtún[*b].

[a] Department of Geography, University of Santiago de Compostela, Santiago de Compostela, Spain.

[b]Unit of Legal Medicine, Department of Physiology and Pharmacology University of Cantabria. Santander, Spain.

[c] Department of Neurology, Hospital Sierrallana-Instituto de Investigación Sanitaria (IDIVAL), Centro Investigación Biomédica en Red Enfermedades (CIBERNED), Santander, Spain.

Ana Santurtún and Javier Riancho shared the last authorship.

*** Corresponding author:**

Ana Santurtún

Unit of Legal Medicine, University of Cantabria.

Av Cardenal Herrera Oria s/n, 39011, Santander, Spain.

Email: ana.santurtun@unican.es.

Phone number: +34 942 201984.

Fax: +34 942 201903

ORCID ID: 0000-0003-3846-556X

ABSTRACT

The understanding of the role of environment on the pathogenesis of stroke is gaining importance in the context of climate change. This study analyzes the temporal pattern of ischemic stroke (IS) in Madrid, Spain, during a 13-year period (2001-2013), and the relationship between ischemic stroke (admissions and deaths) incidence and environmental factors on a daily scale by using a quasi-Poisson regression model. To assess potential delayed and non-linear effects of air pollutants and Apparent Temperature (AT), a biometeorological index which represents human thermal comfort on IS, a lag non-linear model was fitted in a generalized additive model. The mortality rate followed a downward trend over the studied period, however admission rates progressively increased. Our results show that both increases and decreases in AT had a marked relationship with IS deaths, while hospital admissions were only associated with low AT. When analyzing the cumulative effects (for lag 0 to 14 days), with an AT of 1.7°C (percentile 5%) a RR of 1.20 (95% CI, 1.05-1.37) for IS mortality and a RR of 1.09 (95% CI, 0.91-1.29) for morbidity is estimated. Concerning gender differences, men show higher risks of mortality in low temperatures and women in high temperatures. No significant relationship was found between air pollutant concentrations and IS morbi-mortality, but this result must be interpreted with caution, since there are strong spatial fluctuations of the former between nearby geographical areas that make it difficult to perform correlation analyses.

KEYWORDS: Ischemic Stroke; Air pollutants; Apparent Temperature; Mortality; Admissions.

53 **Compliance with Ethical Standards**

54 **Conflict of Interest**: Dominic Royé, María T. Zarrabeitia, Javier Riancho and Ana Santurtún
55 declare that they have no conflict of interest.

56 **Ethical approval:** This article does not contain any studies with human participants or animals
57 performed by any of the authors.

58

59 The authors received **no specific funding** for this work.

60

61

HIGHLIGHTS

- Environment is gaining importance in the understanding of stroke.
- A time series analysis between ischemic stroke and environmental factors was performed.
- The incidence of hospital admissions followed an upwards trend and a seasonal pattern.
- Apparent Temperature has a strong non-linear relationship with Ischemic Stroke.
- No relationship was found between air pollutant concentrations and Ischemic Stroke.

1. INTRODUCTION

Stroke is a major global health issue and, particularly, it is the second cause of death for people above the age of 60 in developed countries and the most frequent cause of disability in adults.

According to Global Burden of Disease Study estimates of stroke incidence for the years 1990 and 2016, the lifetime risk of stroke was 24.9% globally. Among the 21 GBD regions, the highest risk was estimated in East Asia (38.8% [37.0–40.6]), while Eastern Sub- Saharan Africa (11.8% [95% UI: 10.9–12.8]) had the lowest risk [1].

About 85% of all strokes are due to ischemia, and in the majority of ischemic stroke events, the mechanism responsible is understood [2].

Global epidemiology of stroke is changing. Standardized rates of stroke mortality by age have decreased in the past 2 decades while the absolute numbers of people who suffer a stroke every year are increasing [3].

In the context of climate change, some authors have analyzed the association of different atmospheric variables (e.g., average temperature, precipitation, barometric pressure or relative humidity) and stroke incidence. However, these studies often report divergent results [4].

For example, in 2018, Chu et al. analyzed the relationship between weather variables and stroke outcomes in the United States, concluding that the increases in temperature and precipitation were associated with lower odds of mortality (OR 0.95, CI 0.93-0.97, P<0.0001 and OR 0.95, CI 0.90-1.00, P=0.035, respectively) [5].

However, Tian et al. in China, when studying the effects of temperature variability on cardiovascular disease, found that the increase in the air temperature was associated with significant growths of ischemic stroke hospital admissions [6].

The use of biometeorological indexes to assess the impacts of atmospheric conditions on human health is preferred to using typical meteorological variables, since organisms are exposed simultaneously to multiple atmospheric factors.

Biometeorological indexes are composed of more than one atmospheric factor and can explain the effect that different environmental variables, in their interaction, cause on health and well-being of people [7]. Moreover, the use of biometeorological indexes is recommended by both the World Meteorological Organization and the World Health Organization to evaluate the impacts of heat stress on human health [8].

For instance, Apparent Temperature (AT) is a biometeorological index that can be used to estimate how the human body reacts to the set of conditions of the thermal environment. AT combines temperature, humidity and wind speed and is able to represent human thermal comfort. Under heat stress situations, the body uses four mechanisms of heat exchange to maintain homeostasis: conduction, convection, radiation, and evaporation; the evaporation process is affected by humidity conditions while the wind is determinant in the convection. Some authors consider AT to be the most important predictor of heat-related mortality [9-10].

This study aims to describe temporal patterns in ischemic stroke (IS) in the Community of Madrid, Spain, between 2001 and 2013, and to analyze the relationship between ischemic stroke (admissions and deaths) incidence and AT and atmospheric pollutants on a daily scale. Furthermore, potential gender and age-group (over vs. under 64 years old) risk differences were also examined.

2. METHODS

2.1. Study Area

The Community of Madrid is an autonomous community of Spain located in the center of the Iberian Peninsula. Its capital is the City of Madrid, which is also the capital of the country. The region of Madrid has a Mediterranean climate with continental influences, characterized by hot summers and cool winters. Madrid's levels of industry set it at fourth place in Spain, and the star-shaped design of the Spanish road network makes it the central transport hub of the country. This, combined with a high amount of registered vehicles (4.221.800 in 2013) in the region, results in a heavy-traffic-supporting metropolitan area that suffers severe road congestion issues. Thus, road traffic is widely recognized as the main source of air pollution in Madrid [11], in which indoor air pollutants and the geographical characteristics of the region also play a relevant role.

Despite general downward trends in emissions over recent years [12], this region still presents exceedances of air quality legal limits according to the Directive 2008/50/EC.

2.2. Data sources

2.2.1. Health and demographic data

Hospital Admissions

Data concerning admissions due to IS in the Community of Madrid, from January 1, 2001, to December 31, 2013, as categorized with ICD-9 (International Classification of Diseases, 9th Revision) codes 433 (Occlusion and stenosis of precerebral arteries), 434 (Occlusion of cerebral arteries) and 435 (Transient cerebral ischemia) were collected, including the date and length of admission and the patient’s sex and age, from the

142 *Encuesta de Morbilidad Hospitalaria* (Hospital morbidity survey) of the Spanish
143 National Institute of Statistics (INE) database.

144 **Mortality data**

145 Mortality data obtained from the INE, for years 2001-2013 (incl.), were categorized
146 according to the International Classification of Diseases (ICD-10), 10th Revision. We
147 focused on mortality cases caused by cerebral infarction (I63) and strokes not specified
148 as hemorrhage or infarction (I64). These cases were divided by the INE into three
149 major age groups (15-44 years old, 45-64 years old and 65 years old or older),
150 excluding deaths of children under the age of 15.

151 **Influenza data**

152 The weekly influenza rates in Madrid were obtained from the *Dirección General de*
153 *Salud Pública* of Madrid's notifiable disease register (not laboratory-confirmed), and
154 were used as an indicator of epidemics, representing a possible confounding variable
155 [13-15].

156 The clinical surveillance of influenza is based on reports made by sentinel general
157 practitioners. The sentinel surveillance system in Madrid reports weekly data on the
158 number of new cases. A new case is defined as a sudden onset (<12 hours) of at least
159 one general symptom (fever, malaise, headache and / or myalgia) and at least one
160 respiratory symptom (cough, sore throat and / or dyspnea) in the absence of another
161 diagnostic suspicion.

162 The data are analyzed according to the population assigned to each sentinel doctor
163 and the number of days of the week that the doctor attended to patients.

164 Moreover, from 2009, an automatic collection of influenza cases from the electronic
165 clinical record of Primary Care has been performed.

Demographic Data

To analyze incidence, annual population data of the Community of Madrid by sex and age groups were obtained, also from the INE. The average annual population during the study period in the Community of Madrid was 5,236,083 (2,516,930 men and 2,719,152 women).

2.2.2. Environmental factors

Air pollutants

We collected data of the main air pollutants (nitrogen dioxide in $\mu g/m^3$ [NO2], ozone in $\mu g/m^3$ [O3], sulfur dioxide in $\mu g/m^3$ [SO2] and particulate matter with a diameter below 10 microns in $\mu g/m^3$ [PM10]) for years 2001-2013 inclusive having almost complete datasets (2% missing values).

Series were obtained from two fixed monitoring stations: one of them (Casa de Campo) is classified as suburban and is located in the vicinity of the largest public park in the city of Madrid and was chosen due to having very few gaps in its temporal series; the second one (Cuatro Caminos) is a traffic station located in the city center, and was chosen as a control station in order to gauge whether our results were dependent on the location of the measurements (Map 1). Data were obtained from the "Red de Vigilancia de la Calidad del Aire" (Air quality monitoring network) of the Ayuntamiento de Madrid (Madrid City Council).

Apparent Temperature

The meteorological data were obtained from the European Climate Assessment and Dataset (ECA, http://eca.knmi.nl/) [16]. Daily average air temperatures (ºC), relative

190 humidity (%), and wind speed (m/s), obtained from the weather station known as
191 "Madrid-El Retiro" (source identifier 230) with blended data for the period 2001-2013,
192 were used. "Blended data" refers to observations of two nearby locations (within a
193 distance of 12.5 km and with height differences of less than 25m), which can be
194 merged seamlessly for climate change research; in our case, less than 0.1% were
195 replaced by data from nearby stations.

196 The daily AT was estimated for shade according to Steadman [17]
197 (Equation 1):

$$AT = -2.7 + 1.047 \cdot T + 2.0 \cdot P_v - 0.65 \cdot v_{10}\ , (1)$$

198 where T is the temperature (°C), P_v is the vapor pressure (hPa), and v_{10} is the wind
199 speed 10 m above the ground. P_v can be estimated with Equation 2:

200 $$P_v = (rh/100) \cdot 6.1094 \cdot e^{(17.625 \cdot T)/(243.04+T)}\ , (2)$$

201 where *rh* is the relative humidity expressed as a percentage [18].

202 **2.3. Statistical Analysis**

203 **2.3.1. Incidence, seasonality and temporal trend**

204 The annual incidence tendency was calculated by using the Kendall rank correlation
205 coefficient. Specifically, the distribution of death rates by age group was analyzed. In
206 order to compare the monthly average number of admissions, we employed an
207 ANOVA F test. Additionally, post hoc t tests (Bonferroni corrected) were conducted for
208 each pair of months separately.

209 **2.3.2. Analysis of the relationship between environmental factors and stroke**

210 The nonlinear relationship between the exposure and response variables was modeled
211 using a distributed lag nonlinear model (DLNM). The DLNM framework simultaneously

212 describes complex nonlinear and delayed effects of an environmental variable on a
213 response variable with a family distribution and link function within generalized linear
214 models (GLM), generalized additive models (GAM), or generalized estimating
215 equations (GEE) [19-20].
216 The possible lagged response on human health is a well-known phenomenon and
217 expresses the temporal change in risk after a specific exposure event. To model the
218 effects of IS for this study, a quasi-Poisson regression with GAM was fitted [21-22].
219 We assumed a non-lineal relationship for the temperature exposure and a lineal
220 relationship for the contaminants.
221 Firstly, to analyze the relationship between AT and IS (controlling the pollution through
222 PM_{10}) the following model was used:
223 $Y_t \sim Quasi - Poisson(\mu_t)$

$$Log(\mu_t) = \alpha + \beta_1 Eat_{t,l} + \beta_2 Epm10_{t,l} + s(Flu, 3) + s(Trend, 7 \cdot 13) + \eta dow_t$$

224 Secondly, the relationship between individual pollutants and IS was studied by using
225 the following model:
226 $Y_t \sim Quasi - Poisson(\mu_t)$

$$Log(\mu_t) = \alpha + \beta_1 Eat_{t,l} + \beta_2 Ec_{t,l} + s(Flu, 3) + s(Trend, 7 \cdot 13) + \eta dow_t$$

227 where *t* is the day of the observation, Y_t is the daily mortality or morbidity rate for IS
228 observed on day *t*, α is the intercept, $Eat_{t,l}$, $Epm10_{t,l}$ and $Ec_{t,l}$ are matrices obtained by
229 applying the DLNM to AT, PM_{10} and single contaminants (NO_2, PM_{10}, SO_2, O_3), β is the
230 vector of coefficients for each matrix and *l* is the lagged effect in days. s(…) is a thin
231 plate regression spline. *Trend* is the long-term trend and seasonality with 7 degrees of
232 freedom (df) each year. *Flu* represents the daily smoothed number of reported
233 influenza cases. dow_t is the day of the week on day *t*, and η is the vector of coefficient.

Sunday is used as the reference day. Three df were used to smooth daily influenza rates considered to be potential confounders.

As far as the influenza rate is concerned, a polynomial local regression function (LOESS) [23] was applied to extrapolate the weekly data and thus obtain approximate daily records. A 14-day smooth window was chosen, which corresponds to smoothed behavior close to the declared cases [24-25].

The selection of the degrees of freedom was made by using the Akaike Information Criterion. To model the nonlinear and lagged AT effects, a cubic B-spline with 3 df was used. For the lagged effects of each contaminants also a cubic B-spline with 3 df was applied.

While it is widely known that the effects of heat on morbi-mortality are quasi-direct with a delay of a few days [26], the effects of cold can be delayed by up to 2 weeks [27]. Hence, a maximum lag of 14 days was used to model the effects of the exposure variables. As a reference value to calculate the relative risks in the case of the AT exposure variable, the threshold of minimum mortality and morbidity was estimated with the method applied by Tobías et al [29].

A specific explanation of the statistical details regarding the distributed lag nonlinear model can be found in Bhaskaran et al. [29] or Gasparrini [30].

In order to determine the possible differences between apparent temperature and air temperature, a sensitivity analysis was conducted. Finally, the sensitivity of using single and multi-air pollutant models was also evaluated.

All models, statistical analysis, and graphic results were made with the free software environment R, version 3.5. The models used in this study have been estimated through packages mgcv, version 1.8-23 [31], and dlnm, version 2.3.4 [32].

3. RESULTS

3.1. Ischemic Stroke Hospital Admissions

During the 13 years study period, there were 106,036 IS hospital admissions (including Transient cerebral ischemia). The average incidence rate was 133.5 cases per 100,000 population (142.8 per 100,000 population in male patients and 124.8 per 100,000 population in female patients). The average length of stay (ALOS) for each admission was 10 days (9.3 in men and 10.3 in women), decreasing every year from 11.8 days in 2001 to 8.3 in 2013 ($p=0.000019$). The ALOS depending on the type of stroke and age-group is shown in Tab. S1.

The secular analysis showed an upward trend in the incidence rate of hospital admissions during the period of study that was statistically significant for the 3 defined age groups ($p<0.005$), Figure 1.

The monthly analysis showed that the number of hospital admissions due to IS followed a seasonal pattern reaching minimum values in August ($p<0.005$, Bonferroni corrected), Figure 2.

3.2. Ischemic Stroke Deaths

Between 2001 and 2013 there were 18,095 deaths by stroke (not including hemorrhagic strokes, but considering those which had not been specified as hemorrhage or infarction). The incidence rate followed a downward trend during the 13 years of analysis in the 3 age-group studied ($p<0.005$). According to Figure 2, the largest decline in mortality rate was observed for people older than 64 years old,

reaching a maximum of 221.8 deaths per 100,000 population in 2001 and a minimum of 95 deaths per 100,000 population in 2013.

While the ANOVA model showed differences between months ($p<0.005$) when analyzing annual patterns, by applying the Bonferroni correction, statistical significance was not found ($p>0.05$).

3.3. Association Between Atmospheric Variables and Ischemic Stroke

Table 1 shows descriptive statistics for meteorological and pollution variables. The wider range of apparent temperatures, compared with the air temperature, can be understood as the result of including wind speed and humidity to correctly describe the perceived thermal environment. The average AT for Madrid is 14.1°C, reaching a maximum of 33.2°C. Figure 3 shows 3D plots of daily morbi-mortality cases for IS according to lag and average AT in Madrid. The estimated associations for AT and IS were nonlinear, with clear associations at high temperatures which persisted, in a decreasing manner, up to a lag of 3 to 4 days. Longer lagged effects could be observed for low temperature ranges between 3 to 10 days. Furthermore, the behavior of lagged effects between IS mortality and morbidity is very contrary. In the latter case, an absence of effects in high temperatures and a lagged effect in low temperatures was found. The minimum mortality and morbidity were estimated at 11.7°C (95% CI, 8.3-16.5) and 33.1°C (95% CI, (-5.7-33.1) for the average AT, respectively. The maximum effect in IS hospital admissions was estimated at a low AT with a lag of 5 days. In Figure 4, the cumulative effects for lag 0 to 14 days are represented for both response variables. With an AT of 1.7°C (percentile 5%) a RR of 1.20 (95% CI, 1.05-1.37) for IS mortality and a RR of 1.09 (95% CI, 0.91-1.29) for morbidity is estimated (Tab 2).

Although the overall risks are not significant for stroke hospital admissions, a RR of 1.02 (95% CI, 1.00-1.04) at lag 5 with -1.5°C AT could be found. In the case of IS mortality the maximum risk at low AT is reached at lag 6, with 1.7°C a RR of 1.03 (95% CI, 1.01-1.04) was estimated.

Higher risks were observed for high temperatures, particularly in stroke mortality, with an estimated RR of 1.37 (95% CI, 1.07-1.75) at 26.2°C (percentile 90%).

In Figure 5, the comparison between the use of apparent and air temperature as an exposure variable for the cumulative effects is presented. It shows clearly that the RR decreases when using AT, particularly in the case of low temperatures.

Regarding gender differences, men show higher risks of mortality in low temperatures and women in high temperatures (Fig. 6), although only significant effects are observed in percentiles 1% for men and over 90% for women. At 27.9°C of apparent temperature (percentile 95%) the RR of mortality is 1.06 (95% CI, 0.97-1.15) in men and 1.17 (95% CI, 1.09-1.26) in women at the same day of exposure. In the case of a low temperature of 1.7°C a risk of 1.03 (95% CI, 1.01-1.06) in men and 1.00 (95% CI, 0.97-1.03) in women for a lag of 7 days is observed. IS hospital admissions also show a non-significant higher risk for low temperature in men than in women (Tab. S2, Fig. S1).

When estimating the effects of the AT only for those older than 64 years, the risks of mortality due to cold effects decreases. For instance, the RR for 1.7°C AT is 1.13 (1.00-1.27), compared to the risk of all ages with 1.20 (95% CI, 1.05-1.37) (Tab. 4, Fig. S2). It is necessary to emphasize the fact that only 3% of IS mortality is population with less than 64 years. On the contrary, this proportion rises to 21% in IS hospital admissions.

People younger than 64 seem to have higher risk for low temperatures, but these effects are not significant. In the case of IS hospital admissions, the risk estimates for 64-year-old group are very similar but become significant.

The results for individual pollutants showed inconsistency and are non-significant in the risk estimation for IS morbi-mortality (Tab. 5). The maximum effect in IS mortality was observed for each increase of 10 μg/m^3 SO_2 with a RR of 1.09 (95% CI, 0.90-1.31). In the case of NO_2 and PM_{10} the RR were 1.01 (95% CI, 0.99-1.04) and 1.02 (95% CI, 0.99-1.05) for each increase of 10 μg/m^3, respectively. In contrast, for IS hospital admissions, only O_3 showed an increasing risk with an RR of 1.01 (95% CI, 0.99-1.02) (per 10 μg/m^3). The sensitive analysis for two or more pollutant models showed that, in general terms, the risk estimates decrease with more contaminants and the effects continue to be non-significant. The risk of mortality for NO_2 and SO_2 showed higher risks for men than for women (Tab S3), although these effects are not significant. Women seem to have higher risks for PM_{10}. We did not observe any gender differences in IS hospital admissions. Finally, for the analyzed age groups we did not find differences for pollutants risk estimates in IS morbi-mortality.

4. DISCUSSION

Over the last decade, the environment, including air pollutants, is gaining more and more importance in the pathogenesis of neurodegenerative disease but also other neurological conditions such as stroke, by either direct or indirect mechanisms that may involve epigenetic changes [33-35].

The present study was conceived to elucidate several issues. First, we assessed the tendency and annual cycle of admission and mortality rates of patients suffering from

IS during a 13-year period in the Spanish province of Madrid. Then, based on the previous literature, we aimed to study if an association existed between IS admissions and mortality rates and the main atmospheric pollutants. Finally, we investigated the relationship between AT and IS.

Regarding the first point, admission rates progressively increased over the studied period, while the average length of stay decreased. These results are in line with other studies in the literature and might be explained both by: i) more aggressive and interventional policies of stroke management and ii) a better identification of stroke in Emergency Departments. Conversely, mortality rate tendencies exhibited a decreasing pattern, which was particularly marked among the oldest patients. The progressive implementation of stroke units entailing more rapid and successful revascularization therapies, as well as a more integrated care of patients suffering from stroke in these units appear to be crucial conditions explaining these facts. Moreover, modifiable risk factors which increase mortality rates among patients who suffered an IS, such as physical inactivity, dyslipidemia, hypertension, diet or cigarette smoking, are well known, and programs to systematically identify and treat those in all patients at risk for stroke are gradually being developed [36].

Subsequently, data analysis showed a seasonal pattern over the whole studied period, with the lowest incidence during summer time. These results are concordant with other published studies which also reported seasonal variations in stroke frequency in different countries [37-39]. Although the precise mechanisms involved have not been fully elucidated yet, some biological explanations have been proposed. Among them, the vasoconstriction due to cold, increased cholesterol and triglyceride concentrations

372 in winter [40], variations in both fibrinogen levels and plasma viscosity [41] as well as
373 some microbiological variations such as seasonal patterns of influenza epidemics and
374 respiratory infections [42] are some of the most relevant ones. Moreover,
375 sociodemographic variables and the personal medical history of the patient may play a
376 role in seasonal vulnerability. In a recent study published by Toyoda et al., significant
377 seasonal variations in IS (with a peak in winter) were only found in patients older than
378 75 years, with moderate-to-severe initial neurological deficits or when limited to those
379 with cardioembolic stroke. Nevertheless, further studies with integrated and
380 complementary approaches will doubtlessly help to clarify this issue, presumably
381 providing us with new preventive and therapeutic strategies.

382 The role of environmental variables in stroke is gaining attention during the past years.
383 To date, several studies have reported an association between environmental
384 variables and stroke incidence [e.g. 35, 43-44]. In the case of air pollutants, different
385 researchers have described a significant correlation between nitrogen dioxide, sulfur
386 dioxide or particulate matter and cerebrovascular diseases [45-47]. Moreover,
387 regarding the possible etiopathogenesis of this association, some authors have stated
388 that a short-term exposure to air pollutants is specifically associated with
389 cardioembolic stroke [48], which would be in agreement with the relationship
390 described between poor air quality and hospital admissions for cardiac arrhythmias in
391 different places [49-50].

392 However, and in line with our results, other authors have not found these relationships
393 [51-52]. Nevertheless, the absence of a significant association with air pollutants
394 should be understood with carefulness. The high pathogenic complexity of stroke

should be considered when interpreting our results, since it can underrepresent the importance of these factors. Moreover, it is noteworthy that comparing results between different studies is not a trivial task, due to the fact that the area of study, the location and characteristics of air quality monitoring stations, the case registration systems, the adjustment for confounding variables and methodological designs, among other factors, vary greatly from work to work. Additionally, we would like to highlight that there are evidences which link chronic air pollution exposure with stroke and with reduced survival after stroke, a factor that is not considered in our study [53].

Considering that climate change increases the risk of extreme events like heat waves and that the Intergovernmental Panel on Climate Change predicts an average global temperature increase in the range of 1.0°C to 6.4°C until 2100 [54], the impact of air temperature is a concern for public health and is currently being thoroughly studied. Specifically, the role of this variable in stroke seems to be widely accepted. Recently, some authors have developed statistical models in order to infer years of life lost from stroke due to temperature variations in China [55].

However, there has been little research on how AT affects human health. This biometeorological index combines several meteorological factors to describe the actual human perception of air temperature in a given environment [7].

In this study we describe a significantly increased stroke-related mortality risk under extreme AT values (both low and high), with a maximum at the highest temperatures.

Although some potential biological mechanisms have been previously shown to explain the seasonal cycle of IS, at this point it must be noted that, besides the factors for IS described above, extreme temperatures have been demonstrated to cause

418 platelet increase, hemoconcentration and the impairment of peripheral vascular
419 endothelial function [56].

420 It is important to highlight that we found a higher RR when analysing the daily average
421 air temperature than in the case of apparent temperature. It seems that the air
422 temperature alone overestimates the potential risks and the combination of air
423 temperature, humidity and wind speed adjusts the exposure to the thermal
424 environment better. In general, the effect of temperature on relative humidity shows
425 daily and seasonal cycles, with lowest relative humidity at high temperature and,
426 conversely, highest relative humidity at low temperature.

427 It must be taken into account that, while different studies found a strong relationship
428 between air temperature or wind speed with IS [57] and most authors describe no
429 association between humidity and IS [58], the effects of the interaction between the
430 different variables with the human body has not been thoroughly studied. Humans use
431 perspiration (sweating) to regulate internal body temperature, and high humidity
432 impairs heat exchange efficiency by reducing the rate of moisture evaporation from
433 skin surfaces. Meanwhile, in windy conditions, the convective rate is enhanced [59].
434 Moreover, from a statistical perspective, combining several variables is advisable to
435 avoid and reduce multicollinearity in the model.

436 The lag structure found for AT with short-term IS mortality of few days at high
437 temperatures and longer lags of more than 4 days at low temperatures is consistent
438 with previous studies [60-62]. This delayed effect may be due to the fact that the
439 exposure to an extreme AT may trigger one of the mechanisms that can cause a
440 cerebrovascular attack (e.g. a prothrombotic situation or an arrhythmia), which may

result in stroke a short time later. On the other hand, in many occasions, stroke-related deaths occur not in the very acute period but few days later.

Regarding the differences found between genders, other authors have described a greater vulnerability of women to dying from heat due to vascular processes [63-64] which has mainly been attributed to physiological differences in thermal regulation between both sexes. It must be considered that women have lower body mass, higher percentage of fat but lower of muscle, and lower circulatory volume than men. In situations of heat stress, the adaptive response is usually more difficult for women, who tend to accumulate more blood peripherally than men, have a decreased sweating capacity, increase their heart rate to a greater extent, and present a higher risk of dehydration [65].

The higher vulnerability of men to die from stroke in cold situations is a novel result. Some previous studies have found a greater vulnerability to cold among men (although not specifically by studying stroke) but there are discordant results in this regard [66-67]. It should be noted that alcohol consumption, which is more prevalent in men, as well as the differences in the type of occupation (for instance, outdoor work, more common in men, is associated with a longer exposure to extreme thermal situations) could be uncontrolled risk factors.

In respect of the lower vulnerability to cold among older people (over 64 years old), it is necessary to ponder if this is a statistical limitation of the study, if the younger age group represents noise for the model, or if there are actually different responses to the thermal environment depending on the age group. Following the hypothesis posed above regarding differences by sex, there exists the possibility that in younger adults,

464 in situations of extreme temperatures, the exposure is more persistent than in the
465 elderly (e.g., work-related exposure), and therefore these effects arise.

466 When hospital admissions were studied, no effect was found under high temperatures
467 while a lagged effect in low temperatures appeared. The characteristics in the
468 response or the vulnerability to heat of some population groups could explain this
469 finding; for example, heat exposure could trigger the release of inflammatory
470 mediators, increase ventilation and exacerbate chronic obstructive pulmonary disease,
471 which is highly prevalent in the elderly and can lead to death after a stroke [68]; also,
472 cardiovascular adjustments to heat stress are attenuated in healthy elder individuals,
473 which could contribute to the greater prevalence of heat-related deaths in them [69].

474 In conclusion, our findings suggest that both increases and decreases in AT had a
475 marked relationship with IS deaths, while hospital admissions were only associated
476 with low apparent temperatures. This leads us to believe that, although high AT does
477 not influence the frequency of stroke it may have an impact in stroke survival.

478 No significant relationship was found between air pollutant concentrations and IS
479 morbi-mortality, but this result must be interpreted with caution, since there are
480 strong spatial fluctuations of the former between nearby geographical areas that make
481 it difficult to perform correlation analyses to the latter.

482

483

5. REFERENCES

1. Feigin VL et al. Global, regional, and country-specific lifetime risk of stroke, 1990–2016. N Engl J Med. 2018. doi: 10.1056/NEJMoa1804492
2. Silva GS, Koroshetz WJ, González RG, Schwamm LH. Causes of Ischemic Stroke. In: González R, Hirsch J, Lev M, Schaefer P, Schwamm L. (eds) Acute Ischemic Stroke. 2011. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-12751-9_2
3. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, Barker-Collo S, Moran AE, Sacco RL, Truelsen T, Davis S, Pandian JD, Naghavi M, Forouzanfar MH, Nguyen G, Johnson CO, Vos T, Meretoja A, Murray CJ, Roth GA; GBD 2013 Writing Group; GBD 2013 Stroke Panel Experts Group. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015. doi: 10.1159/000441085
4. Guan W, Clay SJ, Sloan GJ, Pretlow LG. Effects of Barometric Pressure and Temperature on Acute Ischemic Stroke Hospitalization in Augusta, GA. Transl Stroke Res. 2018. doi: 10.1007/s12975-018-0640-0
5. Chu SY, Cox M, Fonarow GC, Smith EE, Schwamm L, Bhatt DL, Matsouaka RA, Xian Y, Sheth KN. Temperature and Precipitation Associate With Ischemic Stroke Outcomes in the United States. J Am Heart Assoc. 2018;7(22):e010020. doi: 10.1161/JAHA.118.010020.
6. Tian Y et al. Association between temperature variability and daily hospital admissions for cause-specific cardiovascular disease in urban China: A national time-series study. PLoS Med. 2019; 16(1): e1002738. doi: 10.1371/journal.pmed.1002738
7. Royé D, Zarrabeitia MT, Fdez-Arroyabe P, Álvarez Gutiérrez A, Santurtún A. Role of Apparent Temperature and Air Pollutants in Hospital Admissions for Acute Myocardial Infarction in the North of Spain. Rev Esp Cardiol. 2018. DOI:10.1016/j.recesp.2018.05.032
8. Wong HT, Wang J, Yin Q, Chen S, Lai PC. The potential benefits of location-specific biometeorological indexes. Int J Biometeorol. 2017. doi: 10.1007/s00484-017-1343-z
9. Steadman RG. A universal scale of apparent temperature. Journal of Climate and Applied Meteorology. 1984; 23, 1674–1687.
10. Royé D, Figueiras A, Taracido M. Short-term effects of heat and cold on respiratory drug use. A time-series epidemiological study in A Coruña, Spain. Pharmacoepidemiol Drug Saf. 2018. doi: 10.1002/pds.4427.
11. Laña I, Del Ser J, Padró A, Vélez M, Casanova-Mateo C. The role of local urban traffic and meteorological conditions in air pollution: A data-based case study in Madrid, Spain. Atmospheric Environment. 2016. https://doi.org/10.1016/j.atmosenv.2016.09.052
12. Querol X et al. 2001-2012 trends on air quality in Spain. Sci Total Environ. 2014; 490:957-69. doi: 10.1016/j.scitotenv.2014.05.074.
13. Ye X, Wolff R, Yu W, Vaneckova P, Pan X, Tong S. Ambient temperature and morbidity: a review of epidemiological evidence. Environ Health Perspect. 2012;120:19-28
14. Thach T-Q, Wong C-M, Chan K-P, Chau Y-K, Thomas GN, Ou C-Q, Yang L, Peiris JSM, Lam T-H, Hedley AJ. Air pollutants and health outcomes: assessment of confounding by influenza. Atmos Environ. 2010;44(11):1437-1442
15. Barnett AG, Stephen D, Huang C, Wolkewitz M. Time series models of environmental exposures: good predictions or good understanding. Environ Res. 2017;154:222-225
16. Klein Tank AMG et al. Daily dataset of 20th-century surface air temperature and precipitation series for the European Climate Assessment. Int. J. of Climatol. 2002. https://doi.org/10.1002/joc.773

17. Steadman RG. A universal scale of apparent temperature. Journal of Climate and Applied Meteorology. 1984; 23, 1674–1687.
18. Alduchov OA, Eskridge RE. Improved Magnus Form Approximation of Saturation Vapor Pressure. J. Appl. Meteor. 1996. 35, 601–609.
19. Gasparrini A. Distributed lag linear and non-linear models in R: the package dlnm. J Stat Softw. 2011; 43, 1–20.
20. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. Stat Med. 2014; 33, 881–889.
21. Hastie T, Tibshirani R. A generalized additive models. Volume 43 of Monographs on Statistics & Applied Probability. Chapman&Hall/CRC. 1990.
22. Wood S. Generalized additive models: an introduction with R. Chapman & Hall/CRC. 2006.
23. Cleveland W, Grosse E, Shyu W. Statistical models in S. Chapter Local regression models. Wadsworth & Brooks/Cole. 1992.
24. Iñiguez C, Ballester F, Pérez-Hoyos S, Saez M. Estimación de los casos diarios de gripe a partir de los casos declarados al Sistema de Enfermedades de Declaración Obligatoria: utilidad en estudios de series temporales. Gac Sanit. 2001; 15, 273–275.
25. Touloumi G, Samoli E, Quenel P, Paldy A, Anderson R, Zmirou D, Galan I, Forsberg B, Schindler C, Schwartz J, Katsouyanni K. Short-term effects of air pollution on total and cardiovascular mortality. The confounding effect of influenza epidemics. Epidemiology. 2005; 6, 49–57.
26. Ye X, Wolff R, Yu W, Vaneckova P, Pan X., Tong S. Ambient temperature and morbidity: A review of epidemiological evidence. *Environ Health Perspect.* 2012; *120*, 19‑28
27. Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, Tobias A, Tong S, Rocklöv J, Forsberg B, Leone M, De Sario M, Bell M, Guo Y, Wu C, Kan H, Yi S, Coelho M, Saldiva P, Honda Y, Kim H, Armstrong B. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet*. 2015; *386*, 369‑375.
28. Tobías A, Armstrong B, Gasparrini A. Investigating uncertainty in the minimum mortality temperature: methods and application to 52 Spanish cities. *Epidemiology*. 2017; *28*, 72–76.
29. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *Int J Epidemiol*,. 2013; *42*, 1187–1195.
30. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. *Stat Med*. 2014; *33*, 881‑889.
31. Wood, S. Package ' mgcv '. Available at: https://cran.rproject.org/web/packages/mgcv/index.html (2013). doi:10.1007/s10853-011-5868-y
32. Gasparrini, A. Distributed Lag Linear and Non-Linear Models in R : The Package dlnm. Journal of Statistical Software. 2011. 43(8). https://doi.org/10.18637/jss.v043.i08
33. Dimakakou E, Johnston HJ, Streftaris G, Cherrie JW. Exposure to Environmental and Occupational Particulate Air Pollution as a Potential Contributor to Neurodegeneration and Diabetes: A Systematic Review of Epidemiological Research. Int J Environ Res Public Health. 2018. doi: 10.3390/ijerph15081704
34. Riancho J, Bosque-Varela P, Perez-Pereda S, Povedano M, de Munaín AL, Santurtun A. The increasing importance of environmental conditions in amyotrophic lateral sclerosis. Int J Biometeorol. 2018. doi: 10.1007/s00484-018-1550-2.
35. McArthur K, Dawson J, Walters M. What is it with the weather and stroke? Expert Rev Neurother. 2010. doi: 10.1586/ern.09.154
36. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MSV, Fornage M, Goldstein LB, Greenberg SM, Horvath SE,

Iadecola C, Jauch EC, Moore WS, Wilson JA. Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2014. doi:10.1161/STR.0000000000000046

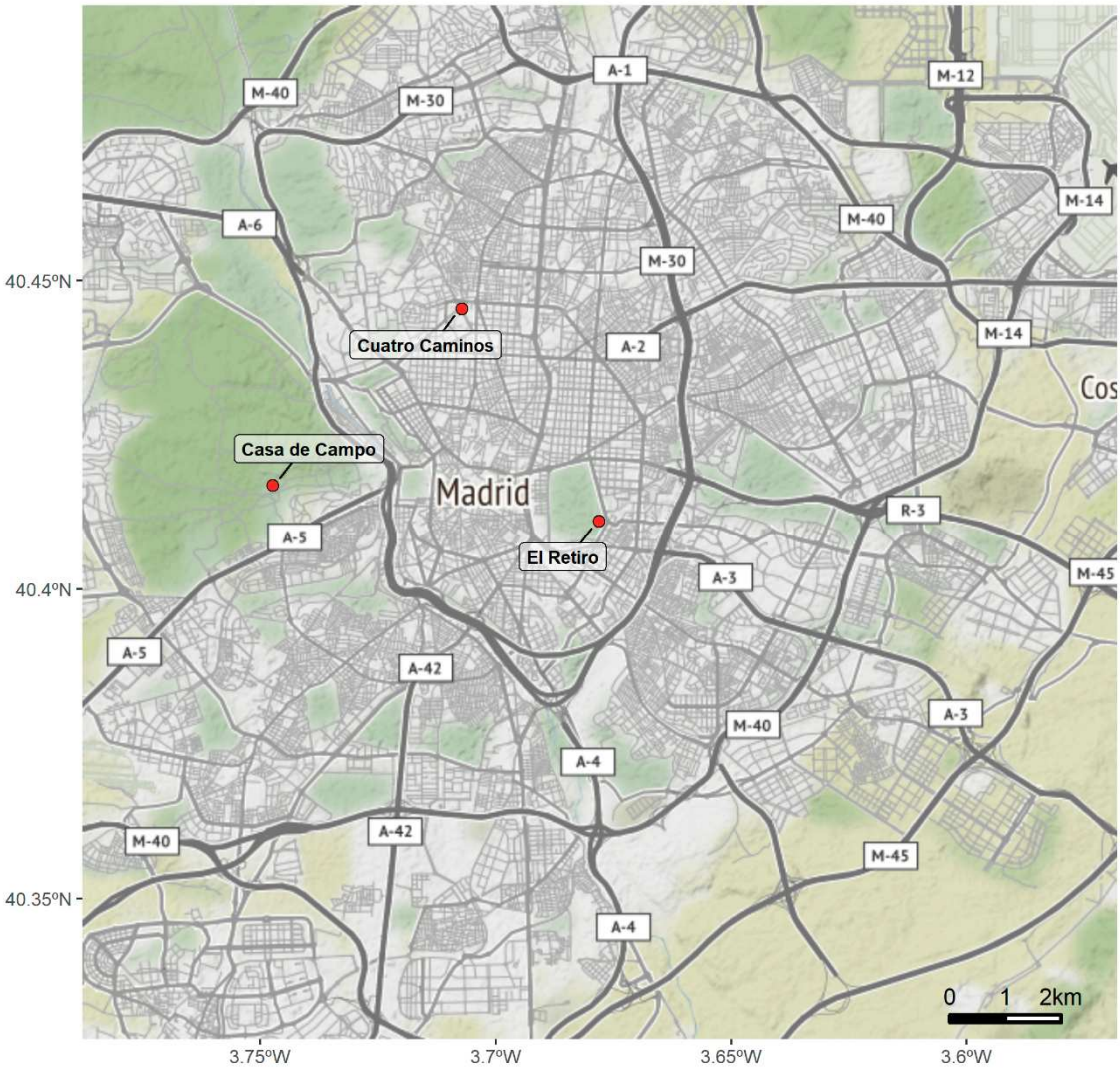
37. Oberg AL, Ferguson JA, McIntyre LM, Horner RD. Incidence of stroke and season of the year: evidence of an association. Am J Epidemiol. 2000; 15;152(6):558-64.
38. Díaz A, Gerschcovich ER, Díaz AA, Antía F, Gonorazky S. Seasonal variation and trends in stroke hospitalizations and mortality in a South American community hospital. J Stroke Cerebrovasc Dis. 2013. doi: 10.1016/j.jstrokecerebrovasdis.2012.04.007.
39. Ha S, Nguyen K, Liu D, Männistö T, Nobles C, Sherman S, Mendola P. Ambient temperature and risk of cardiovascular events at labor and delivery: A case-crossover study. Environ Res. 2017. doi: 10.1016/j.envres.2017.09.010
40. Gordon DJ, Hyde J, Trost DC, Whaley FS, Hannan PJ, Jacobs DR, Ekelund LG. Cyclic seasonal variation in plasma lipid and lipoprotein levels: the Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group. J Clin Epidemiol. 1998; 41(7):679-89.
41. Stout RW, Crawford V. Seasonal variations in fibrinogen concentrations among elderly people. Lancet. 1991; 338(8758):9-13.
42. Grau AJ, Marquardt L, Lichy C. The effect of infections and vaccinations on stroke risk. Expert Rev Neurother. 2006. DOI:10.1586/14737175.6.2.175
43. Lim JS, Kwon HM, Kim SE, Lee J, Lee YS, Yoon BW. Effects of Temperature and Pressure on Acute Stroke Incidence Assessed Using a Korean Nationwide Insurance Database. J Stroke. 2017. doi: 10.5853/jos.2017.00045.
44. Gunes H, Kandis H, Saritas A, Dikici S, Buyukkaya R. The relationship between ischemic stroke and weather conditions in Duzce, Turkey. World J Emerg Med. 2015. doi: 10.5847/wjem.j.1920-8642.2015.03.008.
45. Zhong H, Shu Z, Zhou Y, Lu Y, Yi B, Tang X, Liu C, Deng Q, Yuan H, Huang Z. Seasonal Effect on Association between Atmospheric Pollutants and Hospital Emergency Room Visit for Stroke. J Stroke Cerebrovasc Dis. 2018. doi:10.1016/j.jstrokecerebrovasdis.2017.08.014.
46. Santurtún A, Ruiz PB, López-Delgado L, Sanchez-Lorenzo A, Riancho J, Zarrabeitia MT. Stroke: Temporal Trends and Association with Atmospheric Variables and Air Pollutants in Northern Spain. Cardiovasc Toxicol. 2017. doi: 10.1007/s12012-016-9395-6.
47. Vidale S, Campana C. Ambient air pollution and cardiovascular diseases: From bench to bedside. Eur J Prev Cardiol. 2018. doi: 10.1177/2047487318766638.
48. Chung JW et al. Air Pollution Is Associated With Ischemic Stroke via Cardiogenic Embolism. Stroke. 2017; 48(1):17-23. doi: 10.1161/STROKEAHA.116.015428.
49. Kowalska M, Kocot K. Short-term exposure to ambient fine particulate matter (PM2,5 and PM10) and the risk of heart rhythm abnormalities and stroke. Postepy Hig Med Dosw (Online). 2016. 28;70(0):1017-1025.
50. Santurtún A, Sanchez-Lorenzo A, Villar A, Riancho JA, Zarrabeitia MT.The Influence of Nitrogen Dioxide on Arrhythmias in Spain and Its Relationship with Atmospheric Circulation. Cardiovasc Toxicol. 2017;17(1):88-96. doi: 10.1007/s12012-016-9359-x.
51. Crichton S, Barratt B, Spiridou A, Hoang U, Liang SF, Kovalchuk Y, Beevers SD, Kelly FJ, Delaney B, Wolfe CD. Associations between exhaust and non-exhaust particulate matter and stroke incidence by stroke subtype in South London. Sci Total Environ. 2016. doi: 10.1016/j.scitotenv.2016.06.009.
52. Stockfelt L, Andersson EM, Molnár P, Gidhagen L, Segersson D, Rosengren A, Barregard L, Sallsten G. Long-term effects of total and source-specific particulate air pollution on incident cardiovascular disease in Gothenburg, Sweden. Environ Res. 2017. doi: 10.1016/j.envres.2017.05.036.

53. Maheswaran R. Air pollution and stroke - an overview of the evidence base. Spat Spatiotemporal Epidemiol. 2016 Aug;18:74-81. doi: 10.1016/j.sste.2016.04.004.
54. Moghadamnia MT, Ardalan A, Mesdaghinia A, Naddafi K, Yekaninejad MS. The Effects of Apparent Temperature on Cardiovascular Mortality Using a Distributed Lag Nonlinear Model Analysis: 2005 to 2014. Asia Pac J Public Health. 2018. doi:10.1177/1010539518768036.
55. Li G, Guo Q, Liu Y, Li Y, Pan X. Projected Temperature-Related Years of Life Lost From Stroke Due To Global Warming in a Temperate Climate City, Asia: Disease Burden Caused by Future Climate Change. Stroke. 2018. doi: 10.1161/STROKEAHA.117.020042.
56. Lian H, Ruan Y, Liang R, Liu X, Fan Z. Short-Term Effect of Ambient Temperature and the Risk of Stroke: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2015. doi: 10.3390/ijerph120809068
57. Kim J, Yoon K, Choi JC, Kim H, Song JK. The association between wind-related variables and stroke symptom onset: A case-crossover study on Jeju Island. Environ Res. 2016; 150:97-105. doi: 10.1016/j.envres.2016.05.041.
58. Cao Y, Wang X, Zheng D, Robinson T, Hong D, Richtering S, Leong TH, Salam A, Anderson C, Hackett ML. Air Pressure, Humidity and Stroke Occurrence: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2016; 13(7): 675. doi: 10.3390/ijerph13070675
59. Vanos JK, Kosaka E, Iida A, Yokohari M, Middel A, Scott-Fleming I, Brown RD. Planning for spectator thermal comfort and health in the face of extreme heat: The Tokyo 2020 Olympic marathons. Sci Total Environ. 2019;657:904-917. doi: 10.1016/j.scitotenv.2018.11.447.
60. Chen R, Wang C, Meng X, Chen H, Thach TQ, Wong CM, Kan H. Both low and high temperature may increase the risk of stroke mortality. Neurology. 2013;81(12):1064-70. doi: 10.1212/WNL.0b013e3182a4a43c.
61. Lavados PM, Olavarría VV, Hoffmeister L. Ambient Temperature and Stroke Risk: Evidence Supporting a Short-Term Effect at a Population Level From Acute Environmental Exposures. Stroke. 2018;49(1):255-261. doi: 10.1161/STROKEAHA.117.017838.
62. Yang J et al. The burden of stroke mortality attributable to cold and hot ambient temperatures: Epidemiological evidence from China. Environ Int. 2016 Jul-Aug;92-93:232-8. doi: 10.1016/j.envint.2016.04.001.
63. Pyrgou A, Santamouris M. Increasing Probability of Heat-Related Mortality in a Mediterranean City Due to Urban Warming. Int J Environ Res Public Health. 2018 25;15(8). doi: 10.3390/ijerph15081571.
64. Achebak H, Devolder D, Ballester J. Heat-related mortality trends under recent climate warming in Spain: A 36-year observational study. PLoS Med. 2018; 15(7): e1002617. doi: 10.1371/journal.pmed.1002617
65. Burse RL. Sex Differences in Human Thermoregulatory Response to Heat and Cold Stress. Human Factors: The Journal of the Human Factors and Ergonomics Society. 1979. 21(6):687-699. https://doi.org/10.1177/001872087912210606
66. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. Am J Physiol Heart Circ Physiol. 2015. 309(11):H1793-812. doi:10.1152/ajpheart.00199.2015.
67. Sartini C, Barry SJE, Wannamethee SG, Whincup PH, Lennon L, Ford I, Morris RW. Effect of cold spells and their modifiers on cardiovascular disease events: Evidence from two prospective studies. Int J Cardiol. 2016. 218: 275–283. doi: 10.1016/j.ijcard.2016.05.012

686 68. Bunker A, Wildenhain J, Vandenbergh A, Henschke N, Rocklöv J, Hajat S, Sauerborn R.
687 Effects of Air Temperature on Climate-Sensitive Mortality and Morbidity Outcomes in
688 the Elderly; a Systematic Review and Meta-analysis of Epidemiological Evidence.
689 EBioMedicine. 2016. doi: 10.1016/j.ebiom.2016.02.034.
690 69. Gagnon D, Schlader ZJ, Crandall CG. Sympathetic activity during passive heat stress in
691 healthy aged humans. J Physiol. 2015. doi: 10.1113/JP270162.
692
693
694
695

696 **MAP**

697 **Map 1: Location of the two air fix monitoring stations, Casa de Campo (suburban**
698 **station) and Cuatro Caminos (traffic station), and of the weather monitoring station**
699 **"El Retiro" in the Community of Madrid.**



700

701

702 **TABLES**

703 **Table 1:** Main characteristics of daily atmospheric and pollution variables during the
704 study period 2001-2013.

	Relative Humidity (%)	Air Temperature (°C)	Wind Speed (km/h)	Apparent Temperature (°C)	SO_2	NO_2	PM_{10}	O_3
Min	22	-1.8	0	-5.8	1	1	3	2
Q1	45	8.8	14	6.8	5	16	13	31
Median	58	14.4	19	13.1	7	28	21	52
Mean	59.7	15.3	20.8	14.1	6.8	31.2	24.2	50.5
Q3	74	22.2	25	21.7	9	42	31	69
Max	97	32.8	106	33.2	23	119	163	148

705

706 **Table 2**: Temperature effect estimates for different percentiles.

		Overall RR 0-14 days (95% CI)	
Percentile	AT	Mortality	Hospital Admissions
1	-1.5	*1.38 (1.13-1.68)*	1.11 (0.93-1.32)
5	1.7	*1.20 (1.05-1.37)*	1.09 (0.91-1.29)
10	3.3	*1.13 (1.02-1.26)*	1.08 (0.91-1.28)
90	26.2	*1.30 (1.05-1.61)*	1.01 (0.95-1.07)
95	27.9	*1.37 (1.07-1.75)*	1.01 (0.96-1.05)
99	30.2	*1.48 (1.11-1.98)*	1.00 (0.98-1.03)

707

708 **Table 3**: Temperature effect estimates by gender

		Overall RR 0-14 days (95% CI)	
Percentile	AT	Male	Female
1	-1.5	*1.42 (1.00-2.02)*	1.20 (0.96-1.51)
5	1.7	1.23 (0.97-1.57)	1.10 (0.95-1.27)
10	3.3	1.17 (0.96-1.42)	1.06 (0.95-1.18)
90	26.1	1.19 (0.86-1.66)	1.30 (0.99-1.72)
95	27.9	1.25 (0.85-1.84)	*1.37 (1.00-1.88)*
99	30.3	1.33 (0.83-2.12)	*1.47 (1.01-2.14)*

709

710 **Table 4**: Temperature effect estimates by age group

		Overall RR 0-14 days (95% CI)	
Percentile	AT	Older than 64 yr	Younger than 64 yr
1	-1.5	*1.25 (1.04-1.51)*	1.87 (0.67-5.22)
5	1.7	*1.13 (1.00-1.27)*	1.55 (0.80-3.01)
10	3.3	1.08 (0.99-1.19)	1.42 (0.85-2.36)
90	26.1	*1.30 (1.04-1.61)*	0.56 (0.17-1.89)
95	27.9	*1.37 (1.06-1.76)*	0.53 (0.13-2.15)
99	30.3	*1.47 (1.09-1.98)*	0.49 (0.09-2.57)

711

712

713 **Table 5**: Contaminant effect estimates (RR, 95% CI) for each increase of 10 μg/m^3.

Contaminants	Hospital Admissions	Mortality
PM_{10}	0,99 (0,97-1,00)	1,02 (0,99-1,05)
O_3	1,01 (0,99-1,02)	0,99 (0,96-1,02)
NO_2	0,99 (0,98-1,00)	1,01 (0,99-1,04)
SO_2	0,93 (0,85-1,01)	1,09 (0,90-1,31)

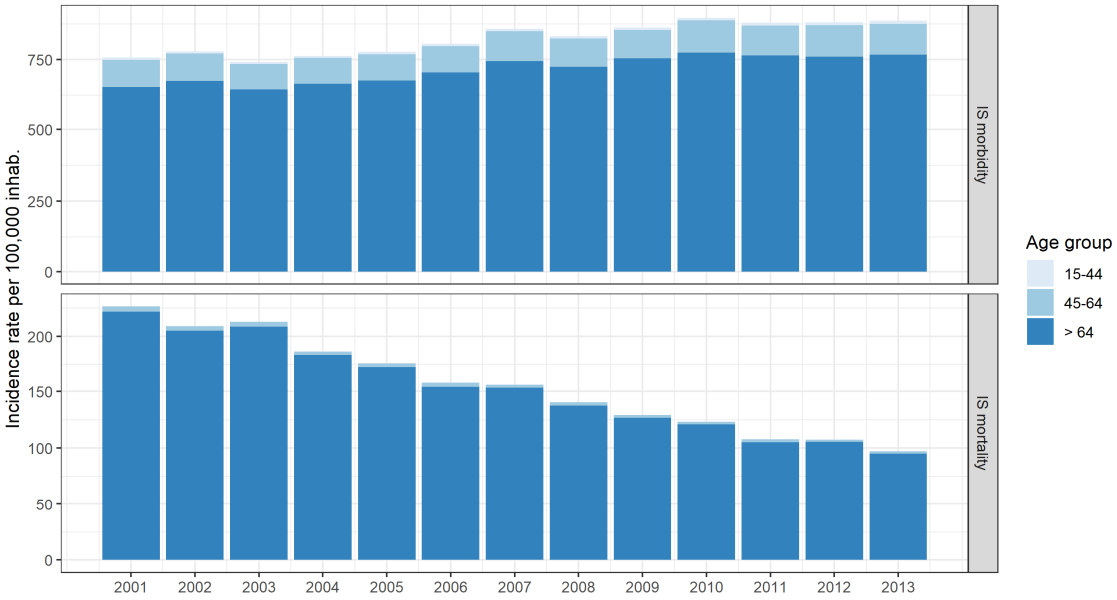
714

715

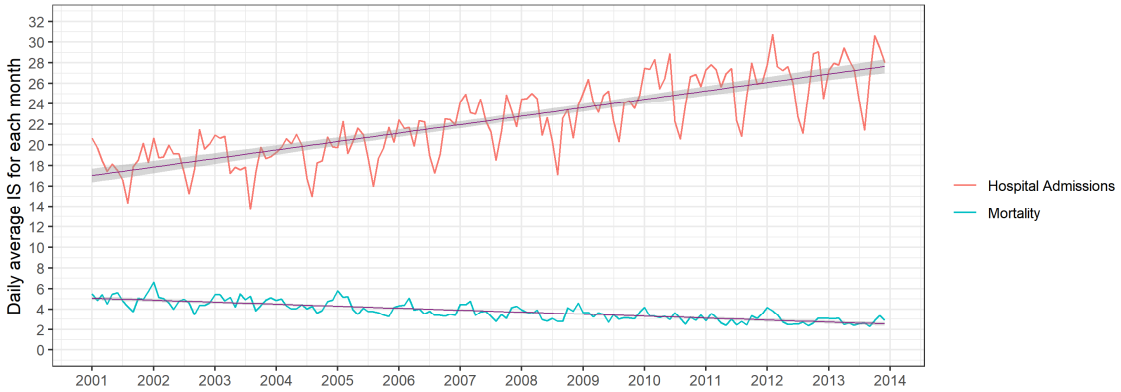
716

FIGURES

Figure 1: Tendency of admission and mortality annual rates of patients suffering from Ischemic Stroke during a 13-year period (2001-2013) by age group in the Spanish province of Madrid.



723 **Figure 2:** Monthly calendar of Ischemic Stroke. Daily average of Ischemic Stroke
724 admissions (red) and deaths (blue) for each month is represented.

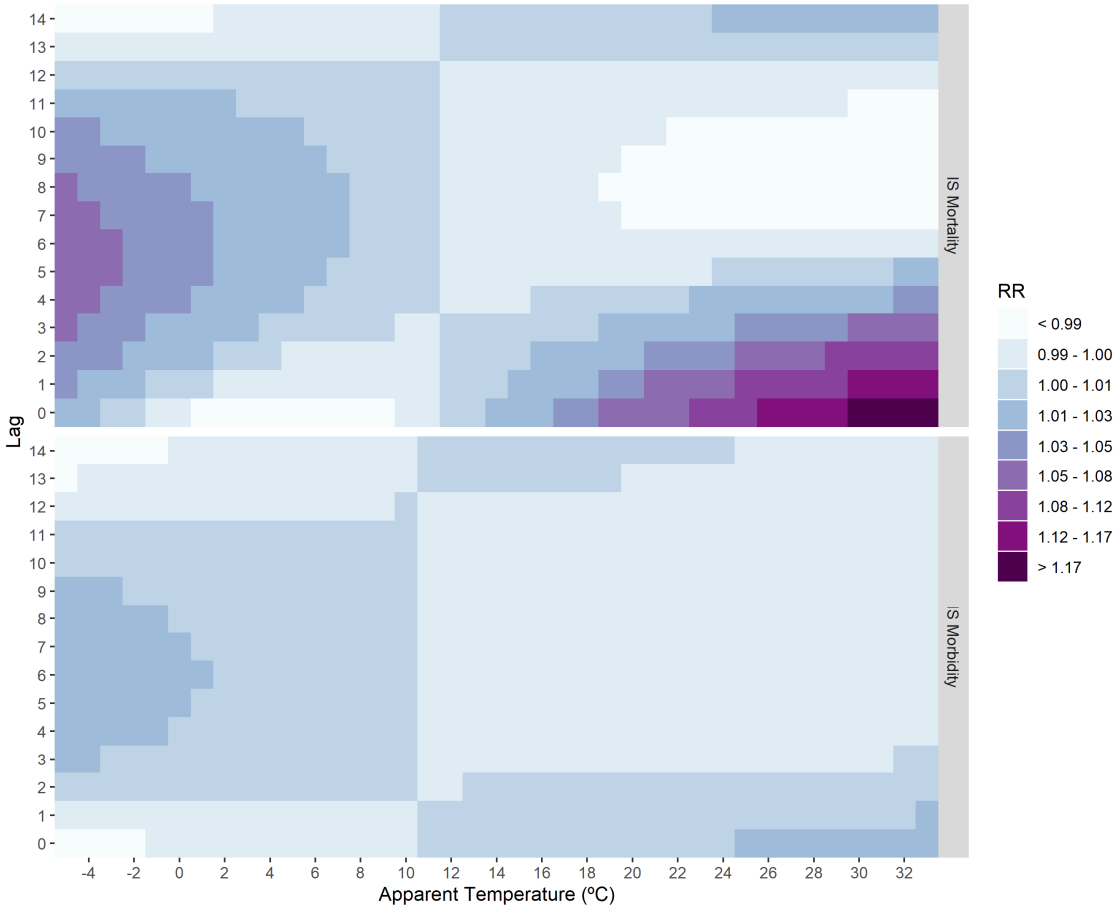


725

726

727 **Figure 3:** Relative risk of daily Ischemic Stroke mortality and hospital admissions as a
728 response to Apparent Temperature by lag period.

729



730

731

732

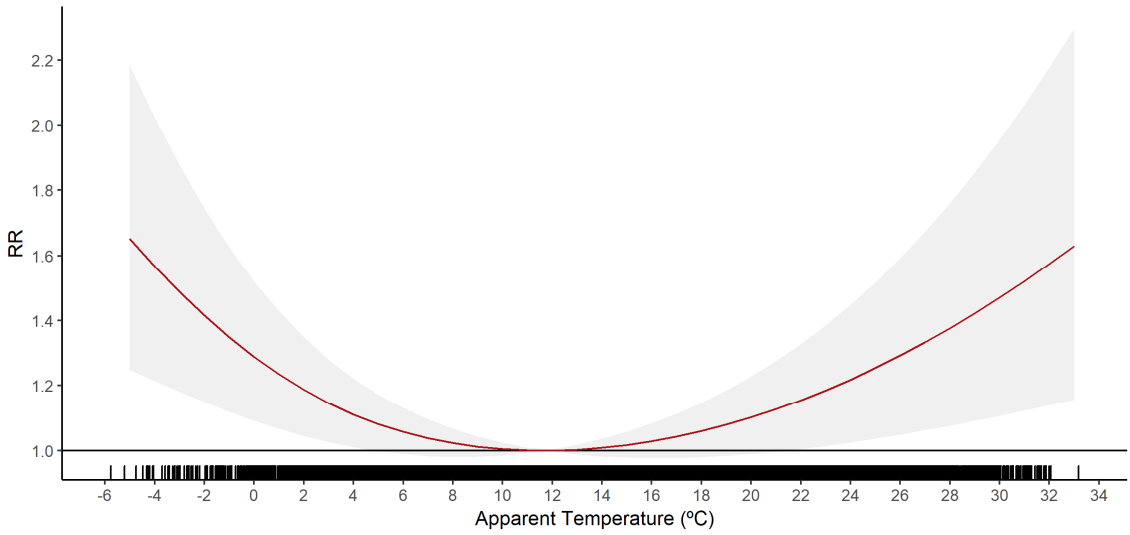
733

734 **Figure 4:** Cumulative RR lag 0–14 of daily Ischemic Stroke mortality (a) and hospital
735 admissions (b) as a response to Apparent Temperature.

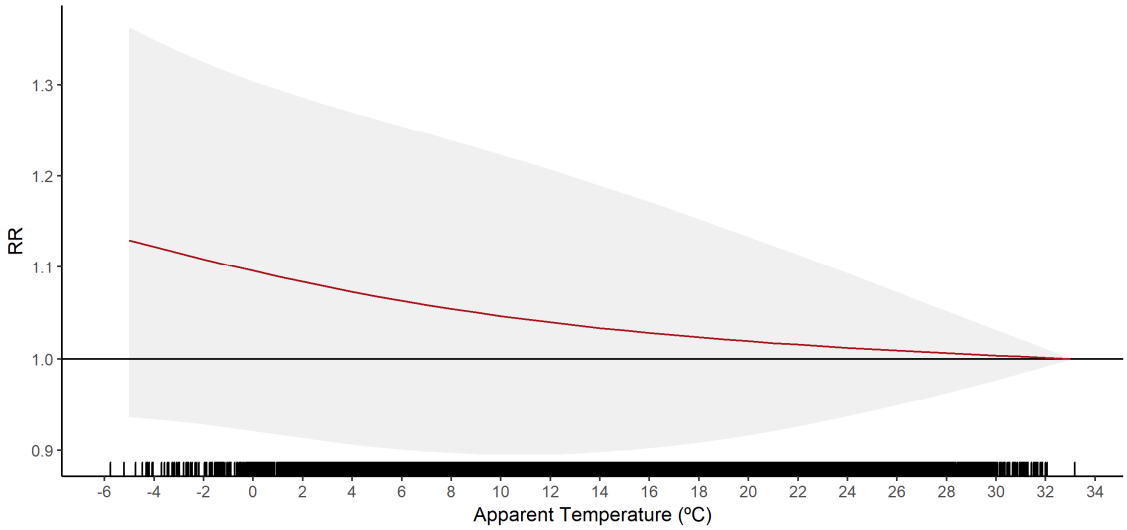
736

737

a)



b)

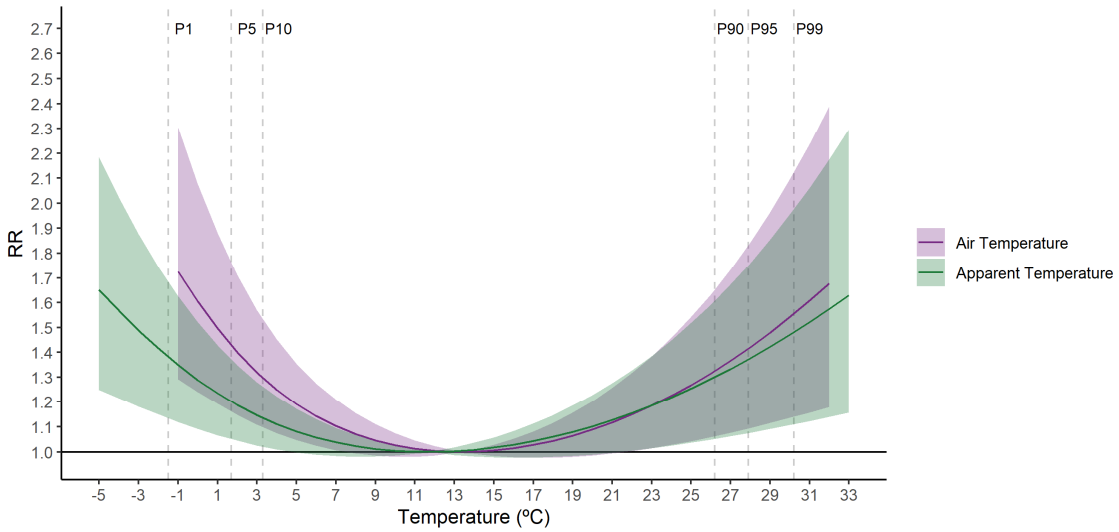


738

739

740 **Figure 5:** Cumulative RR lag 0–14 of daily Ischemic Stroke mortality as a response to
741 Apparent Temperature and air temperature.

742



743

744

745

746

747

748

749

750

751

752

753

754

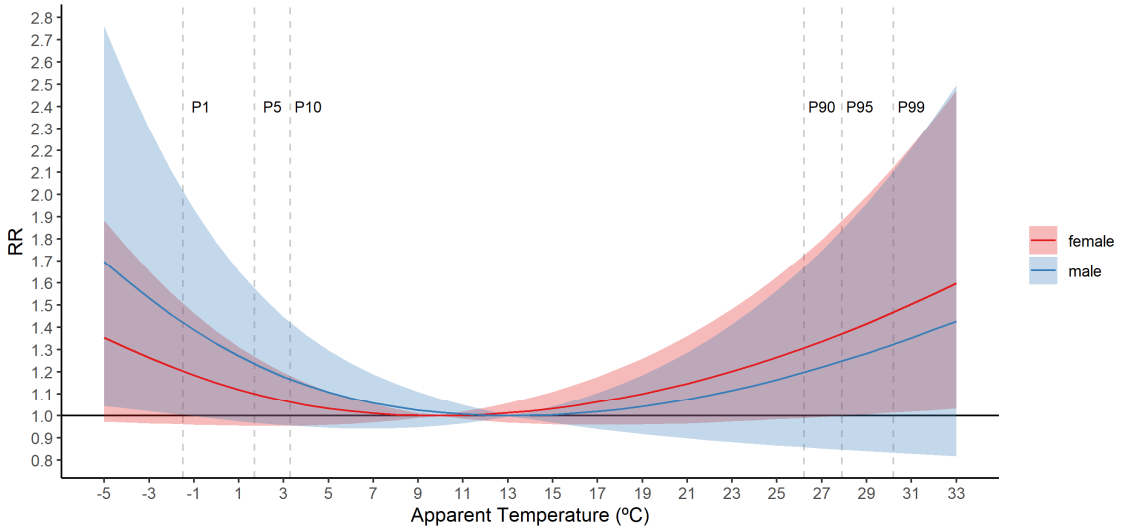
755

756

757

758

759 **Figure 6:** Cumulative RR lag 0–14 of daily Ischemic Stroke mortality by gender as a
760 response to Apparent Temperature.



761

762

763

764

765 **SUPPLEMENTARY MATERIAL**

766 **Table S1**: Average Lenght of Stay according to the type of stroke, sex and age group.

		Average Lenght of Stay (Days)		
ICD- 9	**Age group**	**Men**	**Women**	**Total**
433 - Occlusion and stenosis of precerebral arteries	15-44	9.30	8.09	8.83
	45-64	7.62	7.40	7.57
	65 or older	8.09	9.19	8.44
434 - Occlusion of cerebral arteries	15-44	10.95	11.42	11.14
	45-64	10.35	10.88	10.51
	65 or older	11.48	12.04	11.80
435 - Transient cerebral ischemia	15-44	6.26	6.35	6.29
	45-64	6.08	6.38	6.19
	65 or older	6.48	6.32	6.39

767

768

769 **Table S2**: Temperature effect estimates for Ischemic Stroke hospital admissions by
770 gender

		Overall RR 0-14 days (95% CI)	
Percentile	AT	Male	Female
1	-1.5	1.07 (0.95-1.22)	1.04 (0.93-1.16)
5	1.7	1.05 (0.96-1.15)	1.03 (0.96-1.11
10	3.3	1.04 (0.96-1.12)	1.02 (0.97-1.08)

771

772

773 **Table S3**: Contaminant effect estimates (RR, 95% CI) for each increase of 10 μg/m^3
774 by gender

IS mortality				
	PM10	O3	NO2	SO2
Women	1.02 (0.98-1.06)	0.99 (0.96-1.03)	1.00 (0.97-1.03)	1.04 (0.83-1.30)
Men	1.01 (0.96-1.06)	0.97 (0.92-1.02)	1.02 (0.98-1.06)	1.09 (0.80-1.47)
IS hospital admissions				
Women	0.99 (0.96-1.01)	1.00 (0.99-1.02)	0.99 (0.98-1.01)	0.96 (0.84-1.08)
Men	0.99 (0.97-1.01)	1.01 (0.99-1.03)	0.99 (0.97-1.00)	0.90 (0.80-1.02)

775

776

777

Figure S1: Cumulative RR lag 0–14 of daily Ischemic Stroke hospital admissions by gender as a response to Apparent Temperature.

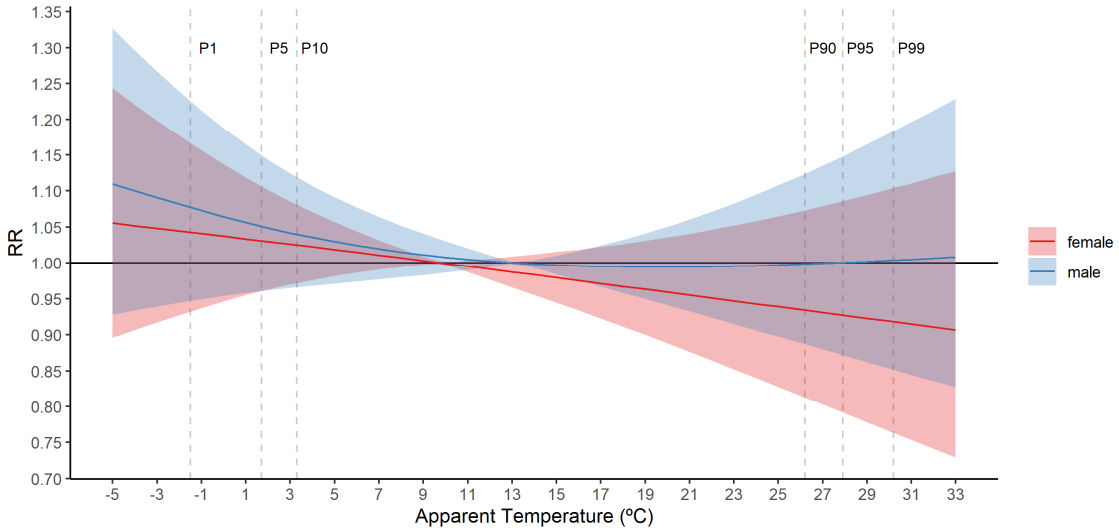


Figure S2: Cumulative RR lag 0–14 of daily Ischemic Stroke hospital mortality by age group as a response to Apparent Temperature.