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The role of ozone as a mediator in the relation between heat waves and mortality in 15 French urban agglomerations

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Abstract

Heat and tropospheric ozone have acute impact on premature deaths. Warm temperature affects the photochemical processes in ozone formation suggesting ozone as a mediator to the acute health effect of heat on mortality. We assembled a summertime daily time-series dataset of 15 French agglomerations during 2000 and 2015 to decompose the acute total effect of heat wave on mortality into natural direct and indirect effects using regression-based product method under the potential outcomes framework. For each agglomeration, we estimated the effect of heat wave on mortality using a quasi-Poisson model with adjustment for covariates like lagged NO_2 concentration, and modeled ozone with a linear regression of heat wave and the same set of covariates. We pooled estimates across agglomerations using random-effect models. We also provide R syntax to reproduce or replicate our analysis. Most agglomerations demonstrated evidence of mediation by ozone, with the pooled natural indirect effect being 1.03(95% confidence interval (CI): 1.02 to 1.05), 1.03(95% CI: 1.01 to 1.04), and 1.02(95% CI: 1.00 to 1.07) for non-accidental, cardiovascular, and respiratory mortality, respectively. We found evidence of mediation effect by ozone in the association between heat wave and mortality in France, which varied by geographical location and cause of mortality.

Introduction

Extreme temperature and ground level ozone are major environmental determinants of population health, both driving increases in premature deaths. Short term health effects of exposure to extreme heat have been largely described in the literature (1–6) and include cardiovascular and respiratory diseases. Similarly, short-term exposure to ozone, even at low concentrations, has been consistently shown to have negative health consequences, as it can cause a large range of cardiovascular and respiratory complications induced notably by oxidative stress, exacerbating existing health conditions and leading to premature death (7,8).

Heat waves and high ozone concentrations frequently co-occur as they are linked by complex atmospheric and chemical patterns. Specifically, warm temperature influences the generation of tropospheric ozone as hot sunny days can trigger photochemical processes (in junction with ozone precursors such as NOx) that are at the basis of ozone formation. There has been debate in the literature about the role of ozone as a confounder, modifier, or mediator in the epidemiologic association between temperature and mortality (9,10). Confounding bias is defined as the presence of a cause that is shared by the exposure X and the outcome Y, which results in an open backdoor path between X and Y (11); in this context, given that air pollution does not influence on the short term the daily ambient temperature, there is no rationale for considering any air pollutant as a true confounder when ambient temperature is the exposure of interest in short-term relation to a given health outcome. Alternatively, a number of recent studies have focused on the possible synergistic effect (or joint effects) of hot temperature and ozone on population health (12–19). Indeed, the simultaneous exposure to high temperature and ozone is likely to make individuals more susceptible to the effects of both environmental stressors; this is often considered through the inclusion of an interaction term or by considering different temperature strata in exposure-response model (12–16). These studies considering ozone as an effect measure modifier of heat-related health effects have denoted synergistic associations that often vary by region of study (12,17–19).

Finally, ozone has also been proposed to be a causal intermediate in the relationship between temperature and mortality, since it is affected by temperature and it can also impact mortality (9,10). If ozone is part of the causal pathway between exposure and outcome, the total effect of temperature on mortality should be decomposed into an indirect effect, which operates through the ozone-effect component, and a direct effect, which consist in the temperature effect aside from the ozone-mediated effect (10). To the best of our knowledge, the role of ozone as a mediator in the relationship between heat and health has not been investigated as no studies assessed such mechanism with empirical data. However, a better understanding of these dynamics would be particularly important to inform policy actions during a heat wave, as, in the context of climate change, heat wave episodes are likely to occur more frequently and at higher intensity (20) and, concurrently, ozone concentrations are expected to increase in most urbanized areas (21–24); therefore, the potential health impact of this simultaneous exposure will become increasingly common.

During the last decades, mitigations strategies that have been commonly adopted by various countries and various cities worldwide are based on two independent systems, heat-health warning systems (HHWSs), which target heat wave episodes as a specific dangerous event for human health (25–28), and systems of air quality alerts (AQA), which aim at preventing adverse health events associated with episodes of extreme air pollutant levels (29–35). A deeper understanding of the relationship between high temperature, ozone and mortality (and the variability across cities) is crucial to better adapt public-health policy measures implemented in the framework of these two systems.

By decomposing the effects of heat on mortality into direct and indirect effects by a causal mediation analysis, we can understand how ozone plays a role in the heat-mortality relationship and determine whether some urban agglomerations would particularly benefit from specific actions to prevent ozone formation during heat waves. With this purpose, we provide a state-of-art causal mediation analysis to decompose the total effect of heat waves on mortality in France during the summer periods from 2000 to 2015.

Methods

Study population

Populations from 15 major urban agglomerations in different regions of France were studied for the summer period from June 1st to September 30th for the years 2000 to 2015 (which corresponds to the dates HHWSs in France are active). Urban populations ranged from 227,151 inhabitants in the agglomeration of Clermont-Ferrand to 6.66 millions inhabitants in Paris in 2010. The selected cities provide a representative panel of different climate profiles existing in France, namely the oceanic, the temperate-oceanic, the semi-continental and the Mediterranean climate (**Figure 1**). The list of the urban agglomerations studied and their main demographic, geographic and climatic information are summarized in **Table 1**.

Outcome data

Daily mortality data for each urban agglomeration for the period from 2000 to 2015 were obtained from the French National Institute of Health and Medical Research (CepiDC). Daily mortality in the whole population was analyzed for the following causes: all non-accidental mortality (ICD10: A00-R99), cardiovascular causes (ICD10: I00-I99), and respiratory causes (ICD10: J00-J99).

Main Definition of Heat Wave Exposure

Daily hourly minimal and maximal temperatures in degree Celsius (°C) were provided by the French national meteorological service Météo-France for one reference station in each urban agglomeration, generally located at the airport station (see **Table 2**) (36). In order to identify heat waves for each urban agglomeration, we referred to the official method used by Météo-France to define heat waves which is used to activate heat warning systems in France. Heat waves were defined as periods where the mean daily temperature exceeded the 97.5th percentile of the local (within each urban agglomeration) mean temperature distribution over the entire year (*initial threshold*) for at least three consecutive days, and for which at least one day recorded a mean daily temperature above the 99.5th percentile of the local temperature distribution for the entire year (*peak threshold*) (36,37). As sensitivity analyses, we also considered additional heat wave definitions (see details below).

Air pollution data

We considered NO_2 as a confounder between ozone and mortality as NO_2 level is one of the main precursors of tropospheric ozone formation. Two sources of air quality data for the 2000-2015 period were utilized. First, daily ozone and NO_2 concentrations in $\mu g/m^3$ were obtained from the open and publicly accessible database of the European Environmental Agency (EEA) (38). The EEA's air quality database contains multi-annual time series of air quality measurement data obtained by the regional entities in charge of monitoring air pollution in each participating countries (including all European Union Member States, as well as EEA cooperating and other reporting countries), which are committed to transmitting their data to the agency. For all urban agglomerations included in the study, relevant stations were selected by only considering stations which monitor pollutants at the hourly level. Information of daily average concentrations for each urban agglomeration were then obtained by averaging hourly data from all the stations within each urban agglomeration. EEA's data were extracted using the R package saqgetr (39).

Second, data from the original source of the network of urban background monitors managed by local French air quality surveillance organizations (https://atmo-france.org/) were also available for the all urban agglomerations included in the study, for the entire study period for ozone but only for the period going from the year 2007 until the year 2015 for NO_2. Thus, this data was used for validation and for imputation of missing data.

Statistical Analysis

Our analysis focused on the summer period, defined as the period from June 1st to September 30th. A formal causal mediation analysis through a regression-based approach was carried out to understand to what extent the association between heat wave (the exposure) and mortality (the outcome) is mediated by ozone (the mediator). This mediation analysis allows to decompose the total effect (TE) of heat wave on different causes of mortality into its natural direct effect (NDE, the effect of the exposure to heat waves on mortality at a level of ozone concentrations observed during non-heat wave events) and its natural indirect effect through the mediator variable (NIE, the effect of the exposure to heat wave which operates through ozone).

Under the counterfactual (or potential outcomes) framework, the NDE is the contrast between mortality risk on heat wave and non-heat wave days holding ozone levels at the value they take on non-heat wave days. The NIE in contrast compares the mortality risk when ozone is at levels observed on heat wave days versus non heat wave days, holding the exposure to a heat wave. In other words, the NIE represents the risk of death when exposure to heat wave is held constant and ozone changes by 1 unit increase to what it would have been for a change in the absence of heat wave.

In order to estimate the NDE and the NIE, two multilevel regression models were fitted following "the Product method" formalized by Baron and Kenny in 1986 (40) and adapted more recently under the potential outcome framework (41–43). For each city, a quasi-Poisson regression (allowing for over-dispersion) was first used for the outcome model, which models daily mortality (**Y**) as a function of heat wave episodes (**hw**), ozone concentration levels (**o3**) and a set of covariates **c** including day of week, bank holidays, calendar month, and two temporal indicators, one for the day of the season going from 1 at the 1st of June until 122 for 30th of September (with 4 degrees of freedom), one for long-term trend (with 4 degrees of freedom) to address potential confounding by long-term trends at a time scale of approximately 4 years (44–47). Among confounding factors which can influence both daily mortality and ozone formation (being one of its precursors), average nitrogen dioxide (NO_2) concentrations levels of the 2 previous days were also included in the set of covariate **c**.

$$E[Y|hw, o3, c] = exp\left(\theta_0 + \theta_1 hw + \theta_2 o3 + \sum \theta_n c_n\right) \tag{1}$$

Then the mediator model was estimated through a linear regression linking ozone concentration levels to heat wave exposure and to the same set of covariates.

$$E[o3|hw, c] = \ \beta_0 + \beta_1 hw + \sum \beta_n \, c \tag{2}$$

The natural direct effect is given by the exponential of the coefficient θ_1 associated to the heat wave variable (**hw**) in the outcome regression model:

$$NDE = \exp(\theta_1) \tag{3}$$

while de NIE is given by the exponential of the product of the coefficient $\theta_1$and the coefficient β_1 associated to the heat wave variable (**hw**) in the mediator model:

$$NIE = \exp(\theta_1 \beta_1) \tag{4}$$

The TE will be given then by the product of these two components.

Sensitivity analyses accounting for potential exposure-mediator interaction were performed through the four-way decomposition method in order to verify whether the overall effect of the temperature on mortality can be decomposed into four components: the portion of the effect that is due to neither mediation nor interaction (the controlled direct effect, CDE), the portion due to just interaction (but not mediation, the reference interaction), the one due to both mediation and interaction (the mediated interaction), and the proportion due to just mediation (but not interaction, the pure indirect effect) (48). In the absence of an exposure-mediator interaction, like in the model presented above, the natural direct effect (NDE) coincides with the controlled direct effect (CDE) and they can be interpreted interchangeably.

When interpreting TEs, NIEs and NDEs we assumed no unmeasured confounding or mediator-outcome confounder affected by the exposure.

TEs, NDEs and NIEs, expressed in terms of Relative Risk (RR), and their 95% Confidence Intervals (CIs) were computed using bootstrapping procedures (700 replications). Urban agglomeration-specific estimates were then combined in a meta-analysis using random-effect models in order to obtain pooled estimates. The presence of heterogeneity was tested and reported using an I^2 statistic, which describes the percentage of variation across agglomeration-specific estimates that is due to heterogeneity rather than chance (49).

Finally, the proportion mediated (PM) was calculated for each urban agglomeration to quantify the contribution of ozone in the excess risk of mortality during heat wave days, using the following formula:

$$PM = RR_{NDE}(RR_{NIE} - 1)/(RR_{NDE} * \ RR_{NIE} - 1) \tag{5}$$

We also conducted additional sensitivity analyses (see details in **Web Appendix**) in which we: i) restricted heat wave and non-heat wave days with overlapping ozone values; ii) removed the year 2003 because of the major heat wave impacting France and iii) explored other heat wave definitions.

All analysis were conducted using the R programming language, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) in the integrated development environment of RStudio (RStudio, PBC, Boston, Massachusetts), using the package *metafor* for meta-analysis and forest plot (50).

Results

During the study period, mean temperatures for the period from June to September varied considerably between urban agglomerations, from a mean value of 16.7 °C in the Rouen agglomeration to a value of 23.3 °C in the Marseille agglomeration. The initial threshold values triggering the beginning of a heat wave and corresponding to the 97.5th percentile of the distribution of temperature values within each urban agglomeration and during the full year varied from a minimum of 21.0 °C in Le Havre agglomeration to a maximum of 27.3 °C in Marseille agglomeration (**Table 2**). The highest value for the peak threshold (99.5th percentile) was reached in Lyon (29.19 °C), while the lowest corresponded again to Le Havre agglomeration (23.99 °C). Complete information about the number of observed days (after selection of summer months and exclusion of day with missing data for mean temperature, ozone and NO_2 concentrations), about temperature values and the number of heat-wave days for each urban agglomeration are provided in **Table 2**. Temperature distributions for each urban agglomeration are also represented in **Figure 2**Erreur ! Source du renvoi introuvable.. Daily concentrations for ozone varied from an average of 50.1 $\mu g/m^3$ in Rouen agglomeration to 77.64 $\mu g/m^3$ in Nice agglomeration. Ozone concentrations values and distributions for each urban agglomeration are provided in **Table 2** and in **Figure 3**.

A total of 450,727 deaths from non-accidental causes were recorded during summer periods from 2000 until 2015, across all the urban agglomerations considered; 117,047 of them were due to cardiovascular causes and 25,438 were due to respiratory causes. For each urban agglomeration, daily mortality was higher during days experiencing a heat wave episode than during normal days (**Table 3** and **Web Figures 1-3**). In a large urban center such as Paris, daily mortality was 2-fold or almost 3-fold higher (for respiratory mortality) during heat-waves compared to the other days of the summer (see **Table 3**). In medium and small size agglomerations (all the agglomerations considered except Paris, Lyon and Marseille) the mean difference in daily mortality between heat-wave days and non-heat-wave days was 3 deaths for non-accidental causes, 1 death for cardiovascular causes, while the mean difference for respiratory mortality was below 1.

Mediation analysis

Non-accidental mortality

After adjustment for calendar variables and ozone and lagged NO_2 concentrations, associations between the occurrence of a heat waves and non-accidental mortality were identified in all urban agglomerations, with a RR_{te} varying from 1.91 in Paris (95% CI: 1.38 to 2.45) to a small RR_{te} for Montpellier (1.18, 95% CI: 0.99 to 1.36) (**Web Table 1** and **Figure 4a**). The estimated NDEs showed a stronger effect in Paris (RR_{nde}=1.81, 95% CI: 1.31 to 2.30) and Bordeaux (RR_{nde}=1.57, 95% CI: 1.33 to 1.81) agglomerations and a weaker effect with 95% CI overlapping the value of 1 in Montpellier agglomeration (RR_{nde}=1.15, 95% CI: 0.97 to 1.34). As showed in **Figure 4b,** the pooled estimate for NDE among all urban agglomerations was 1.33 (95% CI: 1.26 to 1.40), with some heterogeneity across urban agglomerations (I^2 = 47.06%). A weak mediation effect was observed in almost all urban agglomerations, except for Nancy, Bordeaux and Le Havre (**Figure 4c**). Several RRs estimated for NIE showed large confidence intervals, in particular among agglomeration with oceanic climate profile (i.e. Le Havre, Nantes, Rennes, Rouen). The pooled RR for NIE was estimated to be 1.03 (95% CI: 1.02 to 1.05), with substantial heterogeneity across locations (I^2=63.31%). The proportion of risk mediated by the exposure to ozone for non-accidental mortality varied from 31% in Nantes to 5% in Nice (**Web Table 1**).

Cardiovascular Mortality

Results on cardiovascular mortality confirmed an effect of heat wave exposure as well as a mediation effect through ozone for some urban agglomerations (see **Web Table 2** and **Figure 4**). TE and NDE estimates were higher than for non-accidental mortality (for example for Clermont-Ferrand [RR_{te}=1.89, 95% CI: 1.45 to 2.32] and for Paris [RR_{te}=1.99 95% CI: 1.38 to 2.59]) but, for several urban agglomerations, more imprecise (**Web Table 2**). Consequently, the pooled estimate for NDE was higher than the one obtained for non-accidental mortality (1.38, 95% CI: 1.26 to 1.51) but with a larger confidence interval, which is due to the smaller number of cardiovascular deaths. Some heterogeneity across agglomerations was also observed for this estimate (I^2=53.30%).

The estimates for NIE on cardiovascular deaths were weak and not statistically different from 1 for almost all the urban agglomerations except Le Havre (RR_{nie}= 1.16, 95% CI: 1.03, 1.28) and Nantes (RR_{nie}= 1.11, 95% CI: 1.02, 1.21), Paris (RR_{nie}= 1.06, 95% CI: 1.01, 1.10), Toulouse (RR_{nie}= 1.07, 95% CI: 1.02, 1.13) and Grenoble (RR_{nie}= 1.08, 95% CI: 1.02, 1.15). Similarly to non-accidental mortality, the pooled value for NIE for cardiovascular mortality was 1.03, with a 95% CI going from 1.01 to 1.04 and moderate heterogeneity across locations (I^2=44.87%). The proportion of cardiovascular mortality risk mediated by ozone varied from 42% in Le Havre to 11% in Paris (**Web Table 2**).

Respiratory Mortality

Associations between the occurrence of heat waves and respiratory mortality were detected only in some, more populated, urban agglomerations, namely Paris (RR_{te}=2.30, 95% CI: 1.63 to 2.98), Lyon (RR_{te}=2.38, 95% CI: 1.74 to 3.03), Bordeaux (RR_{te}=2.35, 95% CI: 1.52 to 3.18), Marseille (RR_{te}=1.40, 95% CI: 1.02 to 1.77) and Toulouse (RR_{te}=1.56, 95% CI: 1.06 to 2.06) agglomerations, as well as in one smaller agglomeration like Strasbourg (RR_{te}=2.09, 95% CI: 1.45 to 2.73) (**Web Table 3** and **Figure 4g**). Estimates for NDEs were generally more imprecise for this mortality cause than for the two others, and they were generally not statistically different for 1, except for the aforementioned agglomerations (**Figure 4h**). The pooled RR for the NDE was estimated to be 1.67, with a 95% CI going from 1.47 to 1.86, and weak heterogeneity was observed across urban agglomerations (I^2=17.01%). Mediation effects were detected only in Nantes (RR_{nie}=1.29, 95% CI: 1.05 to 1.52), Lyon (RR_{nie}=1.16, 95% CI: 1.07, 1.25) and in Paris (RR_{nie}=1.08, 95% CI: 1.03 to 1.13). The proportion of respiratory mortality risk mediated through ozone in these agglomerations was 14% in Paris, 23% in Lyon and 57% in Nantes. The pooled RR estimated for the NIE was 1.04 (95% IC: 1.00 to 1.07), with some heterogeneity across locations (I^2=44.66%). We tested the presence of a possible exposure-mediator interaction and no evidence of an interaction effect was found for any of the three causes of mortality. Description and results for sensitivity analyses are included in **Web Appendix**, **Web Tables 4-7** and **Web Figures 4-10**.

Discussion

Our analysis showed that the effect of heat waves on mortality may be partially mediated through ozone with important variability across French urban agglomerations. In some agglomerations, like Nantes, mediation through ozone accounted for 31% of the total risk associated with heat wave exposure on non-accidental mortality, for 35% on cardiovascular mortality and for up to 57% on respiratory mortality. In contrast, in few urban agglomerations like Nancy, evidence of a mediation effect of heat wave exposure through ozone was not found for cardiovascular, respiratory mortality risk, or non-accidental mortality risk. Some heterogeneity was found across different locations studied in the decomposition of the total effect of heat wave on non-accidental and cardiovascular mortality, while heterogeneity was less important when considering respiratory mortality.

These results are valuable for several reasons. First, from an etiological point of view, understanding the mechanisms driving the effect of high temperatures on population health through ozone has important implications for risk assessment; it allows to better understand the excess of mortality observed during heat waves. Both extreme temperatures and exposure to ozone concentrations have been shown to have adverse health effects and several epidemiological studies confirmed that mortality or morbidity risk associated with extreme temperatures is larger on days with elevated ozone concentrations (12,15,19,51,52). Our results regarding total effects are comparable to previous studies conducted in France focusing on the effects of extreme heat and mortality (1,36,44). Our mediation analysis contributes to a better understanding of this phenomenon by suggesting that, as a secondary pollutant that is generated by photochemical processes occurring during warm days, ozone can be considered a causal intermediate between heat waves and population health (10). Understanding where and when theses mechanisms operate can help to determine the proportion of mortality/morbidity due to heat exposure itself and which portion is attributable to ozone concentrations exposure. This could be particularly important not only for etiological reasons, but also in the perspective of adapting public health interventions. National early warning systems and HHWSs have been widely developed in the last decades (28). HHWSs use weather-based forecasting to predict the occurrence of a heat wave event in order to alert stakeholders and trigger preventing measures to inform the general public and protect vulnerable populations. The definition of a heat wave varies by region and country according to geographic, population and climatic characteristics, and it can be settled on different event-duration criteria and based on threshold values for temperature or on biometeorological index value that have significant health effects (25–27).

Even though evaluations of the effectiveness of HHWSs are still scarce in the literature (25,53), some studies reported a reduction in health impacts of heat waves following their implementation (54–56), while other reported limited effects (53). Moreover, systems of air quality alerts (AQA) have been widely adopted in various big cities in different countries in order to prevent adverse health events associated with episodes of extreme air pollutant levels (defined as “air pollution episodes”), which are identified through specific threshold values (57). These systems are focused on reducing emissions on days when air pollution concentrations exceed a given threshold and, despite their widespread acceptance, evidence about their impacts on population health is still limited (29–34). Preventive actions for the reduction of ozone precursors (e.g. traffic related emissions) where a mediation effect is detected can help mitigating the total effects of heat waves on population health (58).

Results of our study showed some spatial variation among studied cities. There are a few possible reasons to explain such heterogeneity. First, ozone formation during heat wave may vary across cities depending on several factors. Indeed, ozone formation is based on complex photochemical process and is directly linked to the presence of NO_2 and the oxidation of volatile organic compounds (VOC). For a given NO_2 concentration, ozone production rates can vary significantly depending on the VOC presence (59) and the level of sunlight which varies considerably across cities in France. Other factors, like wind intensity and direction, can also drive tropospheric ozone concentrations in urban environments (60). Second, health effects of ozone exposure may vary across cities due to differences in several socio-demographic factors that have been shown to shape population vulnerability to air pollution. In particular, older individuals and communities with low socio-economic status have been shown to be particularly susceptible to ozone (61–64).

Some limitations have to be pointed out. First, we focused on the official climatologic heat wave definition which corresponds to a small number of heat waves. This impacted the statistical power of our analysis, especially for small-size urban agglomerations and for some specific causes of mortality. This may explain the absence of a precise mediation effect detected on respiratory mortality in most of the urban agglomerations studied. Second, we did not take into account a possible lag structure for heat wave effects and we did not consider the effect of a continuous variable for temperature, which would likely have a non-linear relation with mortality. However, the choice of considering heat waves as a binary exposure (heat wave and non-heat wave days) is more pertinent when referring to the policy approach generally adopted in HHWSs. Finally, our observations were at the urban-agglomeration scale and a finer spatial resolution would allow more precise and reliable estimations; indeed, we only considered city-level exposures and we had no access to the information about individual exposures that people actually experience.

Some factors, which could not be integrated in our analysis, would be interesting to consider for future research: for example, the potential benefit on mortality of the French HHWS started in 2004 could be considered and integrated in the analysis, as well as a possible difference in the health effect of heat waves according to their timing during the season, for which a heat wave occurring at the beginning of the summer may not have the same effect on the population health than one occurring at the end of the summer (65,66).

Conclusion

Using empirical data, this study decomposed the total effect of heat wave on mortality in 15 urban agglomerations in France in summers from 2000 until 2015. Our results show that the effect of heat waves on mortality is partially mediated through ozone; this means that heat waves impact human health not only by exposing populations to extreme hot temperatures, but also by generating higher ozone concentrations. This is the first epidemiological study which empirically assesses which proportion of mortality is due to exposure to heat itself and which portion is attributable to ozone concentrations exposure. Further studies in other countries with different climate profiles and population susceptibilities would be useful to better understand the role of ozone as a mediator in the relationship between heat waves and mortality.

References

1. Pascal M, Wagner V, Corso M, et al. Heat and cold related-mortality in 18 French cities. *Environ. Int.* [electronic article]. 2018;121(June):189–198. (https://doi.org/10.1016/j.envint.2018.08.049)

2. Guo Y, Gasparrini A, Armstrong BG, et al. Temperature variability and mortality: A multi-country study. *Environ. Health Perspect.* 2016;124(10):1554–1559.

3. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet*. 2015;14(6):464–465.

4. Basu R. High ambient temperature and mortality: A review of epidemiologic studies from 2001 to 2008. *Environ. Heal. A Glob. Access Sci. Source*. 2009;8(1).

5. Ponjoan A, Blanch J, Alves-Cabratosa L, et al. Effects of extreme temperatures on cardiovascular emergency hospitalizations in a Mediterranean region: a self-controlled case series study. *Environ. Heal. A Glob. Access Sci. Source*. 2017;16(1):1–9.

6. Anderson BG, Bell ML. Weather-related mortality: How heat, cold, and heat waves affect mortality in the United States. *Epidemiology*. 2009;20(2):205–213.

7. Magzamen S, Moore BF, Yost MG, et al. Ozone-Related Respiratory Morbidity in a Low-Pollution Region. *J. Occup. Environ. Med.* 2017;59(7):624–630.

8. Vicedo-Cabrera AM, Sera F, Liu C, et al. Short term association between ozone and mortality: global two stage time series study in 406 locations in 20 countries. *BMJ*. 2020;368:1–10.

9. Buckley JP, Samet JM, Richardson DB. Does air pollution confound studies of temperature? *Epidemiology*. 2014;25(2):242–245.

10. Reid CE, Snowden JM, Kontgis C, et al. The role of ambient ozone in epidemiologic studies of heat-related mortality. *Environ. Health Perspect.* 2012;120(12):1627–1630.

11. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615–625.

12. Analitis A, De' Donato F, Scortichini M, et al. Synergistic effects of ambient temperature and air pollution on health in europe: Results from the PHASE project. *Int. J. Environ. Res. Public Health*. 2018;15(9):1–11.

13. Breitner S, Wolf K, Devlin RB, et al. Short-term effects of air temperature on mortality and effect modification by air pollution in three cities of Bavaria, Germany: A time-series analysis. *Sci. Total Environ.* [electronic article]. 2014;485–486(1):49–61. (http://dx.doi.org/10.1016/j.scitotenv.2014.03.048)

14. Lee W, Choi HM, Kim D, et al. Synergic effect between high temperature and air pollution on mortality in Northeast Asia. *Environ. Res.* [electronic article]. 2019;178(September):108735. (https://doi.org/10.1016/j.envres.2019.108735)

15. Chen K, Wolf K, Breitner S, et al. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. *Environ. Int.* [electronic article]. 2018;116(December 2017):186–196. (https://doi.org/10.1016/j.envint.2018.04.021)

16. Burkart K, Canário P, Breitner S, et al. Interactive short-term effects of equivalent temperature and air pollution on human mortality in Berlin and Lisbon. *Environ. Pollut.* [electronic article]. 2013;183:54–63. (http://dx.doi.org/10.1016/j.envpol.2013.06.002)

17. Anenberg SC, Haines S, Wang E, et al. Synergistic health effects of air pollution, temperature, and pollen exposure: a systematic review of epidemiological evidence. *Environ. Heal. A Glob. Access Sci. Source*. 2020;19(1).

18. Pattenden S, Armstrong B, Milojevic A, et al. Ozone, heat and mortality: Acute effects in 15 British conurbations. *Occup. Environ. Med.* 2010;67(10):699–707.

19. Scortichini M, De Sario M, De’donato FK, et al. Short-term effects of heat on mortality and effect modification by air pollution in 25 italian cities. *Int. J. Environ. Res. Public Health*. 2018;15(8).

20. Guo Y, Gasparrini A, Li S, et al. Quantifying excess deaths related to heatwaves under climate change scenarios: A multicountry time series modelling study. *PLoS Med.* 2018;15(7):1–17.

21. Doherty RM, Heal MR, Wilkinson P, et al. Current and future climate- and air pollution-mediated impacts on human health. *Environ. Heal. A Glob. Access Sci. Source*. 2009;8(SUPPL. 1):1–8.

22. Doherty RM, Heal MR, O’Connor FM. Climate change impacts on human health over

Europe through its effect on air quality. *Environ. Heal. A Glob. Access Sci. Source*. 2017;16(Suppl 1).

23. Horne JR, Dabdub D. Impact of global climate change on ozone, particulate matter, and secondary organic aerosol concentrations in California: A model perturbation analysis. *Atmos. Environ.* [electronic article]. 2017;153(2017):1–17. (http://dx.doi.org/10.1016/j.atmosenv.2016.12.049)

24. Nolte CG, Spero T, Bowden JH, et al. The potential effects of climate change on air quality across the conterminous U.S. at 2030 under three Representative Concentration Pathways. *Atmos. Chem. Phys.* 2018;1–33.

25. Kovats RS, Kristie LE. Heatwaves and public health in Europe. *Eur. J. Public Health*. 2006;16(6):592–599.

26. Lowe D, Ebi KL, Forsberg B. Heatwave early warning systems and adaptation advice to reduce human health consequences of heatwaves. *Int. J. Environ. Res. Public Health*. 2011;8(12):4623–4648.

27. McElroy S, Schwarz L, Green H, et al. Defining heat waves and extreme heat events using sub-regional meteorological data to maximize benefits of early warning systems to population health. *Sci. Total Environ.* [electronic article]. 2020;721:137678. (https://doi.org/10.1016/j.scitotenv.2020.137678)

28. Casanueva A, Burgstall A, Kotlarski S, et al. Overview of existing heat-health warning systems in Europe. *Int. J. Environ. Res. Public Health*. 2019;16(15).

29. Lin, Cyc Zhang, Wei Umanskaya VI. The Effects of Driving Restrictions on Air Quality: São Paulo, Bogotá, Beijing, and Tianjin. *Agric. Appl. ...* [electronic article]. 2011;(http://ageconsearch.umn.edu/bitstream/103381/2/Wei_AAEA_2011_Driving restrictions.pdf)

30. Mullins J, Bharadwaj P. Effects of short-term measures to curb air pollution: Evidence From Santiago, Chile. *Am. J. Agric. Econ.* 2015;97(4):1107–1134.

31. Chen H, Li Q, Kaufman JS, et al. Effect of air quality alerts on human health: a regression discontinuity analysis in Toronto, Canada. *Lancet Planet. Heal.* 2018;2(1):e2–e3.

32. Neidell M. Air quality warnings and outdoor activities: Evidence from Southern

California using a regression discontinuity design. *J. Epidemiol. Community Health*. 2009;64(10):921–926.

33. Mason TG, Mary Schooling C, Ran JJ, et al. Does the AQHI reduce cardiovascular hospitalization in Hong Kong’s elderly population? *Environ. Int.* 2020;135(November 2019):1–8.

34. Mason TG, Schooling CM, Chan KP, et al. An evaluation of the air quality health index program on respiratory diseases in Hong Kong: An interrupted time series analysis. *Atmos. Environ.* [electronic article]. 2019;211(April):151–158. (https://doi.org/10.1016/j.atmosenv.2019.05.013)

35. WHO for European. Air Quality Guidelines. *Air Qual. Guidel.* 2006;(91):1–496.

36. Pascal M, Wagner V, Alari A, et al. Extreme heat and acute air pollution episodes: A need for joint public health warnings? *Atmos. Environ.* 2021;249(January):118249.

37. Soubeyroux J-M, Ouzeau G, Schneider M, et al. Les vagues de chaleur en France : analyse de l’été 2015 et évolutions attendues en climat futur. *La Météorologie*. 2016;8(94):45.

38. European Environmental Agency. Data - Air Quality e-Reporting (AQ e-Reporting). *April 25, 2018*. (https://www.eea.europa.eu/ds_resolveuid/DAT-3-en)

39. Grange SK. saqgetr: Import Air Quality Monitoring Data in a Fast and Easy Way. *January 12, 2021*. (https://cran.r-project.org/package=saqgetr). (Accessed March 15, 2021)

40. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* 1986;51(6):1173–1182.

41. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3:143–55.

42. Pearl J. Direct and Indirect Effects. In: *UAI ’01: Proceedings of the 17th Conference in Uncertainty in Artificial Intelligence*. 2001:411–420.

43. VanderWeele TJ. Mediation Analysis: A Practitioner’s Guide. *Annu. Rev. Public Health*. 2016;37:17–32.

44. Guo Y, Gasparrini A, Armstrong BG, et al. Heat wave and mortality: A multicountry, multicommunity study. *Environ. Health Perspect.* 2017;125(8):1–11.

45. Hajat S, Armstrong B, Baccini M, et al. Impact of high temperatures on mortality: Is there an added heat wave effect? *Epidemiology*. 2006;17(6):632–638.

46. Gasparrini A, Armstrong B. The impact of heat waves on mortality. *Epidemiology*. 2011;22(1):68–73.

47. Zeng W, Lao X, Rutherford S, et al. The effect of heat waves on mortality and effect modifiers in four communities of Guangdong Province, China. *Sci. Total Environ.* [electronic article]. 2014;482–483(1):214–221. (http://dx.doi.org/10.1016/j.scitotenv.2014.02.049)

48. VanderWeele TJ. A unificaiton of mediation and interaction: a four-way decomposition : eAppendix. *Epidemiology*. 2014;206(i):1–15.

49. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *Br. Med. J.* 2003;327(7414):557–560.

50. Wolfgang Viechtbauer. metafor: Meta-Analysis Package for R. 2010;

51. Analitis A, Michelozzi P, D'Ippoliti D, et al. Effects of heat waves on mortality: Effect modification and confounding by air pollutants. *Epidemiology*. 2014;25(1):15–22.

52. Ren C, Williams GM, Morawska L, et al. Ozone modifies associations between temperature and cardiovascular mortality: Analysis of the NMMAPS data. *Occup. Environ. Med.* 2008;65(4):255–260.

53. Weinberger KR, Zanobetti A, Schwartz J, et al. Effectiveness of National Weather Service heat alerts in preventing mortality in 20 US cities. *Environ. Int.* [electronic article]. 2018;116(April):30–38. (https://doi.org/10.1016/j.envint.2018.03.028)

54. Fouillet A, Rey G, Wagner V, et al. Has the impact of heat waves on mortality changed in France since the European heat wave of summer 2003? A study of the 2006 heat wave. *Int. J. Epidemiol.* 2008;37(2):309–317.

55. Toloo G, Fitzgerald G, Aitken P, et al. Evaluating the effectiveness of heat warning systems: Systematic review of epidemiological evidence. *Int. J. Public Health*. 2013;58(5):667–681.

56. Benmarhnia T, Schwarz L, Nori-Sarma A, et al. Quantifying the impact of changing the threshold of New York City heat emergency plan in reducing heat-related illnesses. *Environ. Res. Lett.* 2019;14(11):114006.

57. World Health Organization (WHO). WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Geneva, Switzerland: World Health Organization. Occupational and Environmental Health Team. (2006) (WHO publication no. WHO/SDE/PHE/OEH/06.02) (http:// https://apps.who.int/iris/handle/10665/69477).

58. Loughner CP, Follette-Cook MB, Duncan BN, et al. The benefits of lower ozone due to air pollution emission reductions (2002–2011) in the Eastern United States during extreme heat. *J. Air Waste Manag. Assoc.* [electronic article]. 2020;70(2):193–205. (http://dx.doi.org/10.1080/10962247.2019.1694089)

59. Camredon M, Aumont B. Chemical modelling of ozone and gaseous oxidants. *Pollut. Atmosphérique*. 2007;193(1):51–90.

60. Pont V, Fontan J. Local and regional contributions to photochemical atmospheric pollution in southern France. *Atmos. Environ.* 2000;34(29–30):5209–5223.

61. Kihal-Talantikite W, Legendre P, Le Nouveau P, et al. Premature adult death and equity impact of a reduction of no2, pm10, and pm2.5 levels in paris—A health impact assessment study conducted at the census block level. *Int. J. Environ. Res. Public Health*. 2019;16(1).

62. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *Am. J. Epidemiol.* 2013;178(6):865–876.

63. Medina-Ramón M, Schwartz J. Who is more vulnerable to die from ozone air pollution? *Epidemiology*. 2008;19(5):672–679.

64. Bell ML, Zanobetti A, Dominici F. Who is more affected by ozone pollution? A systematic review and meta-analysis. *Am. J. Epidemiol.* 2014;180(1):15–28.

65. Achebak H, Devolder D, Ingole V, et al. Reversal of the seasonality of temperature-attributable mortality from respiratory diseases in Spain. *Nat. Commun.* [electronic article]. 2020;(2020). (http://dx.doi.org/10.1038/s41467-020-16273-x)

66. Nori-Sarma A, Benmarhnia T, Rajiva A, et al. Advancing our understanding of heat wave criteria and associated health impacts to improve heat wave alerts in developing country settings. *Int. J. Environ. Res. Public Health*. 2019;16(12):1–13.

Tables

Table 1. Main demographic, geographic and climatic information for the 15 French urban agglomerations included in the study, 2000-2015.

Urban Agglomeration	Weather station (Météo-France name)	Longitude (°)	Latitude (°)	Altitude (m)	N municipalities in the area	Population (2010)
Oceanic climate						
Bordeaux	Bordeaux Merignac[a]	-0.57	44	16	22	651,902
Le Havre	Le Havre – Cap de la Hève	0.13	49	70	16	241,037
Nantes	Nantes-Bougenais[a]	-1.55	47	20	27	601,460
Rennes	Rennes Saint-Jacques[a]	-1.68	48	35	4	240,769
Rouen	Rouen-Boos[a]	1.08	49	22	42	447,009
Temperate-oceanic climate						
Paris	Paris Montsouris	2.33	48	60	124	6,666,103
Toulouse	Toulouse Blagnac[a]	1.43	43	146	51	764,268
Semi-continental climate						
Clermont-Ferrand	Clermont-Ferrand	3.08	45	365	16	227,151
Grenoble	Grenoble[a]	5.72	45	212	46	472,741
Lyon	Lyon-Bron[a]	4.85	45	166	18	1,038,916
Nancy	Nancy-Essey[a]	6.2;	48	222	38	331,903
Strasbourg	Strasbourg – Entzheim[a]	7.75	48	144	20	440,426
Mediterranean climate						
Marseille	Aéroport de Marignane[a]	5.4;	43	20	8	970,751
Montpellier	Montpellier[a]	3.88	43	35	22	390,962
Nice	Nice[a]	7.25	43	10	4	435,428

[a] Airport stations

Table 2. Temperature and Ozone Distribution Values in 15 urban agglomerations in France, 2000-2015.

Urban Agglomeration	N obs	Temperature					N Heat Waves	Ozone		
		25 Perc	Mean	75 Perc	97.5 Perc[a]	99.5 Perc[b]		25 Perc	Mean	75 Perc
Bordeaux	1927	17.95	20.29	22.3	25.34	28.17	26	52.44	65.02	76.18
Le Havre	1943	15.26	16.97	18.2	21.00	23.99	23	51.4	60.67	68.09
Nantes	1950	16.33	18.42	20.23	23.25	26.16	24	50.22	62.75	72.59
Rennes	1909	15.9	17.93	19.75	22.35	25.30	32	42.07	54.1	62.82
Rouen	1950	14.54	16.72	18.46	21.53	24.07	25	38.24	50.1	60.06
Paris	1950	16.67	19.18	21.36	24.60	27.50	27	40.24	52.58	62.78
Toulouse	1950	18.7	21.18	23.61	26.20	28.46	29	54.5	66.82	77.79
Clermont-Ferrand	1944	16.35	19	21.5	24.70	27.84	24	53.17	65.23	76.07
Grenoble	1935	16.3	18.76	21.35	24.05	26.30	36	42.21	57.83	71.98
Lyon	1950	18	20.71	23.38	26.45	29.19	32	46.44	61.52	75.3
Nancy	1948	15.7	18.2	20.76	23.60	26.30	32	38.84	52.01	62.28
Strasbourg	1947	16.3	18.79	21.35	24.14	26.81	38	41.52	56.51	69.95
Marseille	1948	21.18	23.25	25.32	27.35	28.89	35	59.62	70.45	80.98
Montpellier	1937	20.7	22.62	24.6	26.84	28.34	28	62.5	73.17	83.7
Nice	1948	21.25	22.96	24.7	26.50	28.04	26	66.13	77.64	89.11

[a] Initial Threshold

[b] Peak Threshold

Table 3: Summer period[a] daily mortality for each French urban agglomeration[b] during normal days and during days experiencing a heat wave episode, 2000-2015.

Urban agglomeration	Non-accidental Causes						Cardiovascular Causes						Respiratory Causes					
	Non-Heat-Wave Days			Heat-Wave Days			Non-Heat-Wave Days			Heat-Wave Days			Non-Heat-Wave Days			Heat-Wave Days		
	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max
Temperate-oceanic climate																		
Paris	60	98.2	286	100	207.5	724	8	23.58	56	13	50.48	179	0	5.45	20	2	14.52	52
Toulouse	2	11.01	34	6	14.62	24	0	2.97	11	0	4.24	9	0	0.56	5	0	0.9	3
Semi-continental climate																		
Clermont	0	5.17	15	4	8.04	16	0	1.46	7	0	2.63	6	0	0.28	3	0	0.38	2
Grenoble	0	7.23	19	3	9.47	16	0	2.01	11	0	2.86	8	0	0.35	4	0	0.72	4
Lyon	4	16.97	36	11	27.78	75	0	4.43	14	2	7.09	22	0	0.89	5	0	2.41	7
Nancy	0	6.29	16	0	9.31	24	0	1.66	7	0	2.66	10	0	0.41	4	0	0.84	4
Strasbourg	1	7.86	18	7	12.32	22	0	2.21	9	0	3.45	7	0	0.44	6	0	0.95	3
Oceanic climate																		
Bordeaux	2	11.54	25	7	18.58	36	0	3.26	13	3	5.81	12	0	0.66	5	0	1.65	6
Le-Havre	0	5.28	14	2	6.96	15	0	1.37	8	0	2	6	0	0.29	3	0	0.52	2
Nantes	1	9.48	23	7	12.88	32	0	2.58	11	0	3.54	10	0	0.51	6	0	1.04	4
Rennes	0	3.57	12	2	5.03	9	0	1.07	5	0	1.58	6	0	0.24	3	0	0.48	3
Rouen	1	9.03	23	6	13.72	28	0	2.49	12	0	3.4	8	0	0.5	5	0	0.96	3
Mediterranean climate																		
Marseille	7	20.09	39	12	24.89	40	0	5.6	17	2	6.29	14	0	1.26	7	0	1.89	5
Montpellier	0	5.83	17	2	6.93	14	0	1.64	8	0	1.79	7	0	0.32	3	0	0.5	2
Nice	2	11.14	24	4	15.27	33	0	3.06	10	0	4.08	11	0	0.65	5	0	1	3

[a] from the 1st of June until the 30th of September

[b] ranked according to their climate profile

Figures Titles

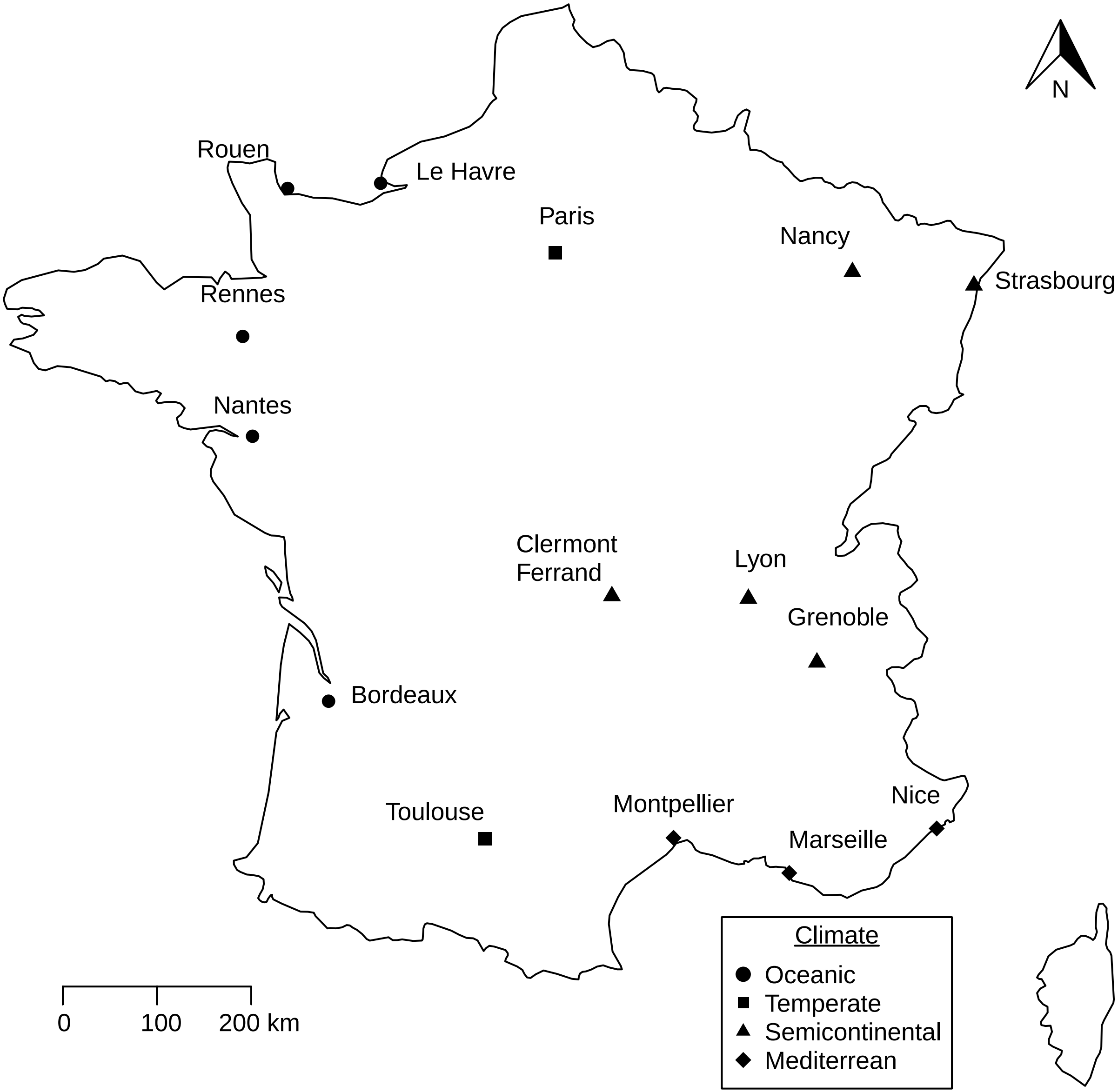
Figure 1. Maps of France and the urban agglomerations studied for the period going from 2000 until 2015.

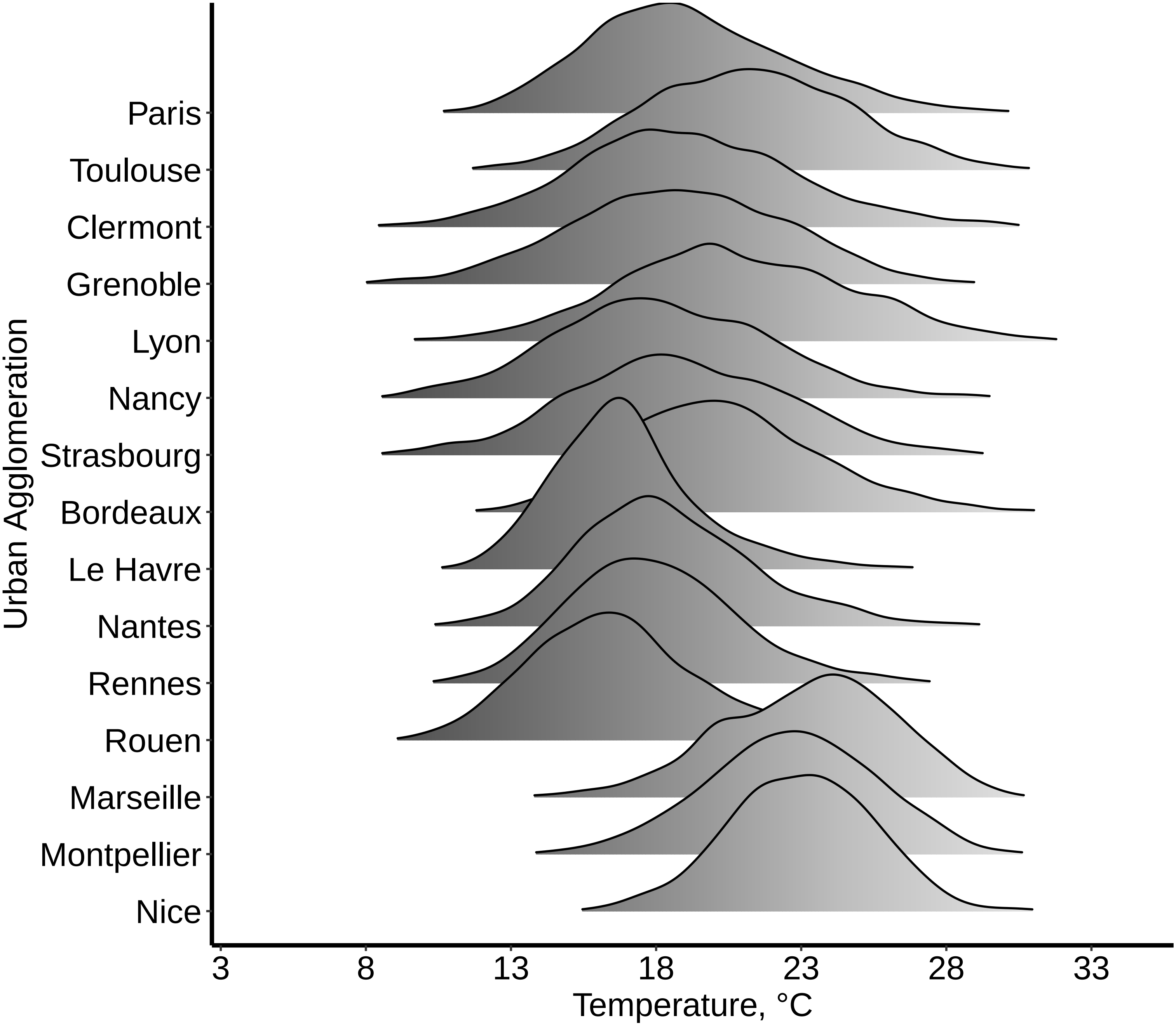
Figure 2. Temperature distributions for each city during summer months (from the 1st of June until the 30th of September) for the study period (2000-2015). French agglomerations are ranked according to their climate profile.

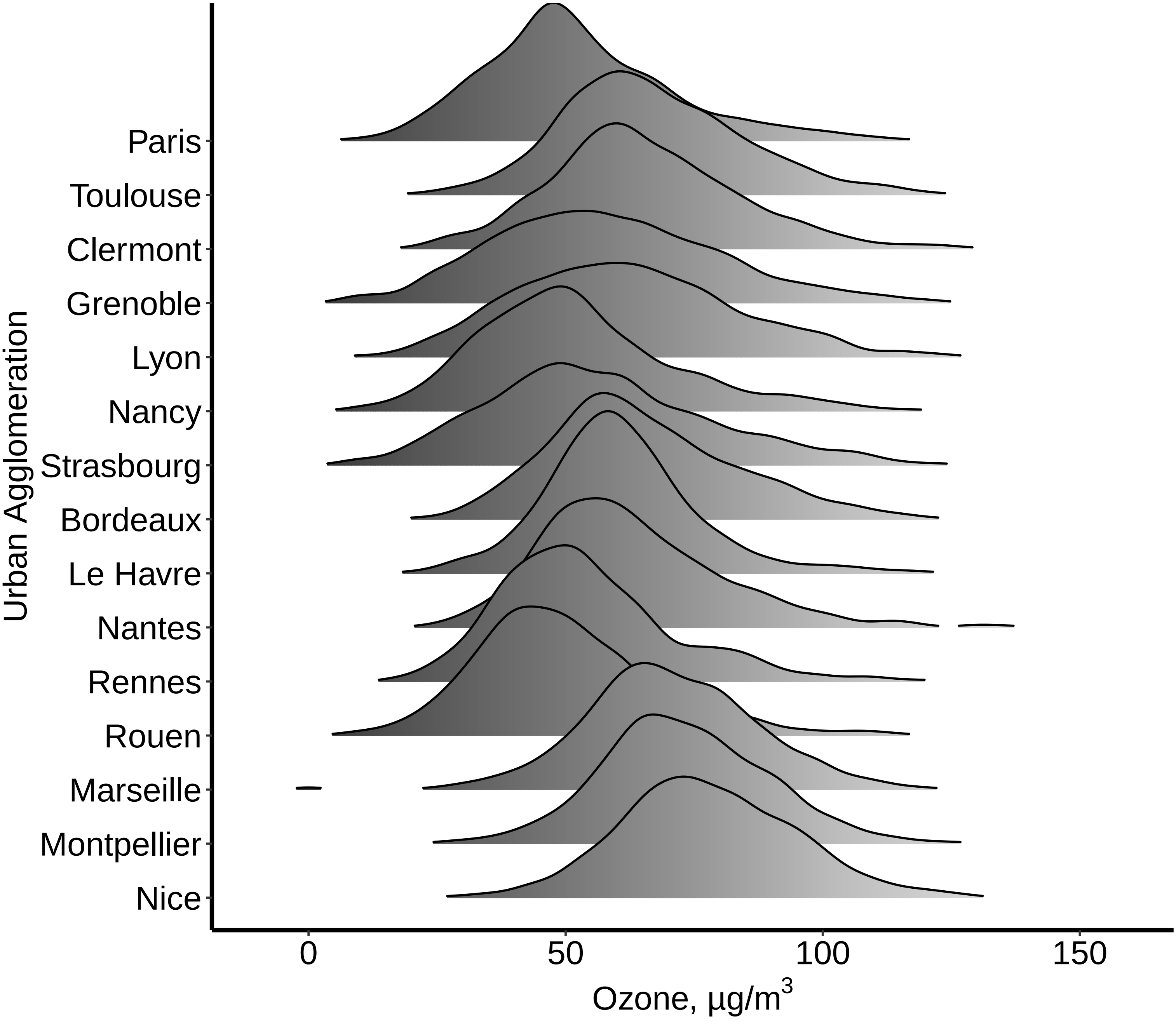
Figure 3. Ozone concentrations distributions for each city during summer months (from the 1st of June until the 30th of September) for the study period (2000-2015) French agglomerations are ranked according to their climate profile.

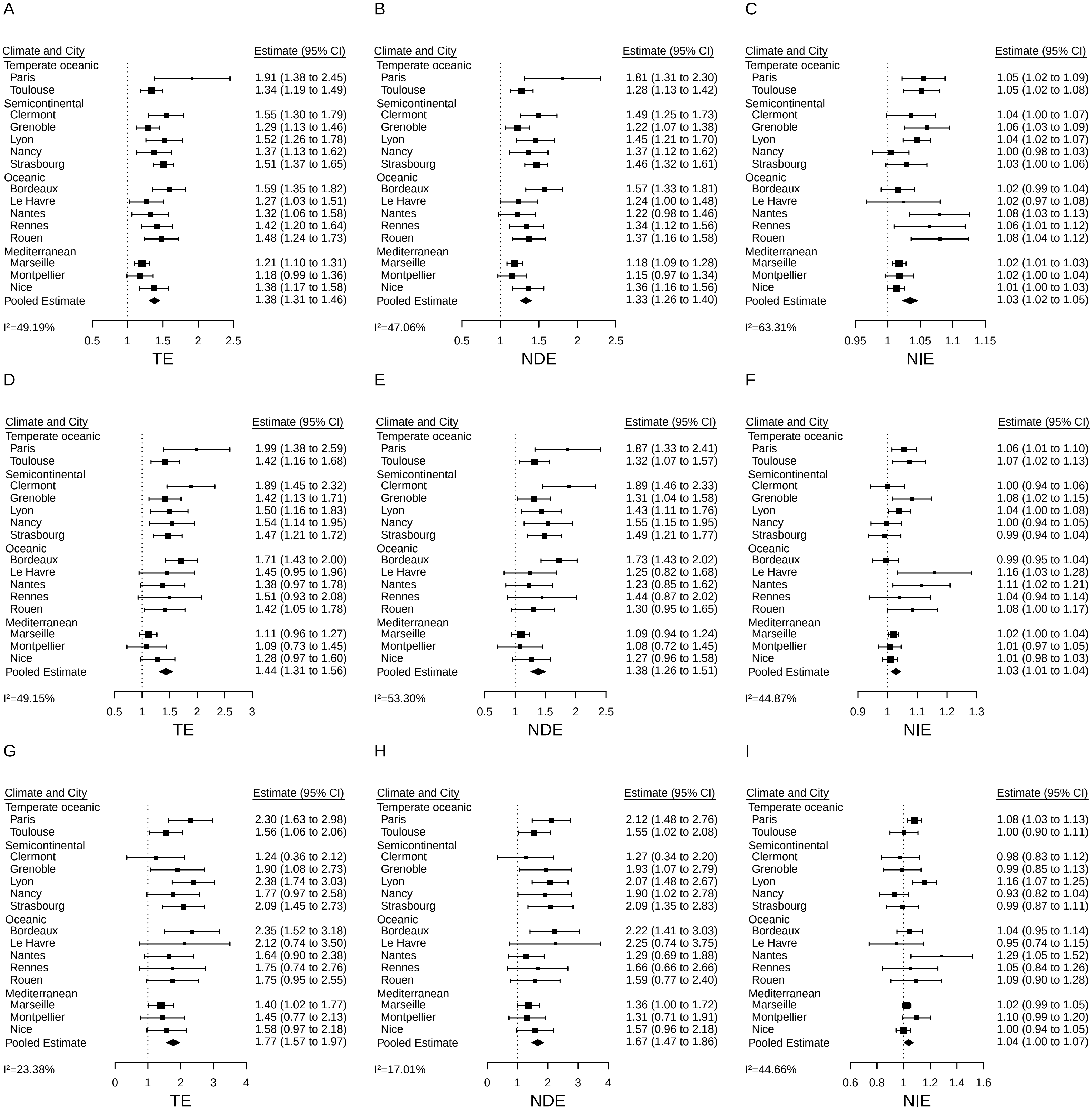
Figure 4. Agglomeration-estimates and pooled estimates for Non-accidental, Cardiovascular and Respiratory Mortality in France, 2000-2015.

Panels A, D and G show estimates for Total Effect (TE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality, respectively.
Panels B, E and H show estimates for Natural Direct Effect (NDE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality, respectively.
Panels C, F and I show estimates for Natural Indirect Effect (NIE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality, respectively.


N
Rouen
Le Havre
Paris
Nancy
Strasbourg
Rennes
Nantes
Clermont Ferrand
Lyon
Grenoble
Bordeaux
Toulouse
Montpellier
Nice
Marseille
Climate
● Oceanic
■ Temperate
▲ Semicontinental
◆ Mediterrean
0
100
200 km


Paris
Toulouse
Clermont
Grenoble
Lyon
Nancy
Strasbourg
Bordeaux
Le Havre
Nantes
Rennes
Rouen
Marseille
Montpellier
Nice
Urban Agglomeration
3
8
13
18
23
28
33
Temperature, °C


Paris
Toulouse
Clermont
Grenoble
Lyon
Nancy
Strasbourg
Bordeaux
Le Havre
Nantes
Rennes
Rouen
Marseille
Montpellier
Nice
Urban Agglomeration
0
50
100
150
Ozone, µg/m3


A
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.91 (1.38 to 2.45)
Toulouse 1.34 (1.19 to 1.49)
Semicontinental
Clermont 1.55 (1.30 to 1.79)
Grenoble 1.29 (1.13 to 1.46)
Lyon 1.52 (1.26 to 1.78)
Nancy 1.37 (1.13 to 1.62)
Strasbourg 1.51 (1.37 to 1.65)
Oceanic
Bordeaux 1.59 (1.35 to 1.82)
Le Havre 1.27 (1.03 to 1.51)
Nantes 1.32 (1.06 to 1.58)
Rennes 1.42 (1.20 to 1.64)
Rouen 1.48 (1.24 to 1.73)
Mediterranean
Marseille 1.21 (1.10 to 1.31)
Montpellier 1.18 (0.99 to 1.36)
Nice 1.38 (1.17 to 1.58)
Pooled Estimate 1.38 (1.31 to 1.46)
I²=49.19%
0.5 1 1.5 2 2.5
TE
B
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.81 (1.31 to 2.30)
Toulouse 1.28 (1.13 to 1.42)
Semicontinental
Clermont 1.49 (1.25 to 1.73)
Grenoble 1.22 (1.07 to 1.38)
Lyon 1.45 (1.21 to 1.70)
Nancy 1.37 (1.12 to 1.62)
Strasbourg 1.46 (1.32 to 1.61)
Oceanic
Bordeaux 1.57 (1.33 to 1.81)
Le Havre 1.24 (1.00 to 1.48)
Nantes 1.22 (0.98 to 1.46)
Rennes 1.34 (1.12 to 1.56)
Rouen 1.37 (1.16 to 1.58)
Mediterranean
Marseille 1.18 (1.09 to 1.28)
Montpellier 1.15 (0.97 to 1.34)
Nice 1.36 (1.16 to 1.56)
Pooled Estimate 1.33 (1.26 to 1.40)
I²=47.06%
0.5 1 1.5 2 2.5
NDE
C
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.05 (1.02 to 1.09)
Toulouse 1.05 (1.02 to 1.08)
Semicontinental
Clermont 1.04 (1.00 to 1.07)
Grenoble 1.06 (1.03 to 1.09)
Lyon 1.04 (1.02 to 1.07)
Nancy 1.00 (0.98 to 1.03)
Strasbourg 1.03 (1.00 to 1.06)
Oceanic
Bordeaux 1.02 (0.99 to 1.04)
Le Havre 1.02 (0.97 to 1.08)
Nantes 1.08 (1.03 to 1.13)
Rennes 1.06 (1.01 to 1.12)
Rouen 1.08 (1.04 to 1.12)
Mediterranean
Marseille 1.02 (1.01 to 1.03)
Montpellier 1.02 (1.00 to 1.04)
Nice 1.01 (1.00 to 1.03)
Pooled Estimate 1.03 (1.02 to 1.05)
I²=63.31%
0.95 1 1.05 1.1 1.15
NIE
D
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.99 (1.38 to 2.59)
Toulouse 1.42 (1.16 to 1.68)
Semicontinental
Clermont 1.89 (1.45 to 2.32)
Grenoble 1.42 (1.13 to 1.71)
Lyon 1.50 (1.16 to 1.83)
Nancy 1.54 (1.14 to 1.95)
Strasbourg 1.47 (1.21 to 1.72)
Oceanic
Bordeaux 1.71 (1.43 to 2.00)
Le Havre 1.45 (0.95 to 1.96)
Nantes 1.38 (0.97 to 1.78)
Rennes 1.51 (0.93 to 2.08)
Rouen 1.42 (1.05 to 1.78)
Mediterranean
Marseille 1.11 (0.96 to 1.27)
Montpellier 1.09 (0.73 to 1.45)
Nice 1.28 (0.97 to 1.60)
Pooled Estimate 1.44 (1.31 to 1.56)
I²=49.15%
0.5 1 1.5 2 2.5 3
TE
E
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.87 (1.33 to 2.41)
Toulouse 1.32 (1.07 to 1.57)
Semicontinental
Clermont 1.89 (1.46 to 2.33)
Grenoble 1.31 (1.04 to 1.58)
Lyon 1.43 (1.11 to 1.76)
Nancy 1.55 (1.15 to 1.95)
Strasbourg 1.49 (1.21 to 1.77)
Oceanic
Bordeaux 1.73 (1.43 to 2.02)
Le Havre 1.25 (0.82 to 1.68)
Nantes 1.23 (0.85 to 1.62)
Rennes 1.44 (0.87 to 2.02)
Rouen 1.30 (0.95 to 1.65)
Mediterranean
Marseille 1.09 (0.94 to 1.24)
Montpellier 1.08 (0.72 to 1.45)
Nice 1.27 (0.96 to 1.58)
Pooled Estimate 1.38 (1.26 to 1.51)
I²=53.30%
0.5 1 1.5 2 2.5
NDE
F
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.06 (1.01 to 1.10)
Toulouse 1.07 (1.02 to 1.13)
Semicontinental
Clermont 1.00 (0.94 to 1.06)
Grenoble 1.08 (1.02 to 1.15)
Lyon 1.04 (1.00 to 1.08)
Nancy 1.00 (0.94 to 1.05)
Strasbourg 0.99 (0.94 to 1.04)
Oceanic
Bordeaux 0.99 (0.95 to 1.04)
Le Havre 1.16 (1.03 to 1.28)
Nantes 1.11 (1.02 to 1.21)
Rennes 1.04 (0.94 to 1.14)
Rouen 1.08 (1.00 to 1.17)
Mediterranean
Marseille 1.02 (1.00 to 1.04)
Montpellier 1.01 (0.97 to 1.05)
Nice 1.01 (0.98 to 1.03)
Pooled Estimate 1.03 (1.01 to 1.04)
I²=44.87%
0.9 1 1.1 1.2 1.3
NIE
G
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 2.30 (1.63 to 2.98)
Toulouse 1.56 (1.06 to 2.06)
Semicontinental
Clermont 1.24 (0.36 to 2.12)
Grenoble 1.90 (1.08 to 2.73)
Lyon 2.38 (1.74 to 3.03)
Nancy 1.77 (0.97 to 2.58)
Strasbourg 2.09 (1.45 to 2.73)
Oceanic
Bordeaux 2.35 (1.52 to 3.18)
Le Havre 2.12 (0.74 to 3.50)
Nantes 1.64 (0.90 to 2.38)
Rennes 1.75 (0.74 to 2.76)
Rouen 1.75 (0.95 to 2.55)
Mediterranean
Marseille 1.40 (1.02 to 1.77)
Montpellier 1.45 (0.77 to 2.13)
Nice 1.58 (0.97 to 2.18)
Pooled Estimate 1.77 (1.57 to 1.97)
I²=23.38%
0 1 2 3 4
TE
H
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 2.12 (1.48 to 2.76)
Toulouse 1.55 (1.02 to 2.08)
Semicontinental
Clermont 1.27 (0.34 to 2.20)
Grenoble 1.93 (1.07 to 2.79)
Lyon 2.07 (1.48 to 2.67)
Nancy 1.90 (1.02 to 2.78)
Strasbourg 2.09 (1.35 to 2.83)
Oceanic
Bordeaux 2.22 (1.41 to 3.03)
Le Havre 2.25 (0.74 to 3.75)
Nantes 1.29 (0.69 to 1.88)
Rennes 1.66 (0.66 to 2.66)
Rouen 1.59 (0.77 to 2.40)
Mediterranean
Marseille 1.36 (1.00 to 1.72)
Montpellier 1.31 (0.71 to 1.91)
Nice 1.57 (0.96 to 2.18)
Pooled Estimate 1.67 (1.47 to 1.86)
I²=17.01%
0 1 2 3 4
NDE
I
Climate and City
Estimate (95% CI)
Temperate oceanic
Paris 1.08 (1.03 to 1.13)
Toulouse 1.00 (0.90 to 1.11)
Semicontinental
Clermont 0.98 (0.83 to 1.12)
Grenoble 0.99 (0.85 to 1.13)
Lyon 1.16 (1.07 to 1.25)
Nancy 0.93 (0.82 to 1.04)
Strasbourg 0.99 (0.87 to 1.11)
Oceanic
Bordeaux 1.04 (0.95 to 1.14)
Le Havre 0.95 (0.74 to 1.15)
Nantes 1.29 (1.05 to 1.52)
Rennes 1.05 (0.84 to 1.26)
Rouen 1.09 (0.90 to 1.28)
Mediterranean
Marseille 1.02 (0.99 to 1.05)
Montpellier 1.10 (0.99 to 1.20)
Nice 1.00 (0.94 to 1.05)
Pooled Estimate 1.04 (1.00 to 1.07)
I²=44.66%
0.6 0.8 1 1.2 1.4 1.6
NIE

Web Material - The role of ozone as a mediator in the relation between heat waves and mortality in 15 French urban agglomerations

Anna Alari, Chen Chen, Lara Schwarz, Kristen Hansen, Basile Chaix, Tarik Benmarhnia

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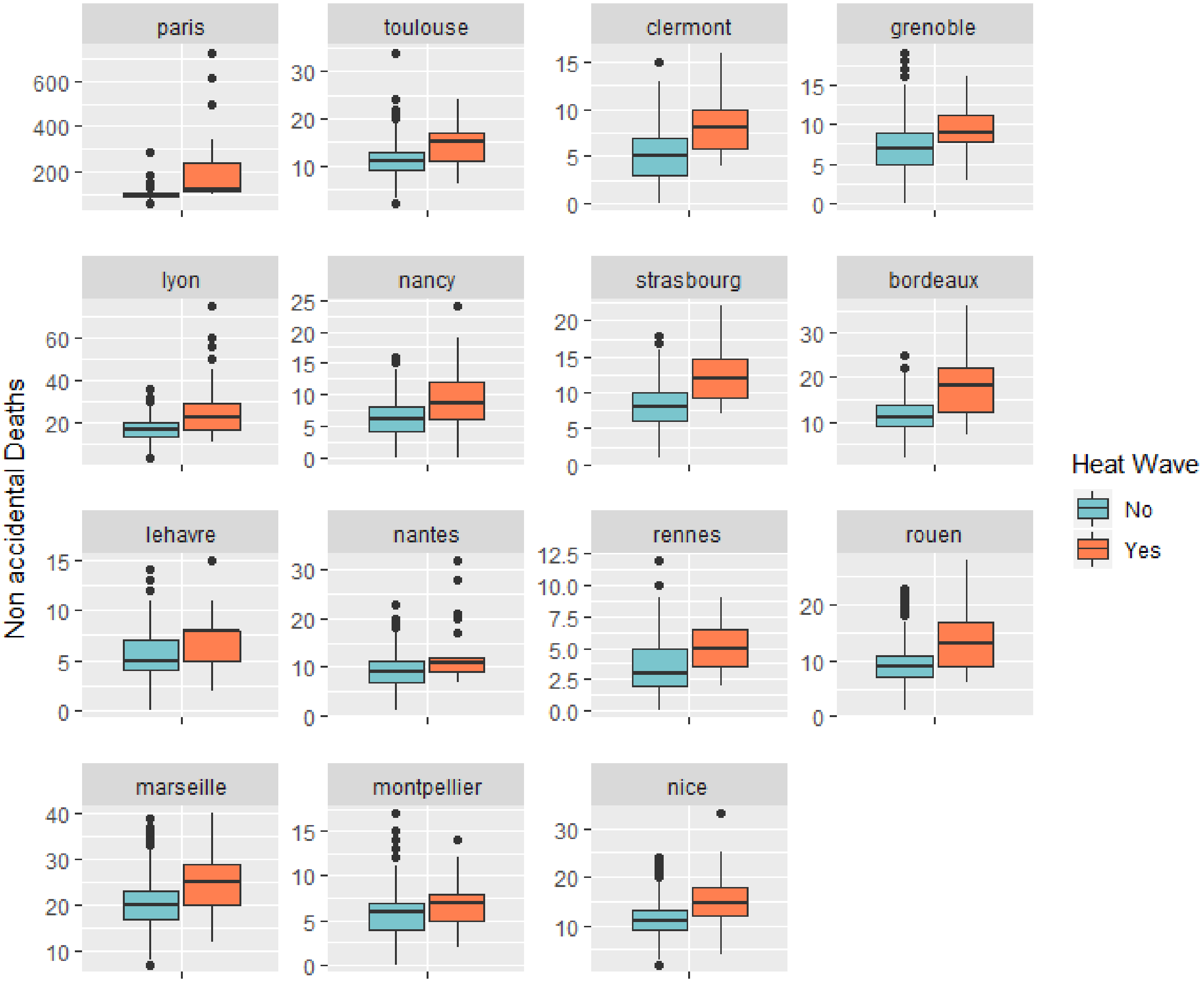
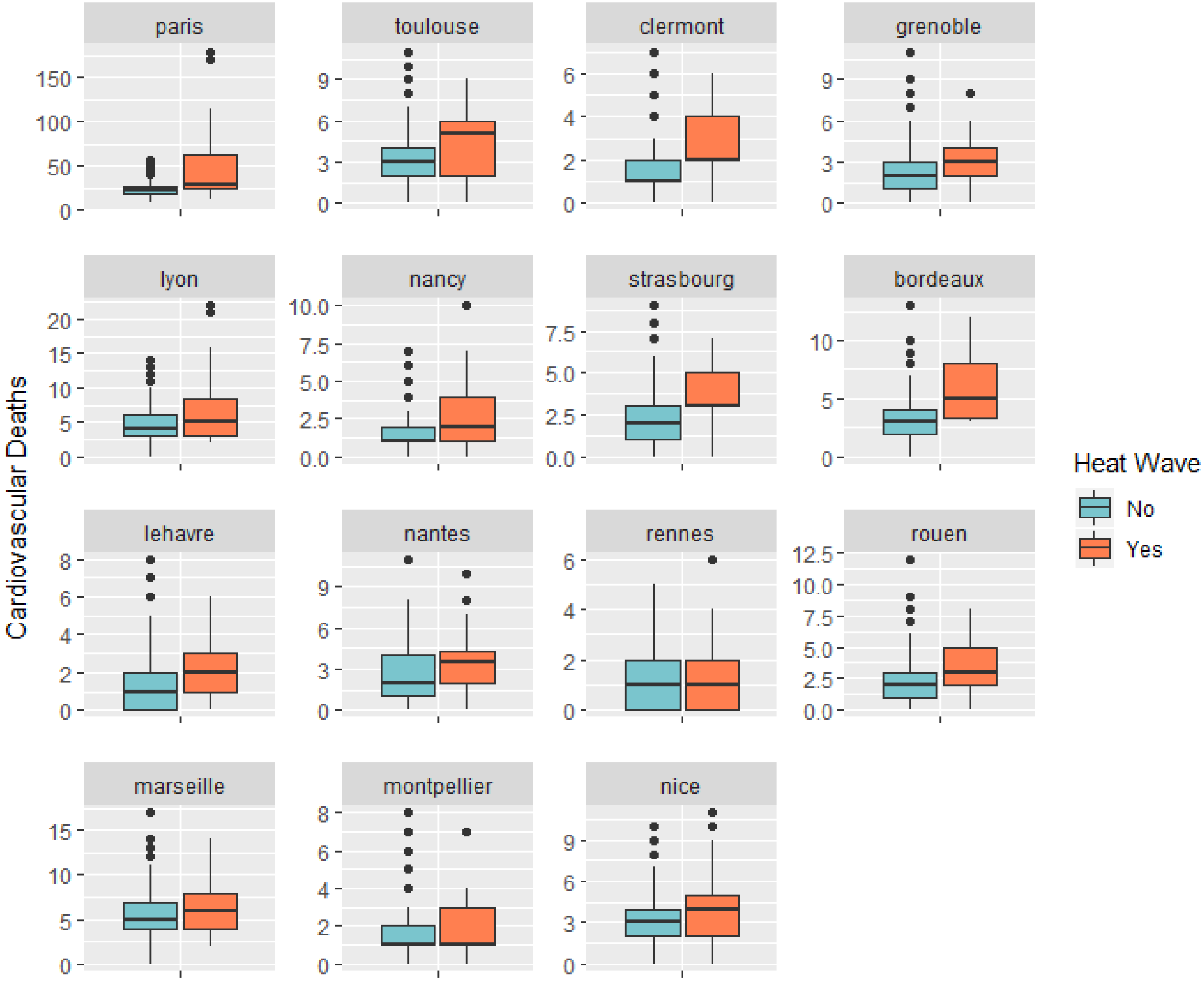
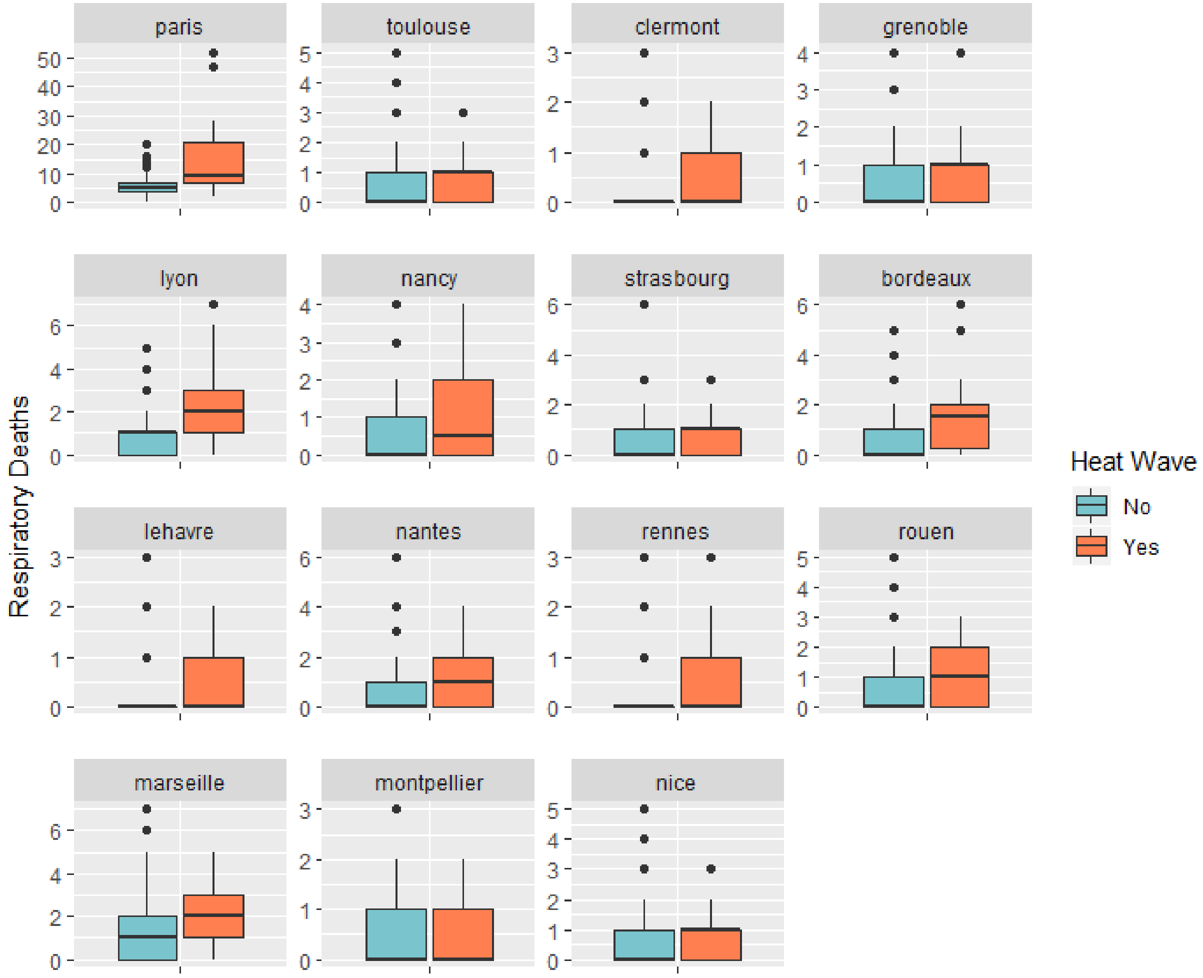
Web Figure 1. Daily number of deaths for non-accidental causes during heat wave days and non-heat-wave days.



Web Figure 2. Daily number of deaths for cardiovascular causes during heat wave days and non-heat-wave days



Web Figure 3. Daily number of deaths for respiratory causes during heat wave days and non-heat-wave days.



Web Table 1. Decomposition of the Total Effects (TEs) of Heat Waves on Non-accidental mortality into Natural Direct Effects (NDEs) and Natural Indirect Effects (NIEs) through O_3 and Proportion of the TE mediated by O_3 (PM).

Urban Agglomeration	TE	95% CI	NDE	95% CI	NIE	95% CI	PM
Temperate-Oceanic climate							
Paris	1.91	[1.38 , 2.45]	1.81	[1.31 , 2.30]	1.05	[1.02 , 1.09]	11%
Toulouse	1.34	[1.19 , 1.49]	1.28	[1.13 , 1.42]	1.05	[1.02 , 1.08]	20%
Semi-continental climate							
Clermont-Ferrand	1.55	[1.30 , 1.79]	1.49	[1.25 , 1.73]	1.04	[1.00 , 1.07]	10%
Grenoble	1.29	[1.13 , 1.46]	1.22	[1.07 , 1.38]	1.06	[1.03 , 1.09]	25%
Lyon	1.52	[1.26 , 1.78]	1.45	[1.21 , 1.70]	1.04	[1.02 , 1.07]	13%
Nancy	1.37	[1.13 , 1.62]	1.37	[1.12 , 1.62]	1.00	[0.98 , 1.03]	2%
Strasbourg	1.51	[1.37 , 1.65]	1.46	[1.32 , 1.61]	1.03	[1.00 , 1.06]	8%
Oceanic climate							
Bordeaux	1.59	[1.35 , 1.82]	1.57	[1.33 , 1.81]	1.02	[0.99 , 1.04]	4%
Le-Havre	1.27	[1.03 , 1.51]	1.24	[1.00 , 1.48]	1.02	[0.97 , 1.08]	11%
Nantes	1.32	[1.06 , 1.58]	1.22	[0.98 , 1.46]	1.08	[1.03 , 1.13]	31%
Rennes	1.42	[1.20 , 1.64]	1.34	[1.12 , 1.56]	1.06	[1.01 , 1.12]	20%
Rouen	1.48	[1.24 , 1.73]	1.37	[1.16 , 1.58]	1.08	[1.04 , 1.12]	23%
Mediterranean climate							
Marseille	1.21	[1.10 , 1.31]	1.18	[1.09 , 1.28]	1.02	[1.01 , 1.03]	10%
Montpellier	1.18	[0.99 , 1.36]	1.15	[0.97 , 1.34]	1.02	[1.00 , 1.04]	11%
Nice	1.38	[1.17 , 1.58]	1.33	[1.16 , 1.56]	1.01	[1.00 , 1.03]	5%

Web Table 2. Decomposition of the Total Effects (TEs) of Heat Waves on Cardiovascular mortality into Natural Direct Effects (NDEs) and Natural Indirect Effects (NIEs) through O_3 and Proportion of the TE mediated by O_3 (PM).

Urban Agglomeration	TE	95% CI	NDE	95% CI	NIE	95% CI	PM
Temperate-Oceanic climate							
Paris	1.99	[1.38 , 2.59]	1.87	[1.33 , 2.41]	1.06	[1.01 , 1.10]	11%
Toulouse	1.42	[1.16 , 1.68]	1.32	[1.07 , 1.57]	1.07	[1.02 , 1.13]	23%
Semi-continental climate							
Clermont-Ferrand	1.89	[1.45 , 2.32]	1.89	[1.46 , 2.33]	1.00	[0.94 , 1.06]	0%
Grenoble	1.42	[1.13 , 1.71]	1.31	[1.04 , 1.58]	1.08	[1.02 , 1.15]	27%
Lyon	1.50	[1.16 , 1.83]	1.43	[1.11 , 1.76]	1.04	[1.00 , 1.08]	12%
Nancy	1.54	[1.14 , 1.95]	1.55	[1.15 , 1.95]	1.00	[0.94 , 1.05]	-2%
Strasbourg	1.47	[1.21 , 1.72]	1.49	[1.21 , 1.77]	0.99	[0.94 , 1.04]	-3%
Oceanic climate							
Bordeaux	1.71	[1.43 , 2.00]	1.73	[1.43 , 2.02]	0.99	[0.95 , 1.04]	-1%
Le-Havre	1.45	[0.95 , 1.96]	1.25	[0.82 , 1.68]	1.16	[1.03 , 1.28]	42%
Nantes	1.38	[0.97 , 1.78]	1.23	[0.85 , 1.62]	1.11	[1.02 , 1.21]	35%
Rennes	1.51	[0.93 , 2.08]	1.44	[0.87 , 2.02]	1.04	[0.94 , 1.14]	11%
Rouen	1.42	[1.05 , 1.78]	1.30	[0.95 , 1.65]	1.08	[1.00 , 1.17]	27%
Mediterranean climate							
Marseille	1.11	[0.96 , 1.27]	1.09	[0.94 , 1.24]	1.02	[1.00 , 1.04]	17%
Montpellier	1.09	[0.73 , 1.45]	1.08	[0.72 , 1.45]	1.01	[0.97 , 1.05]	3%
Nice	1.28	[0.97 , 1.60]	1.27	[0.96 , 1.58]	1.01	[0.98 , 1.03]	4%

Web Table 3. Decomposition of the Total Effects (TEs) of Heat Waves on Respiratory mortality into Natural Direct Effects (NDEs) and Natural Indirect Effects (NIEs) through O_3 and Proportion of the TE mediated by O_3 (PM).

Urban Agglomeration	TE	95% CI	NDE	95% CI	NIE	95% CI	PMM
Temperate-Oceanic climate							
Paris	2.30	[1.63 , 2.98]	2.12	[1.48 , 2.76]	1.08	[1.03 , 1.13]	14%
Toulouse	1.56	[1.06 , 2.06]	1.55	[1.02 , 2.08]	1.00	[0.90 , 1.11]	-1%
Semi-continental climate							
Clermont-Ferrand	1.24	[0.36 , 2.12]	1.27	[0.34 , 2.20]	0.98	[0.83 , 1.12]	0%
Grenoble	1.90	[1.08 , 2.73]	1.93	[1.07 , 2.79]	0.99	[0.85 , 1.13]	-2%
Lyon	2.38	[1.74 , 3.03]	2.07	[1.48 , 2.67]	1.16	[1.07 , 1.25]	23%
Nancy	1.77	[0.97 , 2.58]	1.90	[1.02 , 2.78]	0.93	[0.82 , 1.04]	-16%
Strasbourg	2.09	[1.45 , 2.73]	2.09	[1.35 , 2.83]	0.99	[0.87 , 1.11]	-2%
Oceanic climate							
Bordeaux	2.35	[1.52 , 3.18]	2.22	[1.41 , 3.03]	1.04	[0.95 , 1.14]	7%
Le-Havre	2.12	[0.74 , 3.50]	2.25	[0.74 , 3.75]	0.95	[0.74 , 1.15]	-11%
Nantes	1.64	[0.90 , 2.38]	1.29	[0.69 , 1.88]	1.29	[1.05 , 1.52]	57%
Rennes	1.75	[0.74 , 2.76]	1.66	[0.66 , 2.66]	1.05	[0.84 , 1.26]	12%
Rouen	1.75	[0.95 , 2.55]	1.59	[0.77 , 2.40]	1.09	[0.92 , 1.28]	24%
Mediterranean climate							
Marseille	1.40	[1.02 , 1.77]	1.36	[1.00 , 1.72]	1.02	[0.99 , 1.05]	8%
Montpellier	1.45	[0.77 , 2.13]	1.31	[0.71 , 1.91]	1.10	[0.99 , 1.20]	26%
Nice	1.58	[0.97 , 2.18]	1.57	[0.96 , 2.18]	1.00	[0.94 , 1.05]	0%

Web Appendix

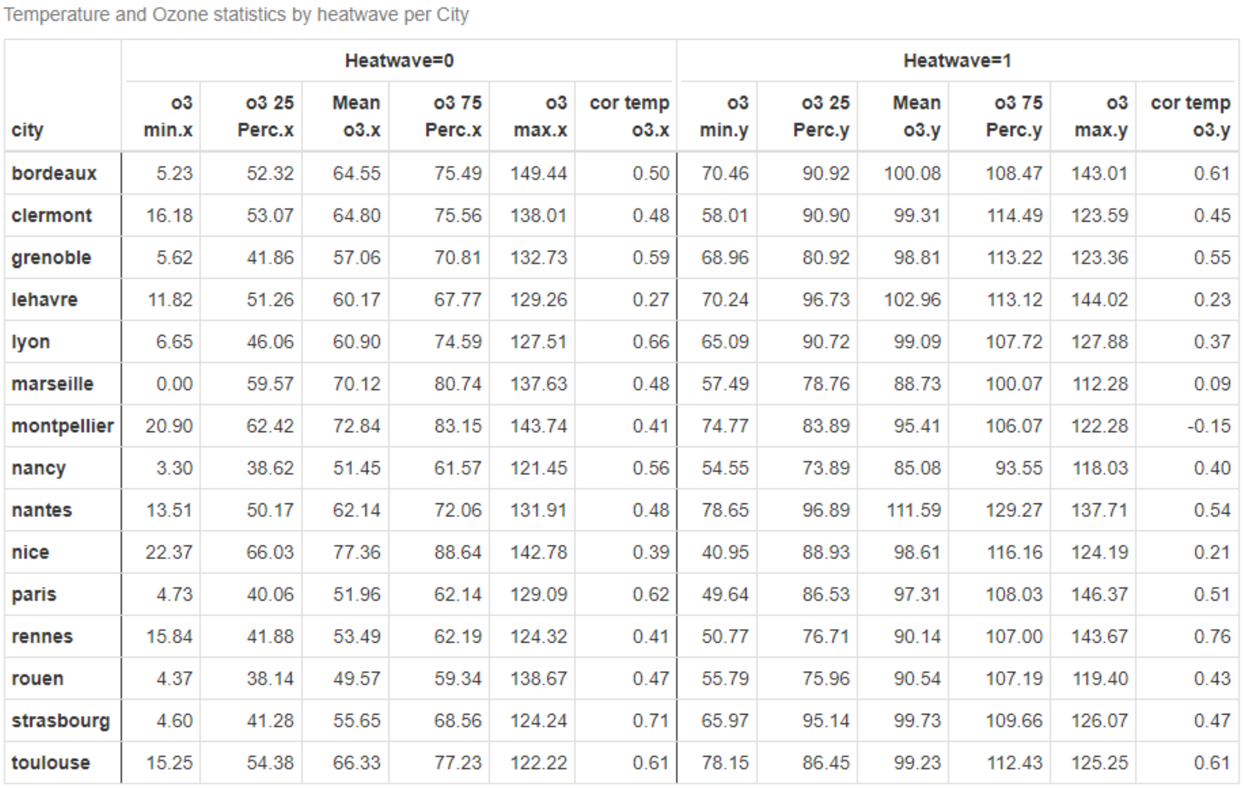
We conducted several sensitivity analyses. First, we summarized the distribution of ozone concentrations and correlations between temperature and ozone in heatwave days and non-heatwave days in Table S4 and Figure S4. Ozone concentrations are higher in heatwave days than non-heatwave days, with varying overlap between them for each city. The correlations between ozone and temperature are relatively low.

We then restricted our analyses to days with ozone levels that were observed in both heatwave and non-heatwave days. In other words, we removed days with ozone larger than the smaller value of maximum ozone concentrations in heatwave and in non-heatwave days, as well as days with ozone smaller than the larger value of minimum ozone concentrations in heatwave and in non-heatwave days. Table S5 and Figure S5 summarized the distribution of ozone concentrations by heatwave day in this subset. The overlap in ozone concentration between heatwave and non-heatwave days increase after applying this restriction. Estimates of pooled effects across cities were smaller than the main analysis, especially for total and natural direct effects, but directions and significances of estimates were the same (Figure S6). Removing extreme ozone concentrations lacking overlap between heatwave and non-heatwave days reduced the estimated direct effect of heatwave but had minimal impact on the estimated indirect effect of heatwave through ozone.

Then, we conducted sensitivity analysis by removing data from the year 2003 due to the major heat wave in France. Table S6 and Figure S7 summarized the distribution of ozone concentrations by heatwave in this subset. Estimates of pooled effects across cities were smaller than the main analysis, especially for total effect and natural direct effect, but directions and significances of estimates were similar (Figure S8). Although extreme heatwave events have a huge impact on the estimated direct effect, it has minimal impact on the effect of heatwave mediated through ozone.

Finally, we conducted sensitivity analyses with two new definitions of heat waves (or extreme heat events): single day with temperature higher than 95th percentile of the entire study period, and single day with temperature higher than 97.5th percentile of the entire study period. Table S7 provides summary of summer days defined as heatwave day for each city under three definitions. As expected, we saw the highest number of heatwave days in 95th percentile definition, followed by the 97.5th percentile definition and main analysis definition, when the criteria for heatwave day become stricter. Estimates of pooled effects across cities were smaller than the main analysis, especially for total effect and natural direct effect, but directions and significances of estimates were similar (Figure S9 and S10). Although different definitions of heatwave change the direct and total effect estimated between heatwave and adverse health outcomes, they did not change our overall conclusions.

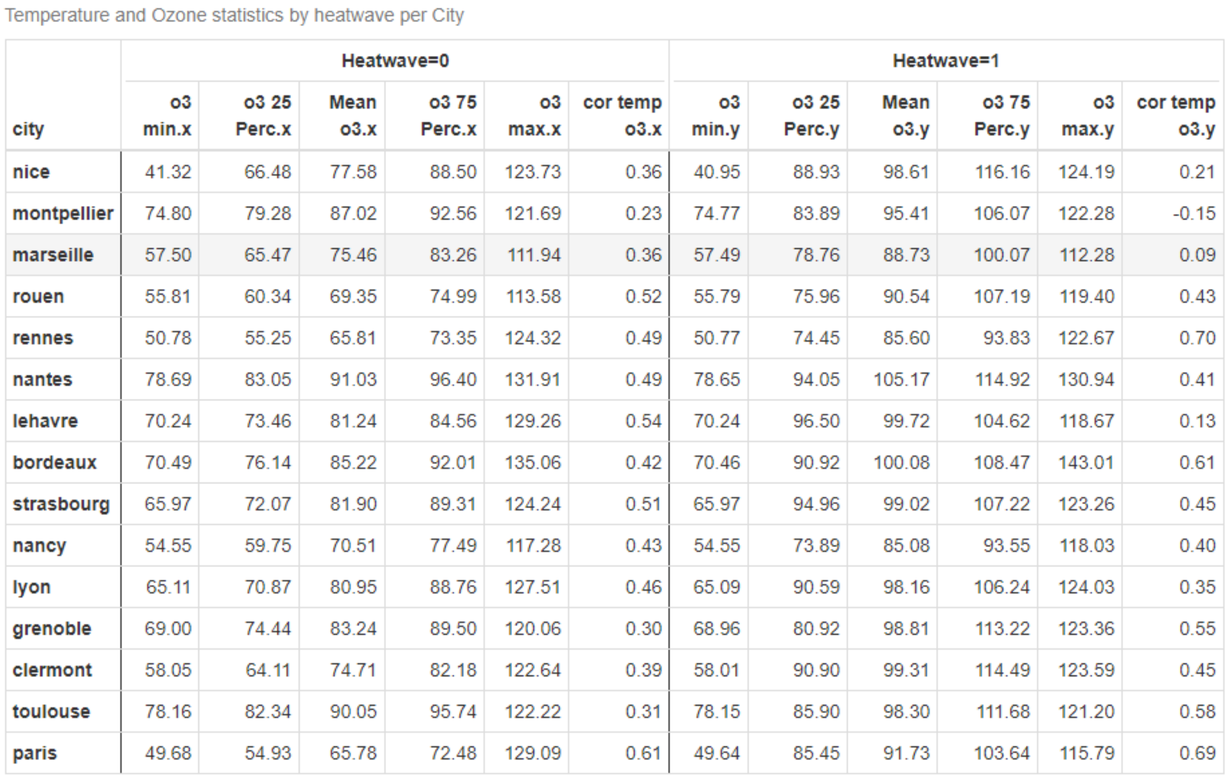
Web Table 4. Distribution of ozone concentrations and correlations between temperature and ozone in heatwave days and non-heatwave days for main analysis dataset.



Temperature and Ozone statistics by heatwave per City

city	Heatwave=0						Heatwave=1					
	o3 min.x	o3 25 Perc.x	Mean o3.x	o3 75 Perc.x	o3 max.x	cor temp o3.x	o3 min.y	o3 25 Perc.y	Mean o3.y	o3 75 Perc.y	o3 max.y	cor temp o3.y
bordeaux	5.23	52.32	64.55	75.49	149.44	0.50	70.46	90.92	100.08	108.47	143.01	0.61
clermont	16.18	53.07	64.80	75.56	138.01	0.48	58.01	90.90	99.31	114.49	123.59	0.45
grenoble	5.62	41.86	57.06	70.81	132.73	0.59	68.96	80.92	98.81	113.22	123.36	0.55
lehavre	11.82	51.26	60.17	67.77	129.26	0.27	70.24	96.73	102.96	113.12	144.02	0.23
lyon	6.65	46.06	60.90	74.59	127.51	0.66	65.09	90.72	99.09	107.72	127.88	0.37
marseille	0.00	59.57	70.12	80.74	137.63	0.48	57.49	78.76	88.73	100.07	112.28	0.09
montpellier	20.90	62.42	72.84	83.15	143.74	0.41	74.77	83.89	95.41	106.07	122.28	-0.15
nancy	3.30	38.62	51.45	61.57	121.45	0.56	54.55	73.89	85.08	93.55	118.03	0.40
nantes	13.51	50.17	62.14	72.06	131.91	0.48	78.65	96.89	111.59	129.27	137.71	0.54
nice	22.37	66.03	77.36	88.64	142.78	0.39	40.95	88.93	98.61	116.16	124.19	0.21
paris	4.73	40.06	51.96	62.14	129.09	0.62	49.64	86.53	97.31	108.03	146.37	0.51
rennes	15.84	41.88	53.49	62.19	124.32	0.41	50.77	76.71	90.14	107.00	143.67	0.76
rouen	4.37	38.14	49.57	59.34	138.67	0.47	55.79	75.96	90.54	107.19	119.40	0.43
strasbourg	4.60	41.28	55.65	68.56	124.24	0.71	65.97	95.14	99.73	109.66	126.07	0.47
toulouse	15.25	54.38	66.33	77.23	122.22	0.61	78.15	86.45	99.23	112.43	125.25	0.61

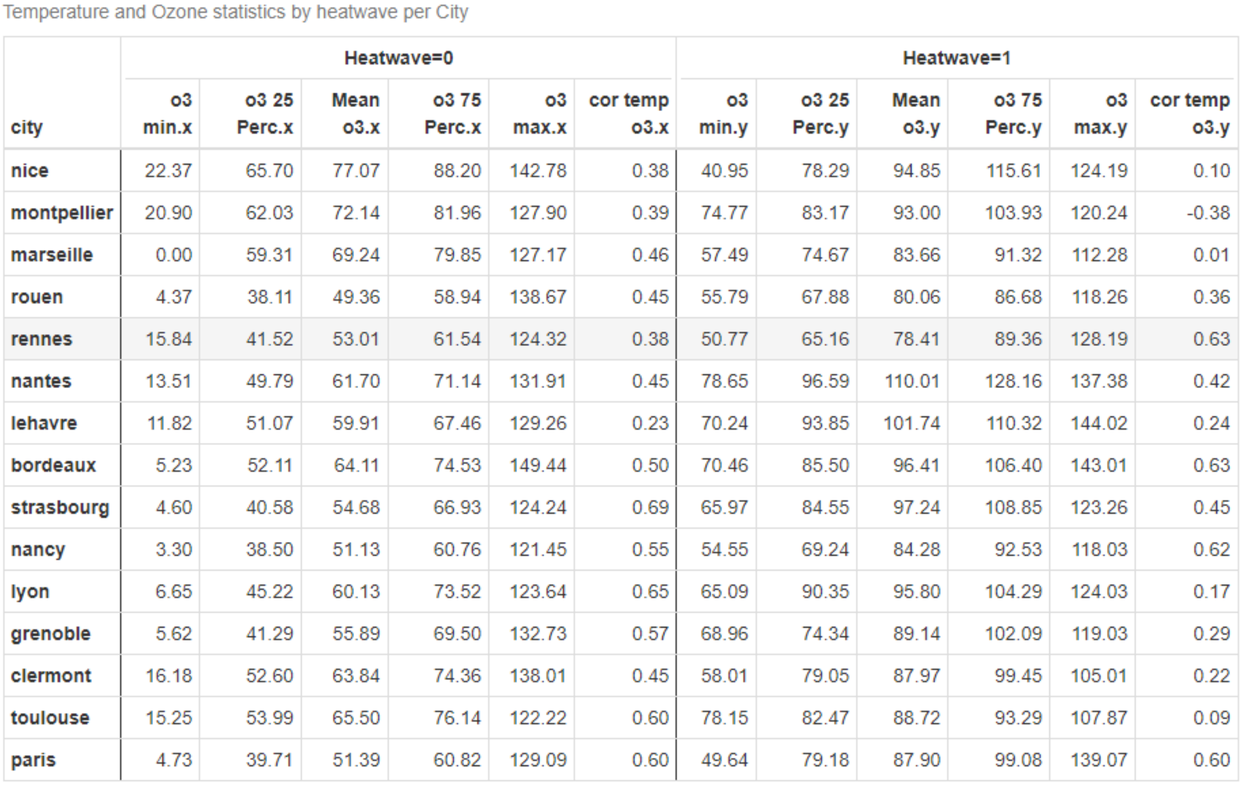
Web Table 5. Distribution of ozone concentrations and correlations between temperature and ozone in heatwave days and non-heatwave days for subset analysis restricted to days with ozone concentration that exists in both heatwave and non-heatwave days.



Temperature and Ozone statistics by heatwave per City

	Heatwave=0						Heatwave=1					
city	o3 min.x	o3 25 Perc.x	Mean o3.x	o3 75 Perc.x	o3 max.x	cor temp o3.x	o3 min.y	o3 25 Perc.y	Mean o3.y	o3 75 Perc.y	o3 max.y	cor temp o3.y
nice	41.32	66.48	77.58	88.50	123.73	0.36	40.95	88.93	98.61	116.16	124.19	0.21
montpellier	74.80	79.28	87.02	92.56	121.69	0.23	74.77	83.89	95.41	106.07	122.28	-0.15
marseille	57.50	65.47	75.46	83.26	111.94	0.36	57.49	78.76	88.73	100.07	112.28	0.09
rouen	55.81	60.34	69.35	74.99	113.58	0.52	55.79	75.96	90.54	107.19	119.40	0.43
rennes	50.78	55.25	65.81	73.35	124.32	0.49	50.77	74.45	85.60	93.83	122.67	0.70
nantes	78.69	83.05	91.03	96.40	131.91	0.49	78.65	94.05	105.17	114.92	130.94	0.41
lehavre	70.24	73.46	81.24	84.56	129.26	0.54	70.24	96.50	99.72	104.62	118.67	0.13
bordeaux	70.49	76.14	85.22	92.01	135.06	0.42	70.46	90.92	100.08	108.47	143.01	0.61
strasbourg	65.97	72.07	81.90	89.31	124.24	0.51	65.97	94.96	99.02	107.22	123.26	0.45
nancy	54.55	59.75	70.51	77.49	117.28	0.43	54.55	73.89	85.08	93.55	118.03	0.40
lyon	65.11	70.87	80.95	88.76	127.51	0.46	65.09	90.59	98.16	106.24	124.03	0.35
grenoble	69.00	74.44	83.24	89.50	120.06	0.30	68.96	80.92	98.81	113.22	123.36	0.55
clermont	58.05	64.11	74.71	82.18	122.64	0.39	58.01	90.90	99.31	114.49	123.59	0.45
toulouse	78.16	82.34	90.05	95.74	122.22	0.31	78.15	85.90	98.30	111.68	121.20	0.58
paris	49.68	54.93	65.78	72.48	129.09	0.61	49.64	85.45	91.73	103.64	115.79	0.69

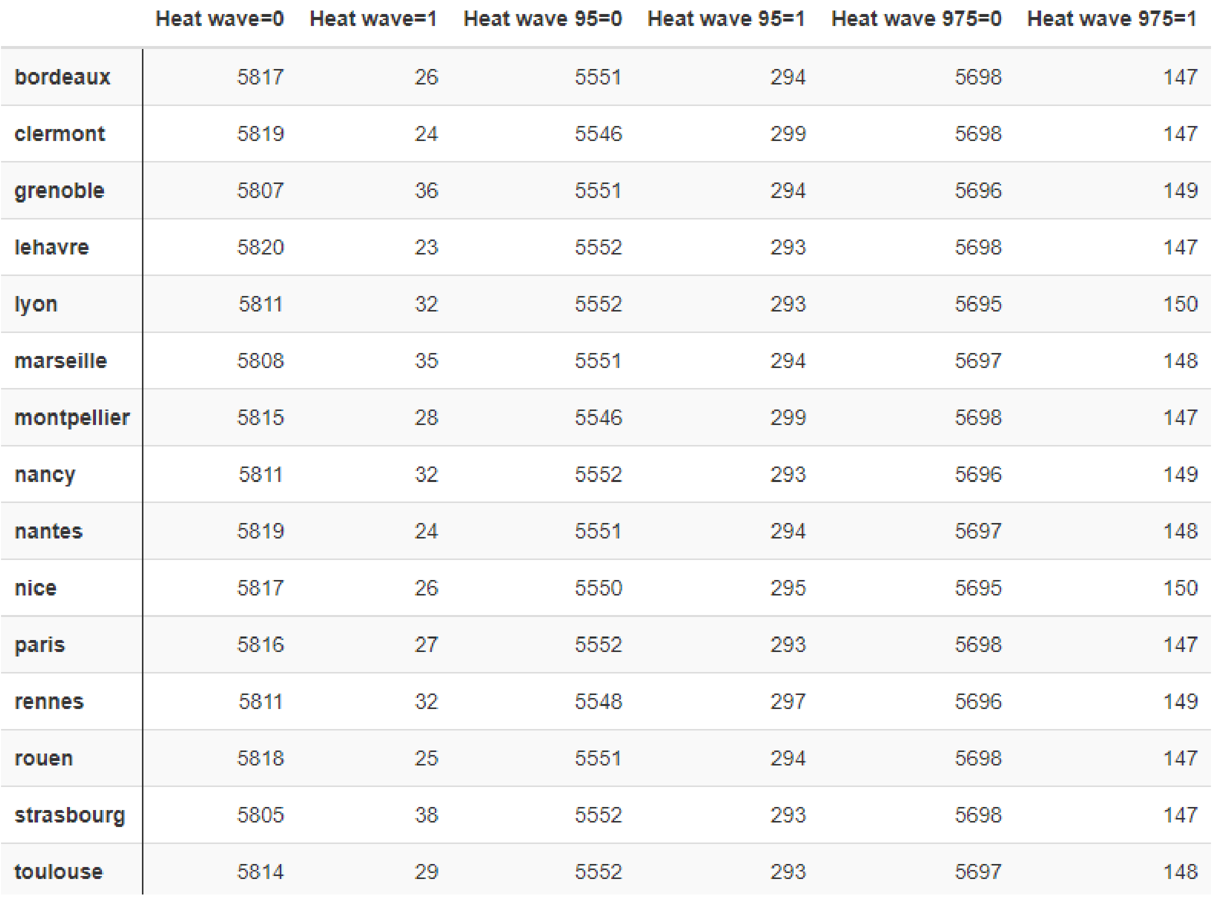
Web Table 6. Distribution of ozone concentrations and correlations between temperature and ozone in heatwave days and non-heatwave days for subset analysis after removing data from the year 2003.



Temperature and Ozone statistics by heatwave per City

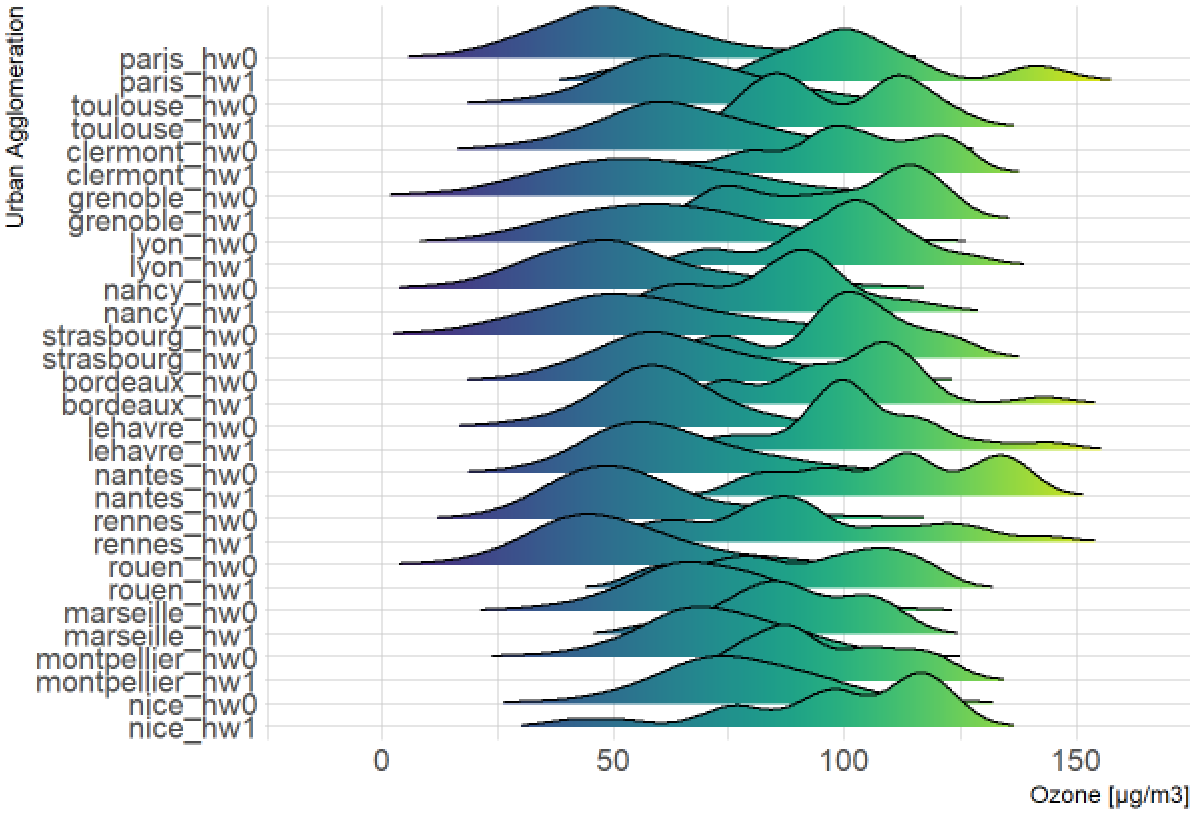
	Heatwave=0						Heatwave=1					
city	o3 min.x	o3 25 Perc.x	Mean o3.x	o3 75 Perc.x	o3 max.x	cor temp o3.x	o3 min.y	o3 25 Perc.y	Mean o3.y	o3 75 Perc.y	o3 max.y	cor temp o3.y
nice	22.37	65.70	77.07	88.20	142.78	0.38	40.95	78.29	94.85	115.61	124.19	0.10
montpellier	20.90	62.03	72.14	81.96	127.90	0.39	74.77	83.17	93.00	103.93	120.24	-0.38
marseille	0.00	59.31	69.24	79.85	127.17	0.46	57.49	74.67	83.66	91.32	112.28	0.01
rouen	4.37	38.11	49.36	58.94	138.67	0.45	55.79	67.88	80.06	86.68	118.26	0.36
rennes	15.84	41.52	53.01	61.54	124.32	0.38	50.77	65.16	78.41	89.36	128.19	0.63
nantes	13.51	49.79	61.70	71.14	131.91	0.45	78.65	96.59	110.01	128.16	137.38	0.42
lehavre	11.82	51.07	59.91	67.46	129.26	0.23	70.24	93.85	101.74	110.32	144.02	0.24
bordeaux	5.23	52.11	64.11	74.53	149.44	0.50	70.46	85.50	96.41	106.40	143.01	0.63
strasbourg	4.60	40.58	54.68	66.93	124.24	0.69	65.97	84.55	97.24	108.85	123.26	0.45
nancy	3.30	38.50	51.13	60.76	121.45	0.55	54.55	69.24	84.28	92.53	118.03	0.62
lyon	6.65	45.22	60.13	73.52	123.64	0.65	65.09	90.35	95.80	104.29	124.03	0.17
grenoble	5.62	41.29	55.89	69.50	132.73	0.57	68.96	74.34	89.14	102.09	119.03	0.29
clermont	16.18	52.60	63.84	74.36	138.01	0.45	58.01	79.05	87.97	99.45	105.01	0.22
toulouse	15.25	53.99	65.50	76.14	122.22	0.60	78.15	82.47	88.72	93.29	107.87	0.09
paris	4.73	39.71	51.39	60.82	129.09	0.60	49.64	79.18	87.90	99.08	139.07	0.60

Web Table 7. Number of heat wave days by different definitions of heat wave (Heat wave is the main analysis definition, Heat wave 95 is the single day 95th percentile definition, and Heat wave 975 is the single day 97.5th percentile definition).

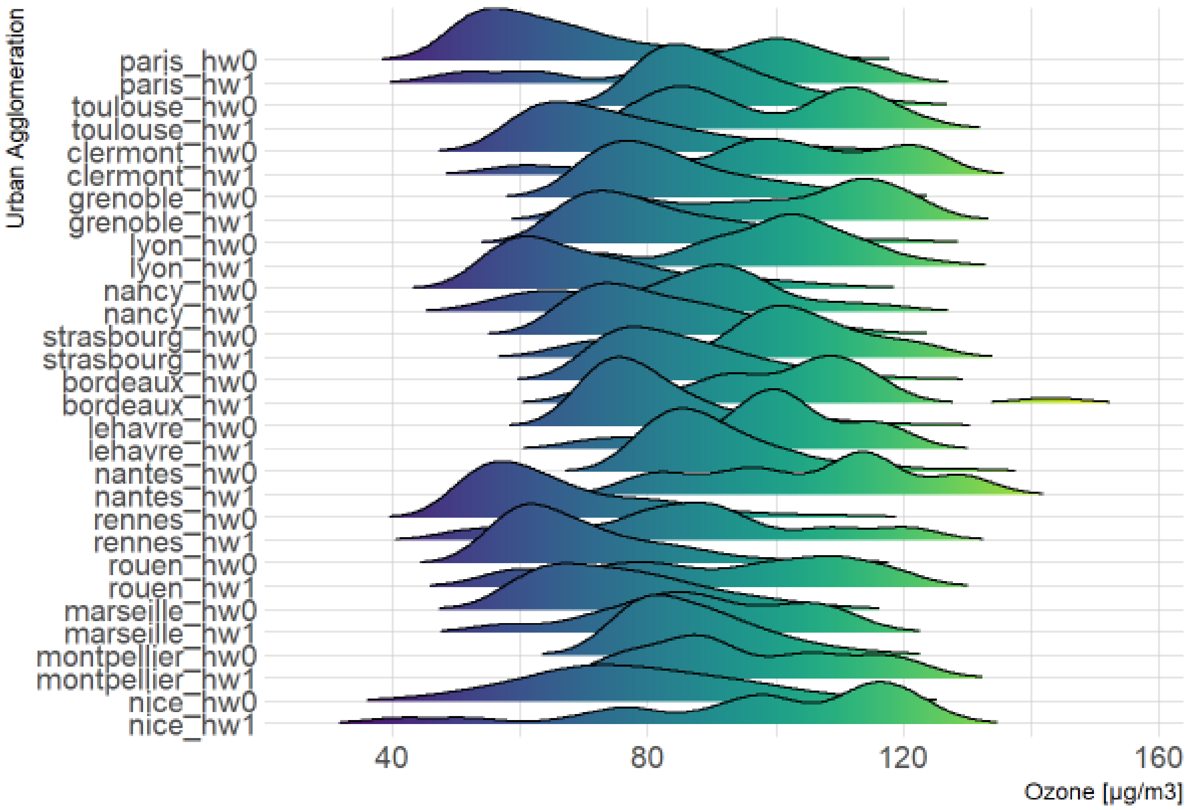


	Heat wave=0	Heat wave=1	Heat wave 95=0	Heat wave 95=1	Heat wave 975=0	Heat wave 975=1
bordeaux	5817	26	5551	294	5698	147
clermont	5819	24	5546	299	5698	147
grenoble	5807	36	5551	294	5696	149
lehavre	5820	23	5552	293	5698	147
lyon	5811	32	5552	293	5695	150
marseille	5808	35	5551	294	5697	148
montpellier	5815	28	5546	299	5698	147
nancy	5811	32	5552	293	5696	149
nantes	5819	24	5551	294	5697	148
nice	5817	26	5550	295	5695	150
paris	5816	27	5552	293	5698	147
rennes	5811	32	5548	297	5696	149
rouen	5818	25	5551	294	5698	147
strasbourg	5805	38	5552	293	5698	147
toulouse	5814	29	5552	293	5697	148

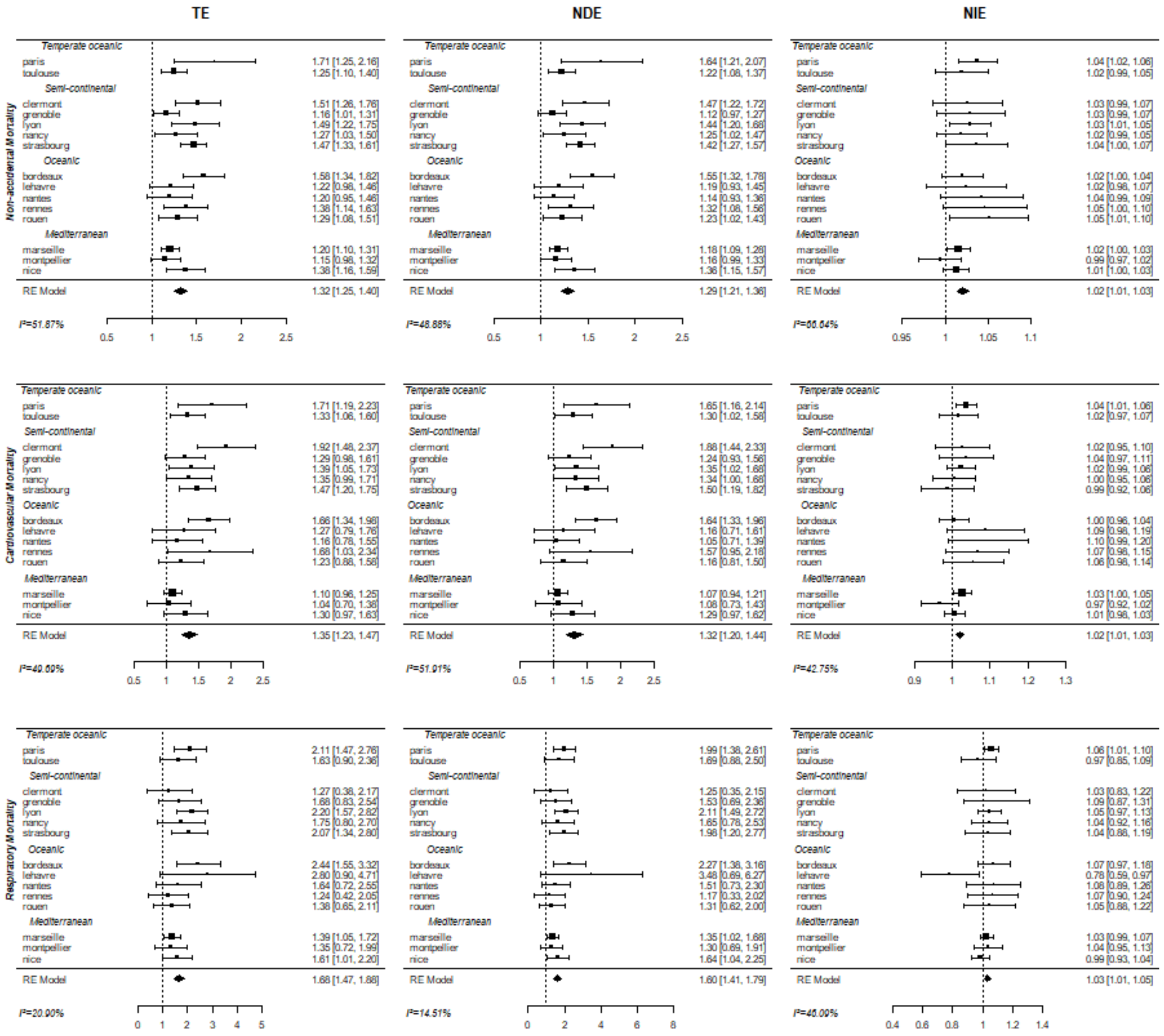
Web Figure 4. Distribution of ozone concentrations for each city during summer months in heatwave days and non-heatwave days for main analysis dataset.



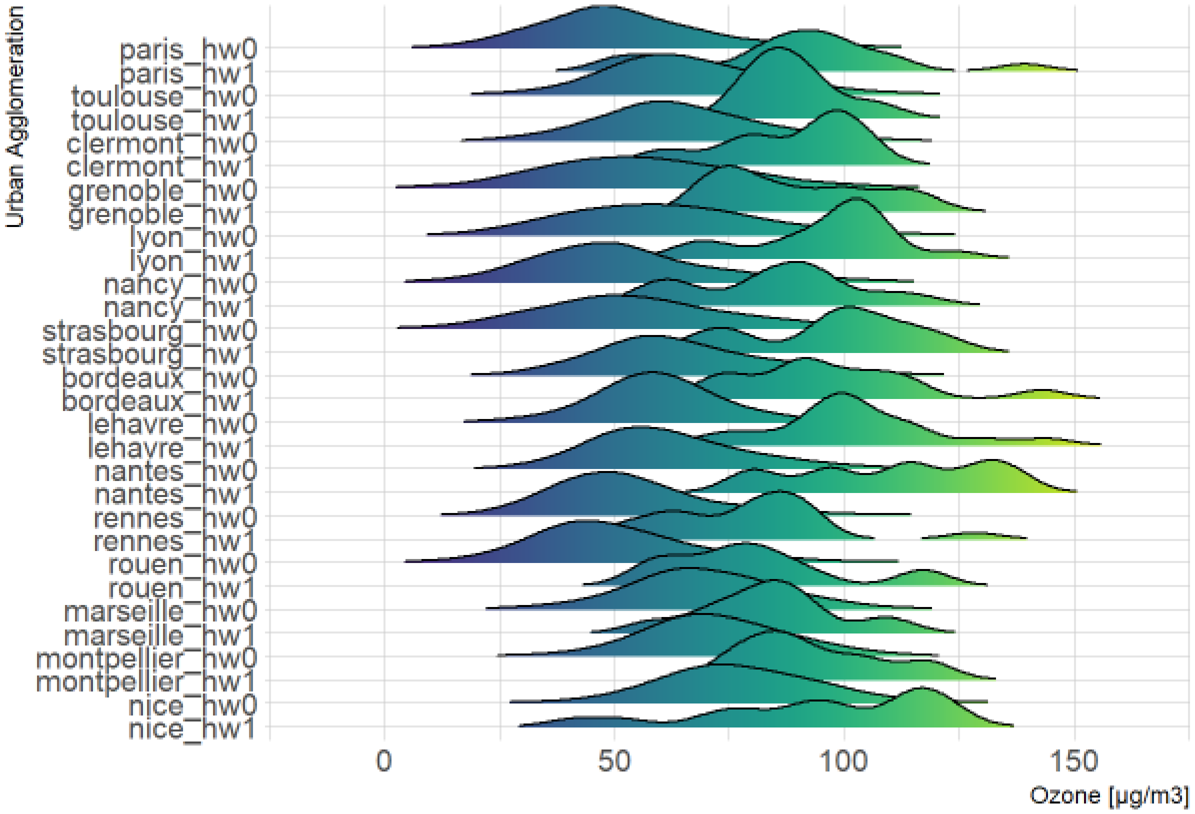
Web Figure 5. Distribution of ozone concentrations for each city during summer months in heatwave days and non-heatwave days for subset analysis restricted to days with ozone concentration that exists in both heatwave and non-heatwave days.



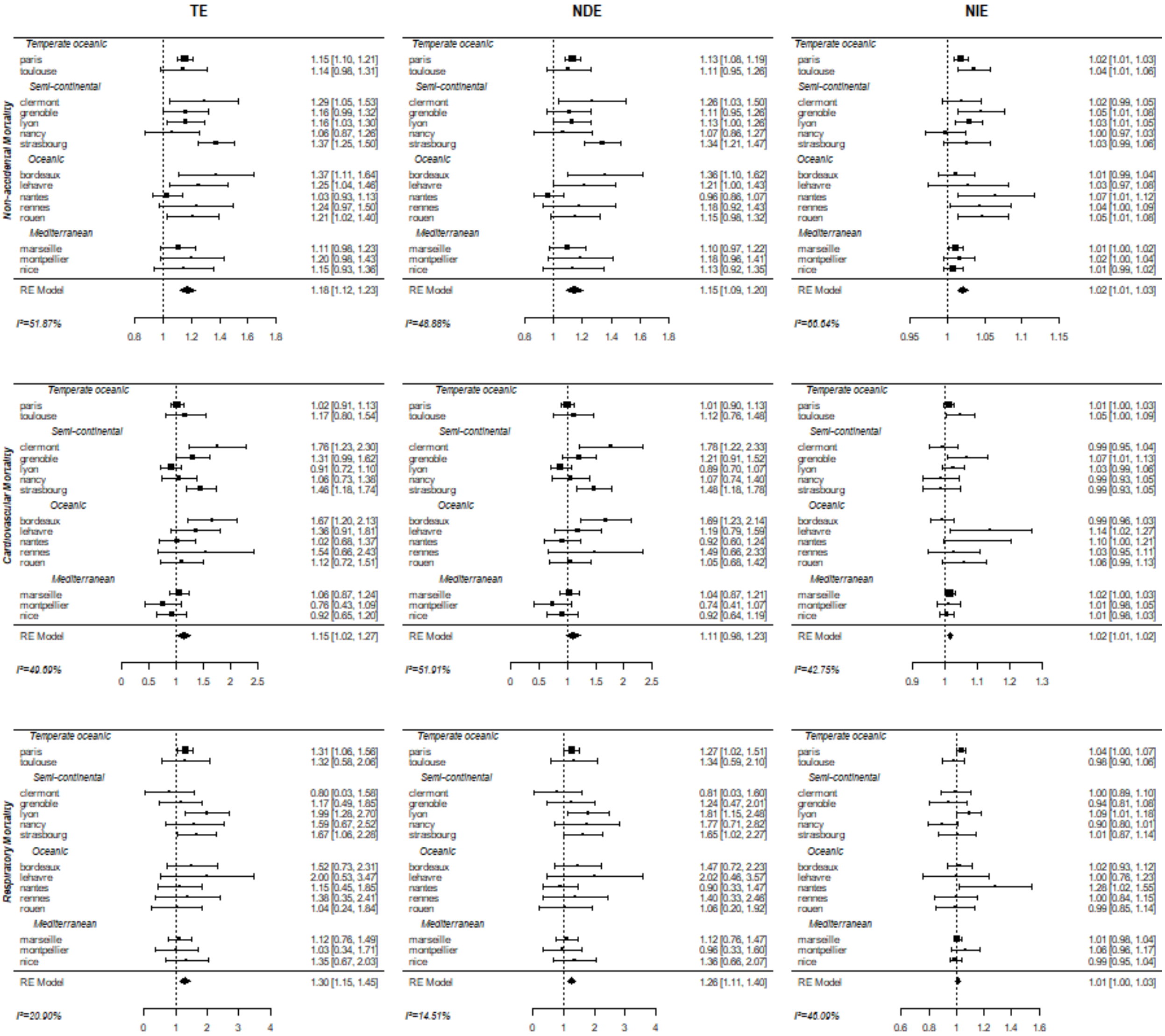
Web Figure 6. City-estimates and pooled estimates for Total Effect (TE), Natural Direct Effect (NDE) and Natural Indirect Effect (NIE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality for subset analysis restricted to days with ozone concentration that exists in both heatwave and non-heatwave days.



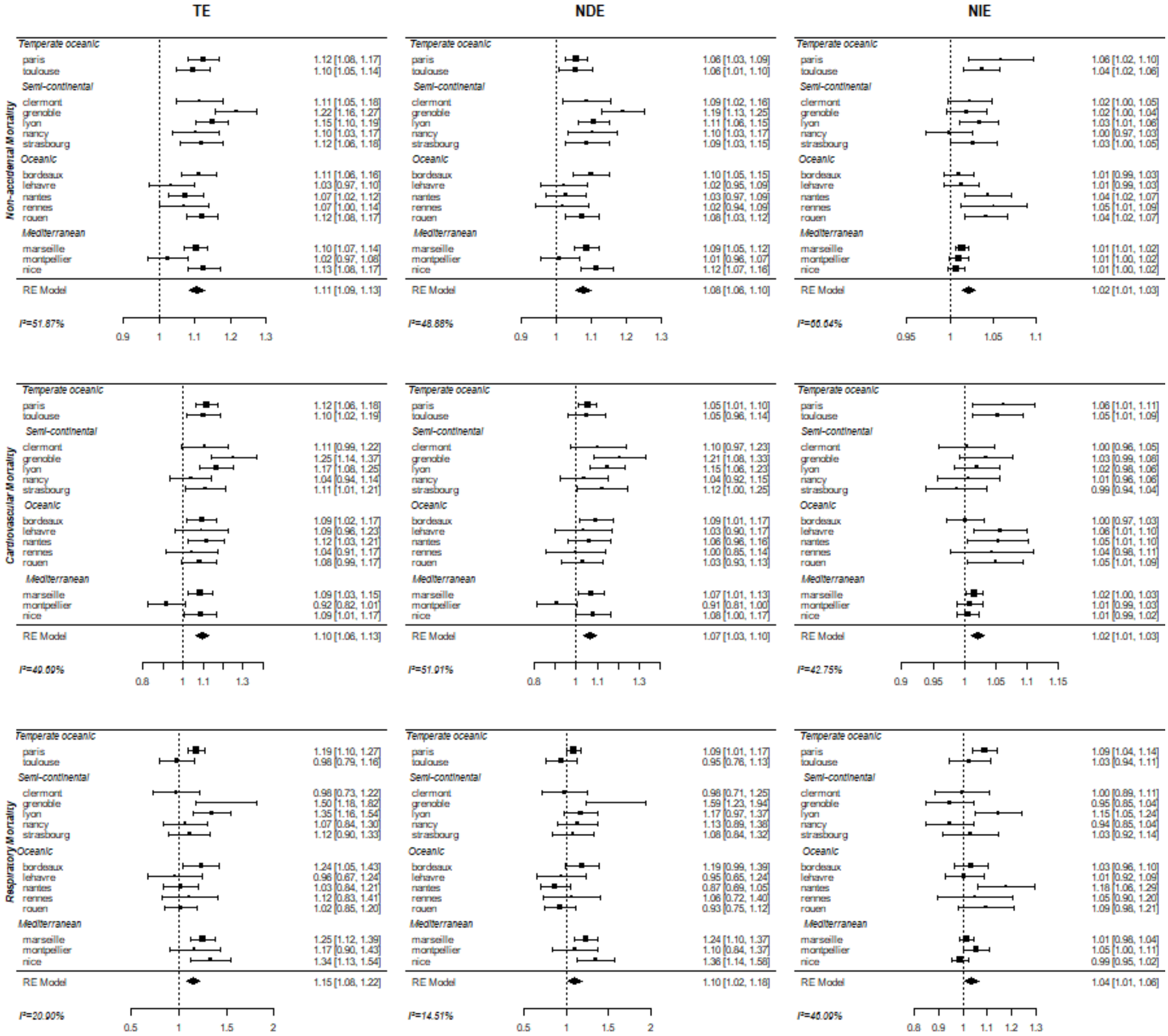
Web Figure 7. Distribution of ozone concentrations for each city during summer months in heatwave days and non-heatwave days for subset analysis after removing data from the year 2003.



Web Figure 8. City-estimates and pooled estimates for Total Effect (TE), Natural Direct Effect (NDE) and Natural Indirect Effect (NIE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality for subset analysis after removing data from the year 2003.



Web Figure 9. City-estimates and pooled estimates for Total Effect (TE), Natural Direct Effect (NDE) and Natural Indirect Effect (NIE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality with heat wave defined as single day with temperature higher than 95th percentile of the entire study period.



Web Figure 10. City-estimates and pooled estimates for Total Effect (TE), Natural Direct Effect (NDE) and Natural Indirect Effect (NIE) of Heat Wave on Non-accidental, Cardiovascular and Respiratory Mortality with heat wave defined as single day with temperature higher than 97.5th percentile of the entire study period.