ΑΡΙΣΤΟΤΕΛΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ
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ΤΜΗΜΑ ΦΥΣΙΚΗΣ
ΕΡΓΑΣΤΗΡΙΟ ΦΥΣΙΚΗΣ ΤΗΣ ΑΤΜΟΣΦΑΙΡΑΣ

Συνδυαστικές επιπτώσεις της ατμοσφαιρικής ρύπανσης και του θερμικού στρες στο περιβάλλον

Διδακτορική Διατριβή της

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Combined effects of atmospheric pollution and thermal stress on the environment

A dissertation by

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“Με τον καιρό να 'ναι κόντρα,

έχει τιμή σαν πετάς.

Κι ας μένεις μόνος.”

Ο ακροβάτης - Χαΐνηδες

Abstract

The scope of the present Doctoral Dissertation is to present a thorough assessment of the compound effects of thermal stress and air pollution on human mortality in the greater area of Thessaloniki, Greece. To meet this goal, daily concentrations of air pollutants (PM10, NO_2 and O_3) and daily values of thermal index (maximum Apparent Temperature, $Tapp_{max}$) during 2006-2016, were utilized.

The work presented in the following chapters was realized in discrete steps:

At a first stage, a Distributed Lag Non-Linear Model (DLNM) was developed for the association of $Tapp_{max}$ and mortality. The obtained results revealed that heat-attributable mortality in Thessaloniki was mainly associated with high temperatures and confirmed that heat has prompt impact on health. As expected, the Elderly (65+) showed increased vulnerability, compared to general population.

At a second stage, the same methodology was followed to examine the effects of short-term exposure to PM10 and O_3 on cause-specific mortality. It was showed that citizens of the city, especially older individuals, were at risk from the current levels of air pollution. O_3 demonstrated more severe impact than PM10, particularly with regards to cardiorespiratory mortality. A secondary aim of this study was to quantify health benefits from two air pollution abatement scenarios that resulted in immediate decreases in mortality risk.

The final objective was to analyze the interactive effects between daily maximum Apparent Temperature and air pollution (NO_2, O_3, PM10) in cause-specific mortality (non-accidental, cardiovascular, respiratory), by developing a Distributed Lag Non-linear Model using the framework of Generalized Additive Models (GAM). Separate analysis was conducted for the Elderly citizens, as well as evaluation of the lag structure. This study found that deteriorated air quality rendered the local population more susceptible to the effects of temperature variability, and vice versa. More specifically, it was revealed that air pollution enhanced temperature effects on daily mortality, and associations between elevated temperatures and casualties were generally stronger at increased pollution levels. Low temperatures were associated with increased mortality as well, but not to the same extent. Impacts of heat were immediate, whereas the prevalence of cold effects became more pronounced as longer time lags were considered. Based on this analysis, the elderly citizens were susceptible to the adverse combination of thermal conditions and poor air quality.

This dissertation presents for the first time a General Additive Model-based approach to assess the synergistic impact of thermal conditions and air quality for the urban area of Thessaloniki, by using an advanced statistical approach that captures the complex non-linear and lagged dependencies in both the exposure-response and lag-response associations, and flexible enough to be modified for other synergies. The

results presented here hold significant significance for the advancement of public health interventions designed to manage and prevent the health outcomes associated with exposure to unfavorable thermal and air quality conditions.

Περίληψη

Σκοπός της παρούσας Διδακτορικής Διατριβής είναι η παρουσίαση της διεξοδικής αξιολόγησης των συνδυαστικών επιπτώσεων της θερμικής καταπόνησης και της ατμοσφαιρικής ρύπανσης στην ανθρώπινη θνησιμότητα, στην ευρύτερη περιοχή της Θεσσαλονίκης. Για την επύτευξη αυτού του στόχου, χρησιμοποιήθηκαν ημερήσιες συγκεντρώσεις ατμοσφαιρικών ρύπων (PM10, NO2 και O3) και ημερήσιες τιμές θερμικού δείκτη, κατά την περίοδο 2006-2016.

Η έρευνα πραγματοποιήθηκε σε διακριτά βήματα:

Σε πρώτο στάδιο, αναπτύχθηκε ένα μη-γραμμικό μοντέλο κατανεμημένης χρονικής υστέρησης (Distributed Lag Non-Linear Model, DLNM) για τη συσχέτιση του θερμικού στρες και της θνησιμότητας. Τα αποτελέσματα που προέκυψαν αποκάλυψαν ότι η αποδιδόμενη από τη θερμότητα θνησιμότητα στη Θεσσαλονίκη συσχετίστηκε κυρίως με υψηλές θερμοκρασίες και επιβεβαίωσαν ότι η ζέστη έχει άμεσο αντίκτυπο στην υγεία. Όπως ήταν αναμενόμενο, τα ηλικιωμένα άτομα (65+) παρουσίασαν αυξημένη ευαλωτότητα σε σύγκριση με τον γενικό πληθυσμό.

Σε δεύτερο στάδιο, ακολουθήθηκε η ίδια μεθοδολογία για την εξέταση των επιπτώσεων της βραχυπρόθεσμης έκθεσης σε PM10 και O_3 στην ημερήσια θνησιμότητα. Αποδείχθηκε ότι ο πληθυσμός της πόλης, ιδιαίτερα τα άτομα μεγαλύτερης ηλικίας, κινδυνεύουν από τα σημερινά επίπεδα ατμοσφαιρικής ρύπανσης. Το O_3 επέδειξε εντονότερη επίδραση από τα PM10, ιδιαίτερα όσον αφορά τη θνησιμότητα από καρδιοαναπνευστικές αιτίες. Ένας δευτερεύων στόχος αυτής της μελέτης ήταν η ποσοτικοποιήση του όφελους για την υγεία από δύο σενάρια μείωσης της ατμοσφαιρικής ρύπανσης, που είχαν ως αποτέλεσμα την άμεση μείωση του κινδύνου θνησιμότητας.

Τελικός στόχος ήταν να εξεταστούν οι διαδραστικές επιδράσεις μεταξύ του ημερήσιου βιομετεωρολογικού δείκτη και της ατμοσφαιρικής ρύπανσης (NO_2, O_3, PM10) στη θνησιμότητα, αναπτύσσοντας ένα DLNM στο πλαίσιο των Γενικευμένων Προσθετικών Μοντέλων (Generalized Additive Models, GAM). Διαπιστώθηκε ότι η επιδείνωση της ποιότητας του αέρα καθιστά τον τοπικό πληθυσμό πιο ευάλωτο στις επιπτώσεις της θερμοκρασίας, και αντίστροφα. Πιο συγκεκριμένα, η ατμοσφαιρική ρύπανση ενίσχυσε τις επιπτώσεις της ζέστης στην ημερήσια θνησιμότητα και οι συσχετίσεις μεταξύ των αυξημένων θερμοκρασιών και των θανάτων ήταν γενικά ισχυρότερες σε αυξημένα επίπεδα ρύπανσης. Οι χαμηλές θερμοκρασίες συσχετίστηκαν και εκείνες με αυξημένη θνησιμότητα, αλλά όχι στον ίδιο βαθμό. Οι επιπτώσεις της ζέστης ήταν άμεσες, ενώ οι συνέπειες λόγω κρύου απαιτούσαν περισσότερες μέρες για να εκδηλωθούν. Με

βάση αυτή τη μελέτη, οι ηλικιωμένοι πολίτες ήταν ιδιαίτερα επιρρεπείς στο δυσμενή συνδυασμό θερμικής επιβάρυνσης και κακής ποιότητας αέρα.

Η παρούσα διατριβή παρουσιάζει για πρώτη φορά μια προσέγγιση βασισμένη σε Γενικό Προσθετικό Μοντέλο για την αξιολόγηση της συνδυαστικής επίδρασης των θερμικών συνθηκών και της ποιότητας του αέρα στην αστική περιοχή της Θεσσαλονίκης, χρησιμοποιώντας μια προηγμένη στατιστική προσέγγιση που αποτυπώνει τις πολύπλοκες συσχετίσεις, η οποία είναι αρκετά ευέλικτη για να επεκταθεί και σε άλλες μελέτες. Τα αποτελέσματα που παρουσιάζονται εδώ συμβάλουν στην ανάπτυξη μέτρων για την προστασία της δημόσιας υγείας από την έκθεση σε δυσμενείς μετεωρολογικές συνθήκες και συνθήκες ποιότητας του αέρα.

Preface

This dissertation is submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy at the Aristotle University of Thessaloniki, Faculty of Sciences, School of Physics, Thessaloniki, Greece. The research presented herein was conducted under the supervision of Professor Dimitrios Melas between January 2018 and September 2023.

Parts of this research have been presented in international scientific journals and proceeding of international peer-reviewed conferences:

Studying the Effects of Urban Heat Island during Hot Days: the Case of Thessaloniki, Greece. Parliari et al (2019). 9th International Symposium on Atmospheric Sciences, October 23-26 2019, Istanbul Turkey.

Short-term effects of temperature and air pollution on human health: the case of Thessaloniki. D. Parliari. (2022). Final Conference of "KASTOM - Innovative System for Air Quality and Forecasting", Thessaloniki, Greece.

Assessment of Heat and Cold Waves Phenomena and Impacts on Environment. Parliari, D., Giannaros, C., Keppas, S. (2022). In: Saxena, P., Shukla, A., Gupta, A.K. (eds) Extremes in Atmospheric Processes and Phenomenon: Assessment, Impacts and Mitigation . Disaster Resilience and Green Growth. Springer, Singapore. https://doi.org/10.1007/978-981-16-7727-4_7

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Short-Term Effects of Air Pollution on Mortality in the Urban Area of Thessaloniki, Greece. Parliari D, Giannaros C, Papadogiannaki S, Melas D. Sustainability. 2023; 15(6):5305. https://doi.org/10.3390/su15065305

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Kushta, J. (2023). EMS Annual Meeting 2023, Bratislava, Slovakia, 4–8 Sep 2023, EMS2023-69, https://doi.org/10.5194/ems2023-69 , 2023.

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Contents

Chapter 1

Introduction

1.1 Problem statement

Rapid urbanization has caused cities to face increasing pressure from growing populations, limited resources and escalating impacts of climate change (World Health Organization, 2017). United Nations estimate that 68% of the world's population will reside in urban areas by 2050 (UN Department of Economic and Social Affairs, 2018) with limited access to nature and increased exposure to environmental hazards, such as air and noise pollution (World Health Organization, 2017). The degradation of air quality has become so prominent in cities that the term urban pollution island (UPI) was recently introduced, to describe the spatial and temporal variations in pollution concentrations between urban and rural areas (Ulpiani, 2021). In modern cities, the synergistic interactions of urban heat islands (UHIs) and UPIs lead to increased pollutant concentrations via various mechanisms, such as accelerated atmospheric chemistry cycles due to high temperatures and increased CO_2 emissions, and ozone-precursors from air-conditioning (Ulpiani, 2021).

Regions with poor air quality are home to approximately 90% of the global population (WHO, 2021), making it the most significant environmental risk to human health (European Environmental Agency, 2020). According to World Health Organization (WHO), the most critical air pollutants are sulfur dioxide (SO_2), nitrogen oxides (NO, NO_2), ground level ozone (O_3) and particulate matter (PM), and the exposure to them is linked to adverse health outcomes (WHO, 2021).

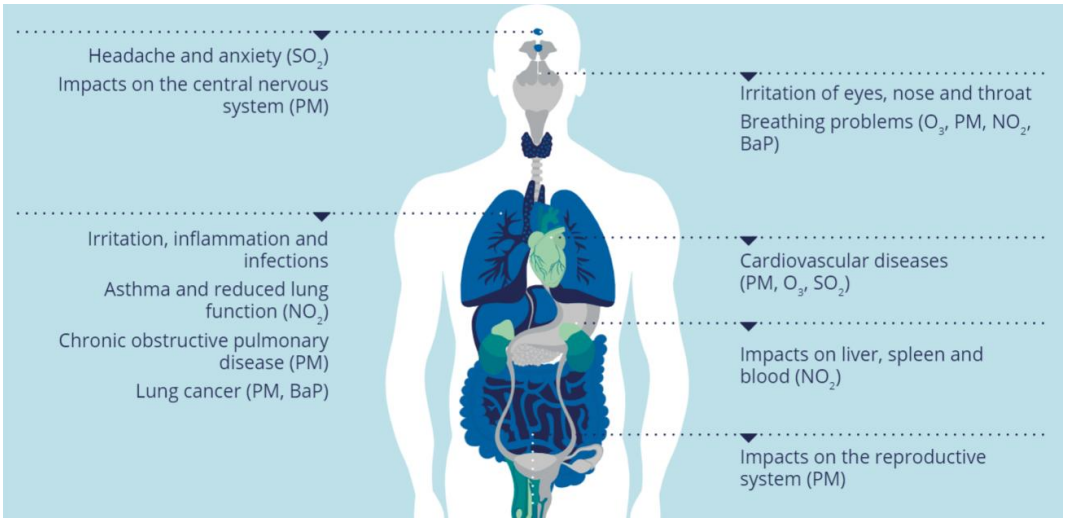


Figure 1.1: Health impacts of air pollution (Adapted from (European Environment Agency, 2019))

Exposure to PM_{10} results in asthma attacks, bronchitis, high blood pressure, heart attack, strokes, immune system reactions, lung irritation, and increased hospitalization due to respiratory and cardiovascular diseases (Larrieu *et al.*, 2007; WHO Regional Office for Europe, 2013; *Health effects of PM10*, 2023). NO_2 is linked to asthma development, inflammation of the airways, reduced lung function and chronic lung disease (*Nitrogen Dioxide | American Lung Association*, no date; D. Jarvis, G. Adamkiewicz, M. Heroux, R. Rapp, 2010; WHO Regional Office for Europe, 2013). Lastly, tropospheric O_3 is associated to human health impacts such as increase in hospital admissions due to cardiovascular and respiratory diseases, shortness of breath, throat irritation, reduced lung function and asthma attacks (WHO Regional Office for Europe, 2013; Yari *et al.*, 2016).

Meanwhile, climate change is one of the most imperative global health threats in the 21st century. Higher average global temperatures are expected to lead to more frequent, persistent, and intense heat waves in the future (Meehl and Tebaldi, 2004) which will undeniably rise climate-sensitive health risks.

As a result, the interactions between ambient temperature and human health have emerged as major issues in the global research community during recent years. Elevated temperatures have profound impact of human health, including increased risks of heat-related illnesses, infectious diseases, malnutrition, and mental health issues (Koppe, C.; Kovats, S.; Jendritzky, G.; Menne, 2004; McGregor *et al.*, 2015). In addition, there is direct link between heat exposure and human mortality from respiratory, cardiovascular and cerebrovascular causes (Brooke Anderson and Bell, 2011; Liu *et al.*, 2011; Gasparrini *et al.*, 2012; Song *et al.*, 2017; World Health Organization, 2022). However, not only extreme temperatures (Basu and

Samet, 2002b; Anderson and Bell, 2009; McGregor *et al.*, 2015), but also changes in moderate temperatures have been shown to present a direct increase in mortality (Analitis *et al.*, 2008).

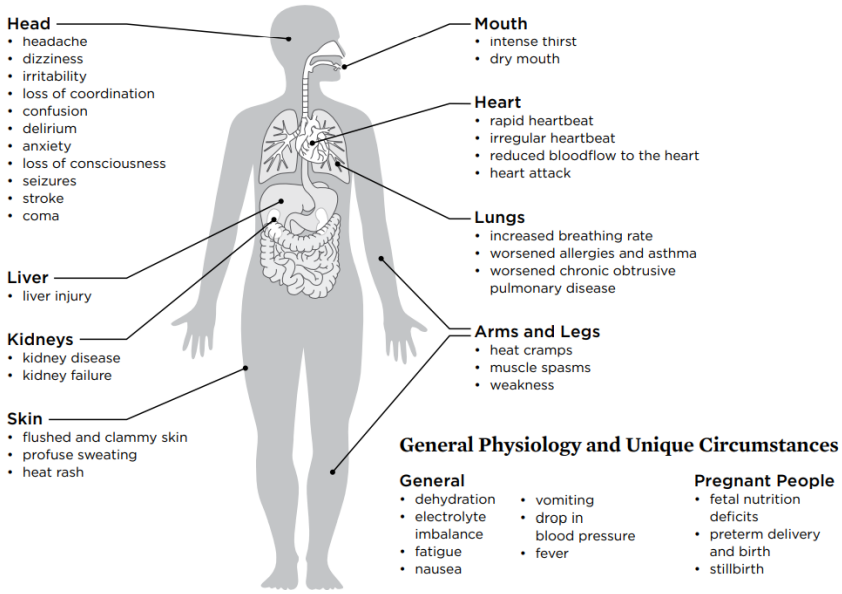


Figure 2.2: Health impacts of heat (Adapted from (Union of Concerned Scientists, 2019))

While adverse environmental conditions impact the entire population, specific groups such as the elderly, pregnant women and individuals with underlying health conditions are more at risk in terms of health. Evidence shows that senior citizens are particularly susceptible to air pollution due to vasodilation, chronic diseases and reduced heat dissipation (Barnett, 2007; Kenney, Craighead and Alexander, 2014). Research also suggests that individuals with reduced ability for thermo-regulation are the most vulnerable groups of the population to the effect of extreme high temperatures (Basu, Dominici and Samet, 2005; Bunker *et al.*, 2016; Chersich *et al.*, 2020).

The combined effect of air quality and thermal stress, coupled with rapid urbanization, pose a growing health concern for urban populations. These phenomena not only affect the well-being of individuals but also have adverse effects on overall prosperity in metropolitan areas. Therefore, there is a critical need to enhance our understanding of the underlying mechanisms of air pollution and the interaction with elevated temperatures. By doing so, we can effectively address this issue and implement proactive measures to mitigate the impacts of environmental stressors on urban communities.

1.2 Research objectives

The principal goal of this dissertation is to analyze in depth the compound effects of thermal stress and air pollution on human mortality in the greater area of Thessaloniki, Greece.

This study represents the pioneering application of the proposed General Additive Model-based approach to evaluate the health impact of thermal conditions and air quality in Thessaloniki's urban area. This advanced statistical method effectively captures the intricate relationships with optimal use of the data and thus ensures optimal statistical significance, being also adaptable to other synergistic analyses. The present work provides valuable insights to the vulnerable Southern European region, emphasizing the significance of comprehending and mitigating the health burdens associated with ambient air pollution and thermal conditions.

Limitations should be recognized, as well. Generalizing our findings to health impact assessments in other regions with different underlying health conditions and air pollution compositions may be constrained due to the localized nature of similar studies. Additionally, using air quality data from stationary monitoring stations rather than individual exposure data may introduce bias due to potential misclassification of exposure, as individual exposure does not always align precisely with measured atmospheric parameters. The limited availability of air quality and morbidity data also restricted our ability to consider important pollutants such as $PM_{2.5}$ and health aspects such as hospitalization and emergency room visits. Finally, further research is required to establish the causal and etiological mechanisms that explain the results obtained in our study.

On the basis of this general research framework, numerous aspects are investigated:

- ✓ Analysis on mortality causes (all causes, cardiovascular, respiratory) specifically linked with effects on health, caused by heat and air pollution.
- ✓ Examination of the contribution of non-optimum temperature ranges coupled with increasing concentrations of pollutants, to the overall mortality burden.
- ✓ Lag structure analysis across biometeorological index range and pollutants' ranges.
- ✓ Investigation of the behavior of vulnerable groups (Elderly citizens, aged 65+).
- ✓ Interpretation of the produced results considering mortality risk and mortality burden.

1.3 Dissertation outline

The outline of the current dissertation is as follows:

In Chapter 1, a concise overview of the environmental issue tackled in this dissertation is provided, along with a clear delineation of the research goals to be accomplished.

Chapter 2 describes the impact of environmental stressors on health, mainly on thermal and air quality conditions.

In Chapter 3 the area under study is presented, started from the general Mediterranean region and then focusing on Thessaloniki.

Chapter 4 contains the description of the statistical approach that was adopted in this work.

Chapter 5 presents the first stage: evidence on the air pollution–mortality relationship in Thessaloniki urban area from 2006 to 2016, accounting for the cause-specific deaths, lag structure and elderly mortality.

Chapter 6 describes second stage: the effects of thermal stress on daily mortality by examining the associations between thermal indicator and cause-specific mortality, and investigation of the effect of time lag and non-optimum temperatures.

The final stage is presented in Chapter 7: the very first application of an innovative GAM-based approach to assess the synergistic impact of thermal conditions and air quality for the urban area of Thessaloniki, with an advanced statistical approach that captures the complex non-linear and lagged dependencies in both the exposure-response and lag-response associations.

Chapter 8 includes the summary and conclusions of this dissertation.

Chapter 2

Health impact of environmental stressors

2.1 Meteorological conditions

The impact of weather conditions on society has been a major concern for the scientific community in recent decades. In particular, extreme temperatures pose a significant global concern due to their substantial effect on several aspects of life.

A prolonged period of intense heat can profoundly influence society, leading to additional pressure on critical infrastructure, such as power, water, and transportation systems. Sectors like clothing and food retail, tourism, and ecosystem services are not immune to the impact of heat waves, creating potential socioeconomic disparities (McGregor *et al.*, 2015). Elevated temperatures pose several environmental risks, e.g. ecosystem imbalances, habitat loss, water scarcity, disruption of phenological patterns and loss of biodiversity (Guo *et al.*, 2017; Union of Concerned Scientists, 2019; Zinzi and Santamouris, 2019; Galanaki *et al.*, 2023). In certain cases, heat waves can even instigate social disruptions across various levels: hot weather has been linked with higher levels of street violence and attacks, as well as rioting and unrest (Rotton and Cohn, 2000).

The economic effects of high temperatures should not be overlooked. Anthropogenic extreme heat has caused losses of about $16 trillion to the global economy during 1992-2013 (Callahan and Mankin, 2022). According to the same study, wealthy regions like Europe and North America encountered an average annual decline of 1.5% in GDP per capita due to extreme heat. In contrast, lower-

income regions such as India and Indonesia suffered a more significant reduction, with a yearly GDP per capita loss of 6.7%. European Environment Agency estimates that between 1980 and 2021, weather- and climate-related extremes caused economic losses estimated at EUR 560 billion in the EU Member States, whereas heat waves were responsible for over 13% of the total losses (European Environment Agency (EEA), 2023).

At present, extreme temperatures have become a public health hazard, contributing to a substantial burden of disease. Heat demonstrates profound impact on human health, including increased risks of heat-related illnesses, infectious diseases, malnutrition, and mental health issues (Koppe, C.; Kovats, S.; Jendritzky, G.; Menne, 2004; McGregor *et al.*, 2015). Increased temperature is also associated with preterm birth and abnormal birth weight (Strand, Barnett and Tong, 2011; Carolan-Olah and Frankowska, 2014). Studies have found links between rising temperatures and a range of mental health issues including mental fatigue, aggression and even higher rates of suicide (Schmit *et al.*, 2017; Miles-Novelo and Anderson, 2019). A 1 °C temperature rise was also associated with a significant increase in mood disorders, organic mental disorders, schizophrenia, neurotic, anxiety disorders and hospitalizations for Alzheimer's disease (Xu *et al.*, 2019; Liu *et al.*, 2021).

Thermal conditions significantly impact morbidity rates and the severity of chronic diseases. Heat-related morbidity appears to be associated with a range of pre-existing chronic health conditions, including cardiovascular, cerebrovascular and respiratory disorders (Brooke Anderson and Bell, 2011; Liu *et al.*, 2011; Gasparrini *et al.*, 2012; Bunker *et al.*, 2016; Song *et al.*, 2017; Campbell *et al.*, 2018; World Health Organization, 2022).

Elevated temperatures have a profound influence on mortality rates, encompassing various causes of death. Heat waves are considered to be the deadliest weather disaster in many parts of the world (Brooke Anderson and Bell, 2011). In a research focusing on heat waves in 43 U.S. cities (1987–2005), it was found that mortality increased by 3.74% during heat waves compared with non-heat wave days (Brooke Anderson and Bell, 2011). A systematic review by (Bunker *et al.*, 2016) reports that a 1 °C temperature rise increased cardiovascular, respiratory, and cerebrovascular mortality by 3.44%, 3.60% and 3.18%, respectively. Similarly, a 1 °C increase in mean temperature above 31°C was associated with a 25.18% increase in non-accidental, 34.10% in cardiovascular and 24.27% increase in respiratory mortality, in a study over Wuhan (Zhang *et al.*, 2016). High temperatures were clearly associated with increased risk for those dying from cardiovascular, respiratory, cerebrovascular, and some specific cardiovascular diseases, such as ischemic heart disease, congestive heart failure, and myocardial infarction in the review of epidemiological studies by (Basu, 2009).

Thermal conditions exert a profound influence on human health. Understanding the relationship between meteorology and mortality/morbidity is essential for developing effective public health strategies and interventions aimed at mitigating the adverse effects of extreme temperatures on human well-being.

2.1.1 Thermal indices

Thermal comfort is the subjective sensation that can be defined as the condition of mind which expresses satisfaction with the thermal environment (Epstein and Moran, 2006). Thermal indices serve as tools to quantify the intricate heat exchange between the human body and its thermal environment. These indices aim to assess comfort levels, as well as the stress imposed on the human body. Outdoor environments are influenced by various factors such as air temperature, relative humidity, water vapor pressure, wind velocity, solar radiation, and mean radiant temperature (Deb and Alur, 2010). Furthermore, personal characteristics and behavioral adaptations, including clothing choices, metabolic rate, activity levels, pre-existing health conditions, and exposure duration, significantly impact the individual's thermal sensation (Brake and Bates, 2002).

Simple indices have advantages such as ease of calculation, forecasting, and communication. However, they suffer from significant drawbacks: neglecting essential variables, producing non-comparable results, leading to misrepresentations of the thermal environment, and relying on arbitrary safety limits (Jendritzky, De Dear and Havenith, 2012). Consequently, only indices that incorporate all relevant parameters can be universally utilized across different climatic zones, regions, and seasons (Jendritzky, De Dear and Havenith, 2012).

According to (Epstein and Moran, 2006), there are 4 criteria that a biometeorological index must meet:

a) Feasibility and accuracy in a wide range of environmental and metabolic conditions.

b) Consideration of all important factors (environmental, metabolic, clothing etc).

c) Relevant measurements should reflect the worker’s exposure.

d) Exposure limits should consider physiologic and/or psychological responses reflecting increased risk to safety or health.

Heat stress indices can be categorized into three groups based on their underlying principles (Parsons, 2003): rational indices, empirical indices, and direct indices. Rational indices involve calculations that incorporate the heat balance equation. Empirical indices are based on objective and subjective measures of strain, while direct indices rely on direct measurements of environmental variables. Implementing indices from the first two groups can be challenging in work environments as they involve numerous variables and, in some cases, invasive

measurements. In contrast, the third group of indices is more user-friendly and practical, as it is based on the monitoring of environmental variables.

2.1.1.1 Wet Bulb Globe Temperature (WBGT)

The WBGT index is a widely used direct thermal index, developed in the US Navy as part of a study on heat related injuries during military training. It takes into account the readings from three different temperature sensors: a wet bulb thermometer, a dry bulb thermometer, and a globe thermometer. It is commonly used in occupational settings, sports events, and military operations to assess the risk of heat-related illnesses and to guide appropriate safety measures.

WBGT is described by

$$\mathrm{WBGT} = 0.567 * \mathrm{T} + 0.393 * \mathrm{vp} + 3.94$$

where T is air temperature and vp is air vapor pressure (Blazejczyk *et al.*, 2012).

2.1.1.2 Physiological Equivalent Temperature (PET)

PET is a universal index for characterising thermal bioclimate, allowing for the evaluation of thermal conditions in a physiologically significant manner. The index is derived from human energy balance models (Deb and Alur, 2010) and takes into account individual metabolic rates and clothing insulation levels.

PET is defined as “the physiological equivalent temperature at any given place (outdoors or indoors) and is equivalent to the air temperature at which, in a typical indoor setting, the heat balance of the human body is maintained with core and skin temperatures equal to those under the conditions being assessed” (Hoppe, 1999).

By using PET, it is possible to evaluate the thermal comfort or discomfort levels for individuals in a specific environment. The index finds applications in urban planning, outdoor activities, and the assessment of thermal comfort in buildings and it is well suited to the human biometeorological evaluation of the thermal component of different climates (Matzarakis, Mayer and Iziomon, 1999).

2.1.1.3 Physiological Equivalent Temperature (DI)

DI was first introduced by (Thom, 1959) and currently, it is expressed by

$$\mathrm{DI} = 0.5*\mathrm{Tw} + 0.5*\mathrm{Ta}$$

where Ta is air temperature and Tw the wet-bulb temperature.

DI is particularly relevant in hot and humid climates where high temperatures combined with high humidity can lead to heat-related discomfort and potential health risks. It helps individuals, especially those who are sensitive to heat or engaged in outdoor activities, to assess the potential impact on their well-being and take appropriate precautions such as staying hydrated, seeking shade, or adjusting clothing choices.

2.1.1.4 Universal Thermal Climate Index (UTCI)

UTCI was conceived as a thermal index covering the whole climate range from heat to cold (Havenith *et al.*, 2012). According to (Jendritzky, De Dear and Havenith, 2012), "UTCI is defined as the isothermal air temperature of the reference condition that would elicit the same dynamic response of the physiological model". It is perceived as one of the most comprehensive indices calculating human thermal stress (Zare *et al.*, 2018).

The formula calculating UTCI index is:

$$\mathrm{UTCI} = 3.21 + 0.87 * \mathrm{T} + 0.25 * \mathrm{Mrt} - 2.51 * \mathrm{v} - 0.02 * \mathrm{RH}$$

where T is air temperature (°C), Mrt is mean radiant temperature (°C), v is wind speed at 10 m above ground (m/s), and RH is relative humidity (%).

2.1.1.5 Apparent Temperature (AT)

AT is a thermal index that expresses thermal stress and comfort perceived by human, defined as "a measure of relative discomfort due to the combination of heat and high humidity" (Baccini *et al.*, 2008). It is computed from temperature and dew-point data as follows:

$$\mathrm{AT} = -2.653 + 0.994 * \mathrm{Ta} + 0.0153 * \mathrm{Td}^2$$

AT is a discomfort index widely met in the literature (de' Donato *et al.*, 2015; Ullah *et al.*, 2021) and it is used operationally as the main thermal index in the Italian National Heat Health Watch Warning Systems (Michelozzi *et al.*, 2010). It is also found that AT is an optimal indicator for predicting all-cause mortality risk and for activating heat alerts and warnings (Lin *et al.*, 2012; Zhang *et al.*, 2014).

2.2 Air Quality conditions

The gradual rise of human activities since the late 18th century, primarily fueled by the burning of fossil fuels and biomass, has led to the deterioration of air quality (Watts, Adger and Agnolucci, 2015; Pozzer *et al.*, 2023). Rapid urbanization rate has caused cities to face increasing pressure from growing

populations, limited resources and escalating impacts of climate change (World Health Organization, 2017). UN estimates that 68% of the world's population (2.5 billion people) will reside in urban areas by 2050 (UN Department of Economic and Social Affairs, 2018) with limited access to nature and increased exposure to environmental hazards, such as air and noise pollution (World Health Organization, 2017). The degradation of air quality has become so prominent in cities that the term urban pollution island (UPI) was lately introduced, to describe the spatial and temporal variations in pollution concentrations between urban and rural areas (Ulpiani, 2021). In modern cities, the synergistic interactions of urban heat islands (UHIs) and UPIs lead to increased pollutant concentrations via various mechanisms (Ulpiani, 2021).

Regions with poor air quality are home to approximately 90% of the global population (WHO, 2021), making it the most significant environmental risk to human health and ranked as the second-greatest environmental concern among Europeans (European Environmental Agency, 2020). According to (WHO, 2021), the most critical air pollutants are sulfur dioxide (SO_2), nitrogen oxides (NO, NO_2), ground level ozone (O_3) and particulate matter (PM), and the exposure to them is linked to adverse health outcomes.

Poor air quality, both ambient and indoor, has become a pressing issue, with more frequent and intense episodes of high pollution levels being prevalent in cities across the globe. (Fuller *et al.*, 2022) estimates that air pollution caused 6.7 million deaths in 2019, and this figure is rising. They also state that more than 90% of pollution-related deaths occur in low-income and middle-income countries. Most evidence has been related to natural, cardiovascular and respiratory causes, nervous system causes, stroke, coronary heart disease and chronic obstructive pulmonary disease (Shang *et al.*, 2013; Chen *et al.*, 2019; Gariazzo *et al.*, 2023).

Air pollution not only impacts mortality, but morbidity as well. According to European Environment Agency, exposure can lead to a wide range of diseases, including stroke, chronic obstructive pulmonary diseases, trachea, bronchus and lung cancers, aggravated asthma and lower respiratory infections (European Environment Agency, no date). The most compelling evidence regarding the health consequences of air pollution relates to cardiovascular and respiratory ailments (European Environment Agency, 2019); nevertheless, studies exploring other health impacts are also increasing (WHO, 2022; WHO Regional Office for Europe, 2022).

Older adults are more susceptible to the negative health impacts of air pollution due to their decreased ability to adapt to stressors on their physiological, metabolic, and compensatory processes, as well as their higher likelihood of having cardiovascular and respiratory diseases (Geller and Zenick, 2005; Shumake *et al.*, 2013). Elderly mortality has been found to be particularly affected by PM10 and O_3, with higher excess risks than other age groups (Cakmak, Dales

and Vidal, 2007; Katsouyanni *et al.*, 2009; Liu *et al.*, 2022; Olstrup, Åström and Orru, 2022).

In literature there is evidence that temperature exacerbates air pollution-related health effects. During the summer season, (Shi *et al.*, 2019) observed that a 1°C increase in temperature corresponds to a rise of 1.05 μg/m^3 in PM2.5 levels and a 1.02% increase in mortality associated with it. In (K. Chen *et al.*, 2018), an increase of 10 μg/m^3 in PM10 was associated with 0.03% and 0.93% increase in total natural mortality at low and high temperatures, respectively. (Jhun *et al.*, 2014) report that high temperatures exacerbate physiological responses to short-term ozone exposure, increasing mortality by 1.35% at a 10-ppb O_3 increase.

It is worth noticing that on days with high air pollution, both heat- and cold-related mortality increases (K. Chen *et al.*, 2018). Although (Stafoggia *et al.*, 2008) found higher PM10 effects on mortality during warmer days (2.54% increase on death rate), there was also an increase (0.2%) in winter, as well. Similarly, a 10μg/m^3 increase in NO_2 was associated with larger raise in non-accidental mortality in summer (2.65%) than winter (0.01%). By contrast, in (Qian *et al.*, 2010), the strongest effects of a 10-μg/m^3 increase in PM10 daily concentration on mortality were reported for winter (0.69%) than summer (0.45%).

Pollution prevention, despite its significant impacts on health, societies, and economies, has received inadequate attention and funding within the international development agenda. International organizations and national governments need to continue expanding the focus on pollution as one of the most imperative global environmental issues.

2.2.1 PM10

Particulate matter is reported to pose significant risk in health (Wang *et al.*, 2009). In 2020, the European population experienced approximately 238,000 premature deaths due to PM10 concentrations exceeding the World Health Organization's 2021 guideline of 45 μgr/m³ (EEA, 2022a).

Exposure to PM10 results to asthma attacks, bronchitis, high blood pressure, heart attack, strokes, immune system reactions, lung irritation, and increased hospitalization due to respiratory and cardiovascular diseases (Larrieu *et al.*, 2007; WHO Regional Office for Europe, 2013; *Health effects of PM10*, 2023).

High levels of PM cause an increase in all-cause, cardiovascular, respiratory and cerebrovascular mortality rates, as well. (Khaniabadi *et al.*, 2017) reports that a 10 μg/m^3 change in PM10 generates 6.6% excess of relative risk in cardiovascular mortality; similar results are obtained by (Christina Adebayo-Ojo *et al.*, 2006), where increase in PM10 concentrations are associated with an increased risk of

2.4% in CVD causes. In the systematic review and meta-analysis by (Orellano *et al.*, 2020), a significant body of evidence shows that an increase in outdoor concentrations of PM10, increases the risk of all-cause and cardiovascular, respiratory, and cerebrovascular mortality in humans. PM10 demonstrated independent effect on mortality in (Olstrup *et al.*, 2019), as an interquartile range increase in pollutant concentration was associated with a 0.8% increase in daily mortality. (Revich and Shaposhnikov, 2010) linked 10 $\mu g/m^3$ increases in daily average measures of PM_{10} with a 0.33% increase in all-cause non-accidental mortality, a 0.66% increase in mortality from ischemic heart disease, and a 0.48% increase in mortality from cerebrovascular diseases.

2.2.2 NO_2

NO_2 is a harmful air pollutant that has detrimental impacts on human health. It is linked to asthma development, increased inflammation of the airways, reduced lung function and chronic lung disease (*Nitrogen Dioxide | American Lung Association*, no date; D. Jarvis, G. Adamkiewicz, M. Heroux, R. Rapp, 2010; WHO Regional Office for Europe, 2013).

As concentration increases, health effects aggravate, too. In 2018, 1.65 million deaths were attributed to ambient NO_2 exposure in China (Zhang *et al.*, 2022). Positive associations to all-cause mortality (0.72%) are reported for 10 $\mu g/m^3$ increase in NO_2 in (Orellano *et al.*, 2020). (Christina Adebayo-Ojo *et al.*, 2006) linked 10.7 $\mu g/m^3$ increase of NO_2 to 2.2% rise in CVD and 4.5% in respiratory mortality; similar results (1.2% excess of RR in cardiovascular mortality) are demonstrated in (Khaniabadi *et al.*, 2017). Short-term exposure to this pollutant is associated to a 0.75% increase of non-accidental mortality for all age-groups (Corso *et al.*, 2020). Per 10 mg/m^3 increase in annual NO_2 exposure was associated with an hazard ratio of 1.127 for all-cause mortality in (Zhang *et al.*, 2022).

According to (Song *et al.*, 2023), more than half a million cases of deaths attributed to NO_2 exposure in urban areas could be prevented worldwide in 2019, if compliance with the latest WHO guideline.

2.2.3 O_3

Tropospheric O_3 is the second most critical pollutant of the atmosphere, playing an important role in climate change and deterioration of air quality (Khaniabadi *et al.*, 2017). It is associated to human health impacts such as increase in hospital admissions due to cardiovascular and respiratory diseases, shortness of breath, throat irritation, reduced lung function and asthma attacks (WHO Regional Office for Europe, 2013; Yari *et al.*, 2016).

Exposure to ozone accounted for 365,000 deaths in 2019 (*Health Impacts of Ozone | State of Global Air*, no date). O_3 emerges as a risk factor to CVD

mortality related to 2% risk increase, based on (Khaniabadi *et al.*, 2017); the respective rise in (Christina Adebayo-Ojo *et al.*, 2006) is equal to 1.4%. (Orellano *et al.*, 2020) reports strong associations between O3 and all-cause mortality (0.43% increase). O_3 was associated with an increase of 2% in daily mortality two days after the exposure and 1.9% after 3 days (Olstrup *et al.*, 2019). All-cause mortality risk found to be increased by 1.09%; mortality from ischemic heart disease increased by 1.61% and 1.28% mortality increase from cerebrovascular diseases was associated to 10 $\mu g/m^3$ O_3 rise, according to (Revich and Shaposhnikov, 2010).

2.2.4 Air Quality indices

Clean air is an essential prerequisite for human health and overall well-being. While air pollution data can be complex and challenging to comprehend, environmental synthetic indices offer a valuable means to condense intricate situations into a single numerical value, enabling comparisons across different time periods and geographical locations (Plaia and Ruggieri, 2011)**.** According to (Shooter and Brimblecombe, 2009), air quality indices (AQIs) serve the purpose of expressing the concentration of individual pollutants on a standardized scale, where the occurrence of effects, particularly health-related effects, is shared among all pollutants. Put simply, air quality indices provide a straightforward and easily understandable method to gauge the quality of air in relation to its potential impact on human health.

(Kanchan, Gorai and Goyal, 2015) set specific criteria that an AQI must fulfill:

1. be readily understandable by the public;
2. include the major criteria pollutants and their synergisms;
3. be expandable for other pollutants and averaging times;
4. be related to National Ambient Air Quality standards used in individual provinces;
5. avoid “eclipsing” (eclipsing occurs when an air pollution index does not indicate poor air quality despite the fact that concentrations of one or more air pollutants may have reached unacceptably high values);
6. avoid “ambiguity” (ambiguity occurs when an air pollution index gives falls alarm despite the fact that concentrations of all the pollutants are within the permissible limit except one);
7. be usable as an alert system;
8. be based on valid air quality data obtained from monitoring stations that are situated so as to represent the general air quality in the community.

AQIs can serve various aims and purposes. They are utilized to effectively communicate air quality information to the public, evaluate the effectiveness of

pollution reduction strategies, monitor medium and long-term trends, and more. While the fundamental concepts behind AQIs remain similar, their practical implementation can vary significantly (Plaia and Ruggieri, 2011). In general, there is not only one system of air pollution indicators, as several countries have created their own sets of indicators tailored to the needs of each country or region, setting national limits for air pollution.

2.2.4.1 AQI system of U.S. Environmental Protection Agency

U.S. EPA's AQI is defined with respect to the five main common pollutants: carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM10 and PM2.5) and sulphur dioxide (SO_2). AQI shows daily how clean or polluted the ambient air is, highlighting the corresponding effects on public health. The index ranges from 0 to 500. The higher its value, the higher the level of air pollution and the greater is the concern for the health of the citizens (United States Environmental Protection Agency, 2014).

AQI is a piecewise linear function of the pollutant concentration calculated as follows:

$$I = \frac{I_{high} - I_{low}}{C_{high} - C_{low}} * (C - C_{low}) + I_{low}$$

where I is the Index for pollutant, C is the rounded concentration of pollutant, C_{high} is the break point that is greater than or equal to C, C_{low} is the breakpoint that is less than or equal to C, I_{high} is the AQI value corresponding to C_{high} and I_{low} is the AQI value corresponding to $C_{low.}$ The highest individual pollutant index, I, represents the Air Quality Index of the location.

Air Quality Index (AQI) Values	Levels of Health Concern	Colors
When the AQI is in this range:	*...air quality conditions are:*	*...as symbolized by this color:*
0 to 50	Good	Green
51 to 100	Moderate	Yellow
101 to 150	Unhealthy for Sensitive Groups	Orange
151 to 200	Unhealthy	Red
201 to 300	Very Unhealthy	Purple
301 to 500	Hazardous	Maroon

Figure 2.1: AQI scale and health warnings (Adapted from (United States Environmental Protection Agency, 2014))

2.2.4.2 European Air Quality Index (EAQI)

EAQI gives to users the opportunity to gain a better understanding of air quality in their respective living, working, or travel locations. By providing real-time information for Europe, users can access valuable insights into the air quality of specific countries, regions, and cities. This index is built upon concentration values for up to five significant pollutants, namely PM10, PM2.5, O_3, NO_2 and SO_2.

EAQI reflects the potential health impact of air quality, focusing on the pollutant with the poorest concentration and its associated health effects. To generate the index, current air quality data reported hourly by member countries of the European Environment Agency are utilized. Additionally, where necessary, the index incorporates modeled air quality data from the European Union's Copernicus Atmosphere Monitoring Service (CAMS).

EAQI is accompanied by health-related messages that provide recommendations for both the general population and sensitive populations. The latter category includes individuals, both adults, and children, who have respiratory problems, as well as adults with heart conditions (European Environment Agency (EEA), 2022).

AQ index	General population	Sensitive populations
Good	The air quality is good. Enjoy your usual outdoor activities.	The air quality is good. Enjoy your usual outdoor activities.
Fair	Enjoy your usual outdoor activities	Enjoy your usual outdoor activities
Moderate	Enjoy your usual outdoor activities	Consider reducing intense outdoor activities, if you experience symptoms.
Poor	Consider reducing intense activities outdoors, if you experience symptoms such as sore eyes, a cough or sore throat	Consider reducing physical activities, particularly outdoors, especially if you experience symptoms.
Very poor	Consider reducing intense activities outdoors, if you experience symptoms such as sore eyes, a cough or sore throat	Reduce physical activities, particularly outdoors, especially if you experience symptoms.
Extremely poor	Reduce physical activities outdoors.	Avoid physical activities outdoors.

Figure 2.2: EAQI health messages (Adapted from (European Environment Agency (EEA), 2022))

2.2.4.3 Air Quality Health Index (AQHI)

In Canada, AQHI was developed as a scale aimed at assessing the effects of air quality on human health, jointly coordinated by the Department of the Government of Canada responsible for National Health Policy and the Department of the Government of Canada responsible for Coordinating Environmental Policies and Programs. This index serves as a tool for safeguarding health and helps individuals make informed decisions to minimize their short-term exposure to air pollution by adjusting their activity levels during periods of heightened pollution. Additionally, AQHI offers guidance on enhancing air quality through recommended behavioral changes that contribute to reducing the environmental impact.

One significant aspect of the index is its focus on individuals who are more susceptible to the impacts of air pollution. It provides specific advice to these sensitive populations on how to safeguard their health during periods of varying air quality, categorized as low, moderate, high, and very high health risks. By tailoring recommendations based on air quality levels, the Air Quality Health Index aims to empower individuals to protect their well-being (Stieb *et al.*, 2008).

AQHI provides a number from 1 to 10+ to indicate the level of health risk associated with local air quality. Occasionally, when the amount of air pollution is abnormally high, the number may exceed 10. The following are the objectives of the AQHI:

- ✓ Create a Canadian communications and planning tool for individuals and caregivers when considering adverse health effects associated with the air pollution mixture.
- ✓ Use "health awareness" as a tool to promote:

  greater understanding of air quality/health links;

  physical activity when health risk/air pollutant levels are low; and

  personal action to reduce air pollution.
- ✓ Create advocates for reducing air pollution.

Health Risk	Air Quality Health Index	Health Messages for At-Risk Population	Health messages for General Population
Low	**1-3**	**Enjoy** your usual outdoor activities.	**Ideal** air quality for outdoor activities
Moderate	**4-6**	**Consider reducing** or rescheduling strenuous activities outdoors if you are experiencing symptoms.	**No need to modify** your usual outdoor activities unless you experience symptoms such as coughing and throat irritation.
High	**7-10**	**Reduce** or reschedule strenuous activities outdoors. Children and the elderly should also take it easy.	**Consider reducing** or rescheduling strenuous activities outdoors if you experience symptoms such as coughing and throat irritation.
Very high	**Above 10**	**Avoid** strenuous activities outdoors. Children and the elderly should also avoid outdoor physical exertion.	**Reduce** or reschedule strenuous activities outdoors, especially if you experience symptoms such as coughing and throat irritation.

Figure 2.3: AQHI scale and health messages (Adapted from (Health Canada, 2010))

2.3 Susceptible population groups

Despite the widespread nature of air quality and thermal stress issues, their impact varies among different groups due to individual physiological sensitivities and varying degrees of exposure influenced by behavioral factors (Makri and Stilianakis, 2008). Extensive evidence demonstrates that the health consequences associated with exposure to air pollution and high temperatures exhibit different degrees of severity based on factors such as life stage (with children and older adults generally being more susceptible), preexisting cardiovascular or respiratory conditions, genetic polymorphisms, and low socioeconomic status (Basu and Samet, 2002a; Sacks *et al.*, 2011). Pregnant women are thought to particularly at risk of heat related effects (Balbus and Malina, 2009), as there is evidence that supports an association between high environmental temperature and preterm birth due to difficulty with thermoregulation and dehydration during heat exposure (Basu, Malig and Ostro, 2010).

Climate change and rapid population ageing are significant public health challenges. Understanding the health risks associated with exposure to adverse conditions on elderly people is vital for preventing related deaths and illnesses in this frail population.

Elderly vulnerability to heat is attributable to physiological and social factors, such as living alone, multiple co-morbidities and high medication use, slow physiological adaptation and behavioral response to thermal stress, vasodilation, limited access to medical care and housing with heating or cooling (Barnett, 2007; Kenney, Craighead and Alexander, 2014; Bunker *et al.*, 2016). In addition, people in the age group 65+ years of age are assumed to be more susceptible to air pollution-induced health effects, due to decreased physiological, metabolic, and compensatory processes, and due to a greater incidence of cardiovascular and respiratory diseases (Geller and Zenick, 2005; Shumake *et al.*, 2013).

(Tsoutsoubi, Ioannou and Flouris, 2021) found high fatality risks due to circulatory causes when older people are exposed to non-neutral environmental

conditions. A 1°C temperature rise increased cardiovascular, respiratory, diabetes mellitus, genitourinary, infectious disease and heat-related morbidity among the elderly (65+ years) in the study by (Bunker *et al.*, 2016). High and very high temperatures increase not only cardiovascular and respiratory mortality of people over 65 years of age by 20% to 35% (Paravantis *et al.*, 2017), but hospital admissions as well (Oudin Åström, Bertil and Joacim, 2011).

On the other hand, the elderly are particularly susceptible to dying from air pollution (Cakmak, Dales and Vidal, 2007). Exposure to PM10 is linked to the development of vascular dementia (Shim, Byun and Lee, 2023) and biomass fuel is associated with 40% risk increase in vision impairment (Zhou *et al.*, 2023). A 10 μgr/m^3 rise of NO_2 concentrations increased the risk of cardiovascular deaths by 0.25% in cold and 3.17% in warm period for people aged > 75 years; the respective values for all-cause mortality were 0.20% and 3.07% (Corso *et al.*, 2020). Last, fine particulate matter is associated to myocardial infarction deaths (Mo *et al.*, 2023) and a variety of air pollutants, such as NO_2, SO_2, O_3 and PM10 results in kidney disease mortality (Cai *et al.*, 2023).

According to (World Health Organization, 2022), public health interventions need to identify and target particularly vulnerable population groups and individuals. This allows for tailored interventions, reduces health disparities, ensures equitable distribution of resources, improves emergency planning, and enhances public awareness and education. These efforts collectively contribute to safeguarding public health, particularly for those who are most susceptible to the impacts of heat and air pollution.

2.4 Mortality displacement

Mortality displacement (or harvesting effect) is identified by a decline in mortality following occurrences of extreme values of environmental stressor under study. The presence of harvesting implies that elevated temperatures and/or pollutant concentrations primarily impact a specific subset of individuals who are already vulnerable to chronic illnesses. These individuals would have succumbed to their conditions within a few days regardless of the weather and air quality conditions.

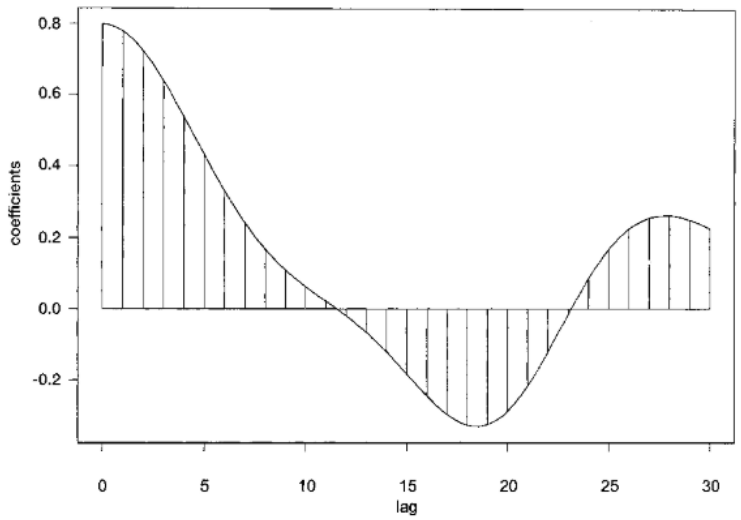


Figure 2.4: Hypothetical lag structure corresponding to the mortality displacement effect (Adapted from (Zanobetti *et al.*, 2002))

This effect is observed in literature (Schwartz, 2000; Hajat *et al.*, 2005; Baccini *et al.*, 2008; McGregor *et al.*, 2015), and it can be potentially attributed to the socio-economic and baseline health status of the population and to possible interactions between heat and air pollution (Kouis *et al.*, 2019). The variability in factors influencing individuals' vulnerability to exposure-related mortality may account for the contrasting findings in studies, where some observe a harvesting effect (Baccini *et al.*, 2008), while others do not (D'Ippoliti *et al.*, 2010).

Harvesting effect does not appear in a uniform way among similar studies and there is evidence that patterns of mortality displacement for heat-related deaths depend on the population at risk. More specifically, (Hajat *et al.*, 2005) observed differences in displacement patterns between low-income and high-income countries, with the first affected mainly by infectious diseases of the young individuals, and the latter by chronic diseases of the elderly.

2.5 Combined effects of heat and air pollution

Air pollution is a leading cause of death and disability, contributing to 6.7 million deaths globally in 2019 (*Global Health Impacts of Air Pollution | State of Global Air*, no date). The exposure to pollutants like PM10, O_3 and NO_2 results to direct increase in all-cause, cardiovascular, respiratory and cerebrovascular mortality (Christina Adebayo-Ojo *et al.*, 2006; Khaniabadi *et al.*, 2017; Shi *et al.*, 2019; Meng *et al.*, 2021; Gariazzo *et al.*, 2023). In the meantime, it is established that non-optimal temperatures disrupt the functioning of the body's thermoregulatory system, leading to various physiological responses (Osilla, Marsidi and Sharma, 2023). These responses can contribute to an increased risk of morbidity and

mortality across diverse health conditions, encompassing cardiovascular ailments, respiratory diseases, diabetes, as well as genitourinary and neurological disorders (Psistaki, Dokas and Paschalidou, 2023).

The available evidence concerning the potential interactive effects of heat and ambient air pollution remains inconclusive, by large. Until recently, the vast majority of relative studies were considering the impact of environmental stressors on human health separately (e.g. (Bao *et al.*, 2016; Kriit *et al.*, 2022)). A limited number of epidemiological studies have examined the influence of temperature while considering daily air pollution levels (Stafoggia *et al.*, 2008; Cheng and Kan, 2012; Meng *et al.*, 2012; Jhun *et al.*, 2014) either in the hot (Meng *et al.*, 2012) or the cold tail (Cheng and Kan, 2012) of the temperature distribution, whereas even less have analyzed the impact of air pollutants while adjusting for daily temperature (Turner *et al.*, 2012; Breitner *et al.*, 2014). (Jhun *et al.*, 2014) report that temperature exacerbates ozone impact on mortality, as a 10-ppb increase in daily 24-h ozone was associated with a 0.47% increase in mortality. (Meng *et al.*, 2012) connected 10 $\mu g/m^3$ increment in PM10 with 0.54% increase of total mortality, 0.56% increase of cardiovascular mortality, and 0.80% increase of respiratory mortality, with results being more prominent at high temperatures. Statistically significant interactions between PM10/O_3 and moderate temperatures were reported for all-cause (0.17%/0.66%), cardiovascular (0.23%/0.88%) and respiratory mortality (0.26%/0.79%) (Cheng and Kan, 2012). According to (Stafoggia *et al.*, 2008), seasons strongly affect the relationship between mortality and PM_{10}, and reported 2.54% increase in death risk in summer compared to 0.20% in winter, for a 10-lg/m3 variation in PM10. When confounding with high levels of O_3 and PM10, the associations between high temperatures and mortality were amplified, leading to increases in non-accidental (11.5%, 10.5%) and cardiovascular mortality (9.6%, 9.4%) (Breitner *et al.*, 2014). (Ren and Tong, 2006) revealed that the maximum temperature had a modifying effect on the relationships between PM10 and various health outcomes, including respiratory hospital admissions, emergency visits, cardiovascular emergency visits, and cause-specific mortality at different time lags.

Either confounding the temperature-mortality relationship with pollutants, or the pollution-mortality association with temperature, no uniform conclusions can be drawn. For example, some publications have provided evidence on the synergistic effects (Baccini *et al.*, 2008), others report no combined impact (Samet *et al.*, 1998; Hales *et al.*, 2000; Basu, Feng and Ostro, 2008), while in some instances, effect modifications are reported for only one of the pollutants under study (Breitner *et al.*, 2014).

The diverse perspectives on this matter continue to be a subject of debate within academic literature. Moreover, there has been relatively limited investigation into the simultaneous interactive effects of temperature and air pollution as predictors of mortality.

Studying synergy and not just confounding is a recent development in this research field. (Burkart *et al.*, 2013a) assessed the interactive effects between UTCI and PM10/O_3 on Berlin and Lisbon mortality by developing response surface models. They found strong increases in death numbers at high temperatures and high levels of O_3 for both cities, while Lisbon demonstrated mortality rise during high PM10 pollution (3% mortality change per 1 °C UTCI increase); nevertheless, changes in cold effects with increasing levels of air pollution were not reported. A similar statistical approach was implemented in (Scortichini *et al.*, 2018), in order to study PM10 and O_3 as potential factors influencing the association between temperature and natural mortality during the summer season. The tensor smoother introduced in the analysis showed an overall increase of the heat effects stratified by levels of PM10 and O_3. (Rai *et al.*, 2023) also reported significant modification of heat effect by various pollutants. Summer temperatures increased respiratory mortality by 7.7%, 11.3% and 14.3% at low, medium, and high levels of PM2.5, respectively. Likewise, cardiovascular mortality increased by 1.6%, 5.1% and 8.7% at low, medium and high levels of O_3.

The combined effect of pollution and heat on human health is complex and multifaceted, requiring further investigation to fully comprehend its impacts. It is crucial to conduct comprehensive research in order to develop effective measures that address both pollution and heat, ensuring the protection of human well-being. Taking proactive steps to mitigate these factors is essential for safeguarding public health and fostering a sustainable and resilient environment.

Chapter 3

Meteorology and air quality in the area

3.1 The Mediterranean region

Mediterranean region occupies a unique geographical position in the transition zone between North Africa and central Europe. Minor modifications of the general circulation can lead to substantial changes in the Mediterranean climate, making the area vulnerable to climatic changes (Ulbrich *et al.*, 2006). Moreover, local population is experiencing adverse health impacts from the impaired air quality due to global air pollution crossroads over the Mediterranean (Lelieveld *et al.*, 2002).

For instance, in a research on 10 Mediterranean metropolitan areas a 10-$\mu g/m^3$ increase in PM2.5 was associated with increases in all-cause (0.55%) and respiratory mortality (1.91%), and effects were more prominent among those ≥ 75 years of age (Samoli *et al.*, 2013); positive associations between PM10 and several different mortality causes (diabetes, cardiac, cerebrovascular, chronic obstructive pulmonary disease) are reported in (Samoli *et al.*, 2014). The conditions become even more adverse, as increased temperatures in the area are linked to high pollutant production (Pyrgou, Hadjinicolaou and Santamouris, 2018).

Threshold violations in air pollutant concentrations are particularly pronounced in Southern and Eastern Europe (EEA, 2018), especially with respect to particulate matter and ozone concentrations in Greece, Spain, and Italy (Pleijel, 2000; Karanasiou *et al.*, 2014; Sicard *et al.*, 2021). The collective impacts of climate

change and air pollution in these areas should be taken into consideration (Bytnerowicz, Omasa and Paoletti, 2007) under the specific topographical and meteorological conditions of each region (Valjarević *et al.*, 2021). More specifically, the ground-level ozone concentrations in Southern Mediterranean countries are often alarmingly high and are comparable to the highest levels of places that are located in the most contaminated parts of Central Europe (Moussiopoulos *et al.*, 2009).

On the other hand, the Mediterranean area is anticipated to experience more intense, severe, and frequent heat waves under warmer and drier future conditions, making it particularly susceptible to temperature increases (Giannakopoulos *et al.*, 2009; Giannaros, Melas and Giannaros, 2019; Georgoulias *et al.*, 2022). Future climate change projections characterize the Mediterranean as a prominent "hot spot" with the potential for scorching summer conditions to become commonplace by the end of the 21st century (Lelieveld *et al.*, 2012).

Warming rate is estimated between 2°C and 5°C, and precipitation decrease will reach 40%, especially in southern Europe (Lelieveld *et al.*, 2012; Zanis *et al.*, 2015). As a result, more dry days are expected while the northern part of the region will experience the most rapid increase in daytime maximum temperatures (Giorgi and Lionello, 2008; Giannakopoulos *et al.*, 2009; Lelieveld *et al.*, 2012). But both maximum and minimum temperatures will rise, exacerbating thermal discomfort conditions (Diffenbaugh *et al.*, 2007; S. C. Keppas *et al.*, 2021). (Kendrovski *et al.*, 2017) studied the projected impact of heat on population mortality across Europe under RCP8.5 and RCP4.5, and reported that heat impacts will dramatically increase over time in Mediterranean and Eastern European countries. Similar results were demonstrated in (Martínez-Solanas *et al.*, 2021), who found that temperature-attributable mortality in Europe will rapidly start to increase in RCP6.0 by the end of the century and in RCP8.5 already by the middle of the century, especially in the Mediterranean countries.

3.2 Greece

Climate change is perceived as “major threat” for Greece (Watts, Adger and Agnolucci, 2015). Studies estimate that the average temperature is projected to increase between 4.6°C and 2.6 °C by the end of the century (S. C. Keppas *et al.*, 2021; Georgoulias *et al.*, 2022), and the decreased mean precipitation will lead to prolonged dry spell length (Gao, Pal and Giorgi, 2006). According to (Vicedo-Cabrera *et al.*, 2021), the proportion of heat-related mortality attributed to human-induced climate change exceeded 20% during the period 1991–2018; in Athens alone, more than 400 heat-attributable deaths per year are expected for 2030 under RCP8.5 (World Health Organization, 2022).

It is worth noticing that Greece’s share of population over 65 is 22.3%, above EU’s average (20.6%), whereas the leading causes of death in 2018 were

ischaemic heart disease and stroke (European Observatory on Health Systems and Policies, 2021).

Detrimental air quality also poses a significant risk in Greece. According to (EEA, 2019) in 2019, Greece was found to be in violation of the three most commonly exceeded EU air quality standards for PM10, O_3, and NO_2. This violation has had severe consequences, with an estimated 75 deaths per 100,000 population attributed to air pollution in 2019. The primary causes of these deaths were ischemic heart disease, stroke, and respiratory infections (WHO Regional Office for Europe, 2022), resulting in approximately 1,101 disability-adjusted life years (DALYs) per 100,000 citizens (WHO, no date a) or 104,000 years of life lost (YLLs) for the entire Greek population (WHO, no date b).

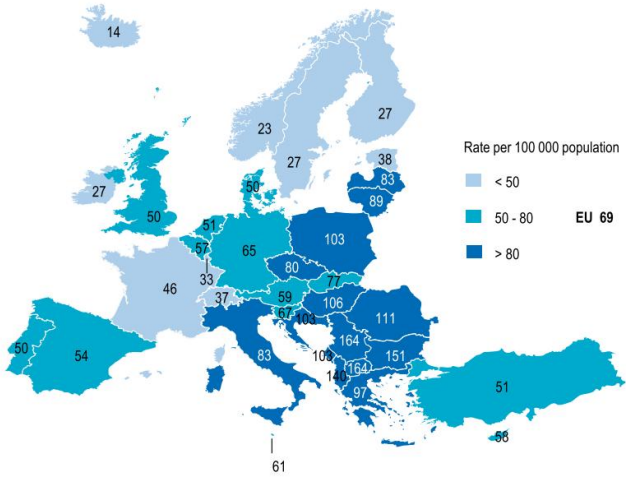


Figure 3.1: Premature deaths due to PM2.5, 2019 (Adapted from (OECD/European Union, 2022))

The acute air quality problems are most pronounced in the country's largest cities due to their dense population and the accumulation of air pollutants influenced by topography and adverse meteorological conditions, such as the urban heat island effect (Poupkou *et al.*, 2011). Athens and Thessaloniki, the two major cities in Greece, significantly exceed the EU air quality standards for PM10 concentrations (Kalabokas, Adamopoulos and Viras, 2010). Moreover, the YLLs are primarily affected by exposure to PM10, with O_3 playing a lesser role, as highlighted by (Kassomenos, Dimitriou and Paschalidou, 2013).

It is worth noting that in 2019, air pollution, specifically fine particulate matter and ozone exposure, accounted for 5% of all deaths in Greece, which is 1% higher than the EU average (European Observatory on Health Systems and Policies, 2021). Greece ranks among the countries with the highest absolute impacts

regarding O_3 and NO_2. In 2019, premature deaths attributed to PM2.5, NO_2, and O_3 reached 10,400, 2,310, and 650 fatalities, respectively (González Ortiz *et al.*, 2021).

Overall, the combined impact of projected elevated temperatures due to climate change and air pollution in Greece presents significant health risks that demand immediate governmental efforts for national adaptation and mitigation.

3.3 Thessaloniki

The urban area of Thessaloniki consists of seven municipalities (Figure 3.2). Accommodating more than 1,000,000 inhabitants (*Population-Housing Census 2021 - ELSTAT*, no date), it is the second largest city in Greece and an important economic and industrial center in the Balkans. Thessaloniki's population has a notable trend of advanced aging with 22.3% of the population aged above 65 years (European Observatory on Health Systems and Policies 2021).

Its Mediterranean climate is significantly affected by the adjacent Thermaikos Gulf in the south; the mean annual temperature of Thessaloniki is ~16 °C and the mean annual relative humidity is 62.4%. The city demonstrates prominent UHI effect with intensity between 1°C and 4°C (Giannaros and Melas, 2012).

The primary causes of air pollution in Greater Thessaloniki Area are road traffic, residential heating (Progiou *et al.*, 2023), biomass burning (Diapouli *et al.*, 2017), and industrial emissions (Moussiopoulos *et al.*, 2009). These activities have led to a decline in air quality (Melas *et al.*, 2017), particularly during the economic crisis (Zyrichidou *et al.*, 2019). In addition, particle pollution in the area is also substantially impacted by dust storms that originate from North Africa (Achilleos *et al.*, 2020; Psistaki *et al.*, 2022; Rizos *et al.*, 2022).

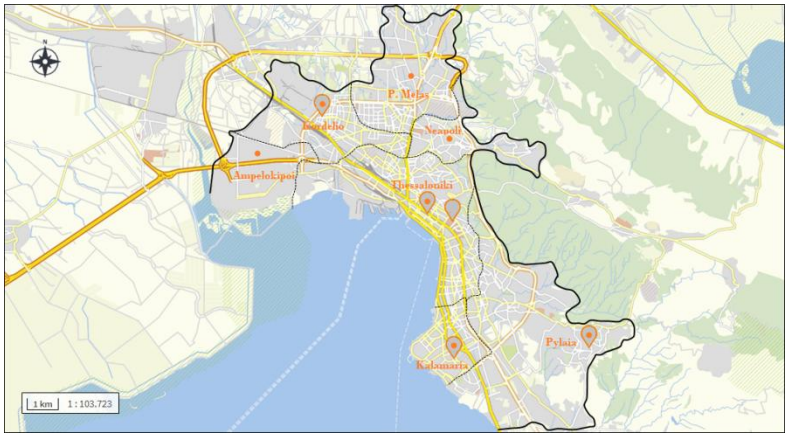


Figure 3.2. The urban area of Thessaloniki. Dashed lines represent municipal borders.

The city experiences exceptionally impaired meteorological and air quality conditions. Despite this fact, current literature focuses almost entirely on Athens, either on heat- (Baccini *et al.*, 2008; Paravantis *et al.*, 2017; Zafeiratou *et al.*, 2019), or pollution-related mortality (Gryparis *et al.*, 2004; Touloumi *et al.*, 2006; Kassomenos, Dimitriou and Paschalidou, 2013). Only recently, a few studies concerning Thessaloniki were published, e.g. (Kouis *et al.*, 2019; Parliari *et al.*, 2022; Psistaki, Dokas and Paschalidou, 2022; Parliari, Giannaros, *et al.*, 2023).

Thessaloniki is one of the most polluted cities in Europe, especially with respect to the PM10 levels (Vlachokostas *et al.*, 2012), but also regarding PM2.5 (Diapouli *et al.*, 2017), O_3, VOCs, and noise pollution levels (Vlachokostas *et al.*, 2013). O_3 limit values are mostly exceeded during the summer months, while winter is the most favorable season for PM10 violations (Moussiopoulos *et al.*, 2009; Kalabokas, Adamopoulos and Viras, 2010). Nevertheless, Thessaloniki's major air quality problem consists of PM10 concentration levels. As a result of consecutive violations of daily PM10 limits established by the EU during 2005-2019, the European Court of Justice recently convicted Greece for the impaired air quality of Thessaloniki (Case C-70/21). Indicatively, 67 PM10 daily exceedances were reported for 2019, instead of 35 permitted by EU rules (Ministry of Environment and Energy, 2020). The increased exposure to PM10 accounted for 530 M€ in 2002, based on the median value-of-a-life-year metric (Vlachokostas *et al.*, 2012).

Exposure to such levels of pollution impacts human health, as expected. (Giannaros *et al.*, 2011) found positive correlation between daily maximum Aggregate Risk Index values and daily hospital admissions for cardiac diseases. Recently, (Parliari, Giannaros, *et al.*, 2023) showed direct increases in all-cause and cardiorespiratory mortality with regard to PM10 (2.3% and 2%) and O_3 (3.9% and 5.3%), which were more prominent between day 0 and 3. Similarly, a 10 μg/m3 increase in PM2.5 resulted in 1.1% rise in cardiovascular mortality, published by (Psistaki *et al.*, 2022). The interaction between air quality and thermal stress is exceptionally important for the local population, as Thessaloniki demonstrates strong Urban Heat Island Effect, ranging from 2°C to 4°C and from 1 °C to 3 °C during summer and winter, accordingly (Giannaros and Melas, 2012). City center, with acute air quality conditions, is characterized by high thermal and strong air quality stress which are extremely detrimental to public health (Zoumakis *et al.*, 2011). (Papanastasiou, Melas and Kambezidis, 2015) revealed combined impact of air pollution and discomfort conditions in Thessaloniki, which was more pronounced during HW days. According to this study, most of the citizens suffered discomfort in 76% of the HW days and in the same period the concentrations of PM10, NO_2 and O_3 increased as well.

Thermal stress conditions, especially elevated temperatures, deteriorate living conditions for the local population. According to (Kouis *et al.*, 2019), heat

depicted immediate increase on cardiovascular (4.4%) and respiratory mortality risk (5.9%) of the city, above 33 °C. Although extreme low temperatures demonstrated larger risk (1.61) to public health than extreme high (1.54), the highest mortality impact was estimated for moderately cold temperatures in the study of (Psistaki, Dokas and Paschalidou, 2022). Based on (Parliari *et al.*, 2022), 2.34% of deaths were attributed to heat and 1.34% to cold; percent changes in mortality per 1°C change above and below 22°C showed larger increases for cause-specific mortalities in heat, in contrast to smaller increases in cold.

Under the influence of climate change, there is urgent need for further study of the area. (S. Keppas *et al.*, 2021) showed that urban heat island intensity during heat waves will exceed 6 °C in Thessaloniki until 2100, whereas number of heat wave days is expected to increase 12 times compared to present. The city is expected to witness an escalation in heat-related cardiorespiratory mortality, with the projected surplus of annual heat-related deaths ranging from 2.4 to 433.7 across different scenarios (2080 – 2099) (Kouis *et al.*, 2021). Last, (Parliari, Keppas, *et al.*, 2023) estimated that mortality burden due to heat will reach 10% during 2096-2100, compared to 6% in current climate conditions (2006-2010), under scenario RCP8.5.

To address these interconnected issues, effective and enduring public action health plans must be identified and put into action (Miranda *et al.*, 2015; Silveira *et al.*, 2016). In general, there is a significant lack of studies that examine the suitability of mitigation measures in terms of health benefits for the area of Thessaloniki. Nevertheless, specific policies to combat particulate air pollution were tested in a recent study (Progiou *et al.*, 2023), which resulted in a more than 20% reduction in the PM10 concentrations in Thessaloniki, Greece. Based on this scenario, (Parliari, Giannaros, *et al.*, 2023) showed respective decrease in total excess mortality by 0.4%. As it is evident, it is necessary to assess the health benefits of the abatement measures by quantifying the impact of air pollution and thermal discomfort on human health for the citizens of Thessaloniki.

Chapter 4

The statistical modeling framework

4.1 Distributed Lag Models

The primary objective of a statistical regression model is to establish the connection between a group of predictors and an outcome variable, and to subsequently estimate the associated impact. However, complications arise when the relationship exhibits temporally delayed effects. For example, in biomedical research it is commonly appreciated that an exposure event produces effects lasting well beyond the exposure period, with an increase in risk occurring from few hours to many years later, depending on the physiological processes linking the exposure and the health outcome.

In such cases, the influence of a predictor, referred to as an “exposure event”, extends beyond the immediate period and affects the outcome over a certain duration. This phenomenon has been associated with chronic exposures to environmental stressors, drug intake or occupational exposures to carcinogenic substances (Gasparrini, 2014b). Addressing this temporal dependency necessitates the use of more intricate models that can accurately capture the association and describe the temporal structure of the relationship (Gasparrini, 2011a).

The solution to this issue comes as the incorporation of an extra dimension to the exposure-response relationship, describing the temporal dependence between the exposure and outcome in terms of temporal lag. This term represents the time interval between the exposure event and the outcome when evaluating the delay of the effect and introduces the concept of exposure–lag–response associations (Gasparrini, 2014b).

Several techniques have been proposed to accommodate the temporal variation in risk because of protracted exposures (Thomas, 1988; Vacek, 1997; Hauptmann *et al.*, 2000; Sylvestre and Abrahamowicz, 2009). However, the main limitation of these statistical methods was the assumption of a linear exposure–response relationship.

Distributed lag models (DLMs) are statistical models based on a distributed lag function, analogous to the weighting function described in previous studies (Hauptmann *et al.*, 2000), and analyzing the relationship between an independent variable (predictor) and a dependent variable (the outcome) while accounting for the time-lag effects. It is an extremely useful statistical modeling tool, firstly introduced in econometrics (Almon, 1965) and then in epidemiological studies that capture the links between environmental stresses (such as heat or air pollution) and health outcomes (Lubczyńska, Christophi and Lelieveld, 2015; Gu *et al.*, 2020; Kriit *et al.*, 2022).

This methodology allows the effect of a single exposure event to be distributed over a specific period of time, using several parameters to explain the contributions at different lags, thus providing a comprehensive picture of the time-course of the exposure-response relationship. The inclusion of lagged values allows for the examination of the dynamic relationship between the variables over time.

Assuming a linear exposure–response relationship between the outcome variable M_t (e.g. mortality counts) and some environmental exposure AT_t (e.g., temperature), DLMs can be generically defined as

$$M_t \sim NegBin(\mu_t, \theta) \quad (1)$$

$$log(\mu_t) = \alpha + \beta_0 AT_t + \beta_1 AT_{t-1} + \cdots + \beta_L AT_{t-L} \quad (2)$$

where L days is the maximum temporal lag. The use of the Negative Binomial distribution (NegBin) is a conventional choice in epidemiological analyses as it extends the Poisson distribution to allow for over-dispersion (extra variance). The linear "effects" β_l act multiplicatively on the mean mortality count μ_t (and additively on $\log(\mu_t)$).

Although simple and effective, the approach assumes that the effect of the exposure at each lag is linear, which is a substantial constraint, particularly with respect to scientific understanding on how temperature relates non-linearly to mortality (Honda *et al.*, 2014). Some attempts to relax this assumption and explore non-linear lagged effects of exposure variables have been proposed (Braga, Zanobetti and Schwartz, 2001; Roberts and Martin, 2007; Muggeo, 2010). The most commonly used development is the one firstly conceived and applied by (Armstrong, 2006), who modeled non-linear and lagged exposure-response relationships as Distributed Lag Non-Linear Models.

4.2 Distributed Lag Non-Linear Models

DLMs are built on the premise of a linear connection between exposure and outcome. Nevertheless, it is crucial to consider the well-established nonlinear relationships, as emphasized by (Braga, Zanobetti and Schwartz, 2001; Gasparrini and Armstrong, 2010).

Distributed Lag Non-linear Models (DLNMs) offer a versatile modeling approach that can effectively capture both the nonlinear and delayed impacts of environmental factors on the outcome. In contrast to conventional models, DLNMs introduce the temporal lag explicitly as a dimension, allowing for the representation of the association between temperature/air pollution and mortality over time. This bi-dimensional space, encompassing both the exposure and the lag, defines the exposure-lag-response relationship, providing a comprehensive characterization of the dependency (Gasparrini, Armstrong and Kenward, 2010; Gasparrini, 2021).

A statistical development of these models is based on the utilisation of basis functions for defining non-linear functions that describe the association of the independent variable (exposure) with the dependent variable (mortality) across different lags. Specifically, two sets of (marginal) basis functions are chosen independently, one for the lag dimension and one for the exposure dimension. These are then combined using the idea of a tensor product, to produce a bi-dimensional cross-basis function (Gasparrini, 2011b, 2014b). The choice of the two sets of basis functions determines the shape of the relationship in each dimension. In this sense, DLMs are a special case of the more general DLNMs, when the exposure-response is assumed linear.

The framework described in Equation (2) can be extended to DLNMs in order for the effect of the exposure at each lag to be non-linear, by extending the formulation of μ_t via:

$$\log(\mu_t) = \alpha + h(0, AT_t) + h(1, AT_{t-1}) + \cdots + h(L, AT_{t-L}) \qquad (3)$$

where $h(l, AT_{t-l})$ is a two dimensional function of lag and the stressor/s. Constructing this function using regression splines can be achieved using tensor products (also termed a cross-basis function) (Wood, 2017; Economou *et al.*, 2023).

DLNMs have become the most commonly used method in literature to quantify the health effects of various environmental stressors, concerning thermal stress (e.g. (de' Donato *et al.*, 2015; Martínez-Solanas *et al.*, 2018; Parliari *et al.*, 2022; Psistaki, Dokas and Paschalidou, 2023)), or air pollutants (e.g. (Psistaki *et al.*, 2022; Font-Ribera *et al.*, 2023; Gariazzo *et al.*, 2023; Parliari, Giannaros, *et al.*, 2023). In order to assess the combined impact of air quality and heat discomfort on health, some studies have either confound the temperature-mortality relationship with pollutants ((Stafoggia et al., 2008; Cheng and Kan, 2012; Meng

et al., 2012; Jhun et al., 2014)), or the pollution-mortality association with temperature ((Turner et al., 2012; Breitner et al., 2014)). Nevertheless, no uniform conclusions have been drawn. For example, some publications have provided evidence on the synergistic effects (Baccini *et al.*, 2008), others report no combined impact (Samet *et al.*, 1998; Hales *et al.*, 2000; Basu, Feng and Ostro, 2008), while in some instances, effect modifications are reported for only one of the pollutants under study (Breitner *et al.*, 2014).

4.3 A unifying modelling approach for distributed lag models

DLNMs have certain restrictions with regards to studying synergy of a combination of different exposures, and over-fitting (over-explaining) the data. Recently, a modelling approach to fitting DLNMs that encompasses all necessary extensions into a unified framework has been developed and implemented by (Economou *et al.*, 2023). More specifically, they proposed to fit DLNMs using the machinery of penalised Generalised Additive Models (GAMs) as implemented in the R package *mgcv* (Wood, 2011, 2017).

The hierarchical nature of the approach is particularly important when considering interactions of an already complex structure (i.e., the 2D exposure-lag function) with other factors, since hierarchical structures are a natural way of dealing with sparse data and the 'curse of dimensionality'. GAMs from the *mgcv* package have been utilised before in fitting DLNMs across a range of application areas and one of the main contribution of this study was to illustrate further the use of GAMs for flexible analyses involving the effect from lagged exposures.

Assuming that $h(l, AT_{t-l})$ in Equation (3) is smooth, then the model is a GAM which (using *mgcv*) can be used to optimally estimate $h(l, AT_{t-l})$ by penalising its flexibility. Penalisation in non-linear regression models is important in order to avoid over-fitting the data, and to also reduce sensitivity to the choice of L (as long as this is large enough).

More generally, equation (3) above can be written as:

$$\log(\mu_t) = \alpha + \sum_{l=0}^{L} h(l, x_{t-l}) + \log(O_t) \quad (4)$$

where x_t is an environmental exposure (AT_t or whichever stressor desired) and O_t is population count, in case we pool data from different regions. Using *mgcv*, the splines are by default constrained to be centered at zero, so that $h(l, x_{t-l})$ is the additive change in the overall log mean count of deaths.

Additionally,

$$RR(l, x_{t-l}) = \exp\{h(l, x_{t-l})\} \quad (5)$$

can be interpreted as the relative risk (RR), the mutltiplicative change with respect to exp{a} (the mean count across the time period of study).

In the work described in the present thesis, we aimed to study the synergistic effect of air pollution (PM10, O_3, NO_2) on daily mortality. For this, we define interactions of the AT-lag effect with other exposures (e.g. with PM10), via

$$\log(\mu_t) = \alpha + h\left(0, AT_t, PM_{10,t}\right) + h\left(1, AT_{t-1}, PM_{10,t-1}\right) + \cdots + h\left(L, AT_{t-L}, PM_{10,t-L}\right). \quad (6)$$

Function $h(\cdot)$ can be also defined using tensor product interactions of regression splines (Wood, 2017), a robust and flexible approach to defining smooth functions across many dimensions. The models presented in Chapter 7 were implemented in the R package *mgcv*, which makes use of penalised maximum likelihood to estimate these smooth functions.

Since we are using *mgcv*, $RR\left(l, AT_{t-l}, PM_{10,t-l}\right) = (\exp\{h(l, AT_{t-l}, PM_{10,t-l})\})$ is still the relative risk compared to the mean mortality count exp{a}. Therefore, $RR(\cdot) > 1$ implies greater than average mortality risk, whereas $RR(\cdot) < 1$ means lower-than-average risk.

4.3.1 Interpretation of estimated quantities

The conventional way of illustrating the estimated effects from DLNMs is a plot of RR over a grid of finite values for x_{t-l} and l (Figure 4.1). This is a 3D plot showing how estimated risk varies for values of the exposure across different lags. It is a counterfactual "statement" of keeping x_{t-l} fixed for all l (e.g. fixing temperature at 40°C for 21 days) and seeing what the associated contributions are to risk for each of lag.

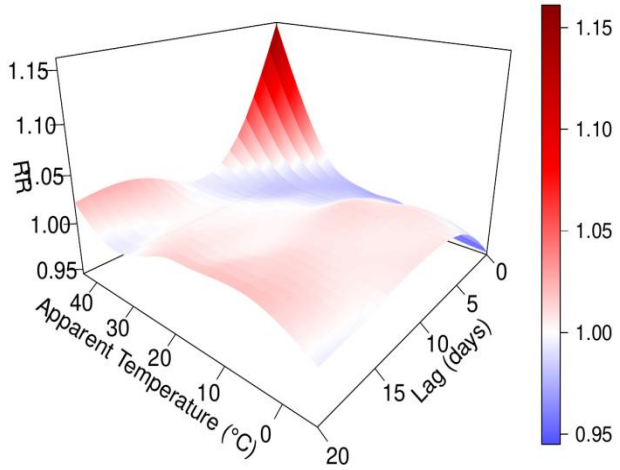


Figure 4.1. Relative risk estimates for the Thessaloniki data based on a Negative Binomial GAM (Adapted from (Economou *et al.*, 2023). Red colour indicates RR>1 and blue shows RR<1.

A useful summary of the effect in the exposure dimension is the cumulative risk (CR) where the additive effects $h(l, x_{t-l})$ are summed across the lags. For instance,

$$CR(AT) = \exp\left\{\sum_{l=0}^{L} h(l, AT)\right\} \qquad (6)$$

is the cumulative risk (CR) for AT_t from model (3).

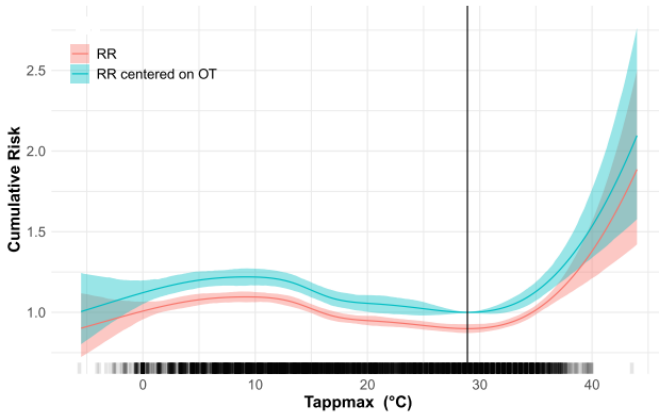


Figure 4.2. Cumulative relative risk estimates for the Thessaloniki data (Adapted from (Economou *et al.*, 2023)).

GAMs implemented in *mgcv* can be interpreted in a Bayesian way (Wood, 2017) and Monte Carlo simulation can be used to quantify the associated uncertainty in estimating the smooth function $h(\cdot)$. This in turn enables the assessment of "significance" in the estimated RR, which here is determined by checking whether the value 1 lies within the 95% credible interval of $\rho(\cdot)$. If it is not, then we can say that with probability 0.95 the value of the RR is not 1 and that the weight of evidence supporting this is strong.

In terms of interpretation, RR and CR are counterfactual quantities, since the variability of the exposure is not allowed for. As a result, metrics such as the Attributable Fraction (AF) have been proposed (Steenland and Armstrong, 2006) to interpret the risk estimates in terms of the observed data. If we define R_0 as the mortality risk at the optimum temperature value (or OT, the exposure value form which cumulative risk it at its minimum) as the risk of the "non-exposed" population, and R_1 as the risk due to any other exposure value x, then

$$AF = 1 - \frac{R_0}{R_1} \quad (7)$$

is one minus the risk ratio which can be interpreted as the fraction of mortality cases attributable to x_t being different to the OT.

For DLNMs we use CR to define risk so for observed exposure x_t on day t:

$$AF\ (x_t) = 1 - \frac{\exp\{\sum_{l=0}^{L} h(l,OT)\}}{\exp\{\sum_{l=0}^{L} h(l,x_t)\}} = 1 - exp\{\sum_{l=0}^{L}[h\ (l,x_t) - \ h(l,OT)]\} \quad (8)$$

The exposure in the sum is x_t rather than x_{t-l} so what is quantified here is how the risk of experiencing x_t "today" is distributed over the next L days. This was termed as the forward AF in (Gasparrini and Leone, 2014) who provide a thorough exposition of attributable risk from DLNMs.

The attributable number (AN) then uses the observed number of cases on day t, y_t to quantify the number of cases attributable to x_t. Specifically, the number of deaths attributed to the exposure being x_t on day t, is:

$$AN\ (x_t) = AF\ (x_t) * \ y_t \quad (9)$$

Chapter 5

Short-Term Effects of Apparent Temperature on Cause-Specific Mortality in the Urban Area of Thessaloniki, Greece

The interactions between ambient temperature and human health have emerged as major issues in the global research community during recent years. Not only extreme temperatures (Basu and Samet, 2002b; Anderson and Bell, 2009; McGregor *et al.*, 2015), but also changes in moderate temperatures have been shown to present a direct increase in mortality (Analitis *et al.*, 2008). Meanwhile, climate change is recognized as one of the most imperative global health threats in the 21st century (S. C. Keppas *et al.*, 2021). Several areas around the globe are at high risk not only in present (Iyakaremye *et al.*, 2021) but in future climate as well (Ullah *et al.*, 2022).

The Mediterranean area is particularly susceptible to temperature increases and it is anticipated to experience more intense, severe and frequent heat waves under warmer and drier future conditions (Giannakopoulos *et al.*, 2009; Giannaros, Melas and Giannaros, 2019; Georgoulias *et al.*, 2022). Concerning Greece, located in southeast Mediterranean, the average temperature under a "business as usual" scenario (Representative Concentration Pathway RCP8.5) is projected to increase by 4.5 °C in summer and 2.6 °C in winter, until 2100 (S. C. Keppas *et al.*, 2021). Taken into consideration poor air quality, comfort conditions become even more unfavorable during heat wave episodes (Papanastasiou, Melas and Kambezidis, 2015).

Global warming is generally predicted to lead to both an increase in heat-related mortality and a decrease in cold-related mortality (Watts, Adger and Agnolucci, 2015). Nevertheless, it is well established that the temperature–mortality relationships demonstrate strong dependencies on local climate characteristics and vary significantly among study areas (Armstrong *et al.*, 2011). Therefore, it is of vital importance to conduct local-based environmental epidemiology studies and thorough investigation on the city level, in order to deliver robust heat-health action plans for the improvement and strengthening of public decision making and health care (Matthies *et al.*, 2008). These action plans should also include meteorological variables such as relative humidity and precipitation, when possible, in order to better formulate adaptation strategies and measures (Mie *et al.*, 2022; Sein *et al.*, 2022). Associating ambient temperatures with health outcomes poses significant challenges. To model the temperature–health dependencies, the dose–response association, which is non-linear and heterogeneous between populations with different demographic characteristics, should be taken into consideration (Gasparrini, Guo and Hashizume, 2015). In addition, the impact of the exposure event may not be immediate, but rather delayed in time by a few days or even weeks (defined lags). Sophisticated statistical approaches are necessary to describe such complex patterns.

Distributed lag non-linear models (DLNMs) is a flexible modeling framework capable of simultaneously representing the nonlinear and delayed effects of temperature on mortality. In addition to the usual exposure–response relationship over the space of the predictor, the lag dimension represents a new space over which the association is defined, by describing a lag–response relationship. The dependency is characterized in the bi-dimensional space of predictor and lag, and it is defined as an exposure-lag-response association (Gasparrini, 2011b). DLNMs have been successfully applied in previous temperature-related epidemiological studies: Nordio et al. (Nordio *et al.*, 2015) investigated 211 US cities from 1962 to 2006, accounting for hot and cold temperatures at different lags, to evaluate change of associations over space and time. An extensive analysis between 1998 and 2012 estimated the location-specific temperature–mortality relationships of 147 regions in 16 European countries (Martínez-Solanas *et al.*, 2021), and de'Donato et al. (de' Donato *et al.*, 2015) evaluated the patterns of changes in the temperature–mortality relationship and the number of deaths attributable to heat in nine European cities before and after summer 2003 (1996–2002 and 2004–2010), also controlling for air pollution.

Greece lies within the Mediterranean climate change hotspot, and according toWHO, more than 400 heat-attributable deaths per year are expected in Athens for 2030 under RCP8.5 (World Health Organization, 2022). Previous studies concerning Athens showed an increase in cardiovascular and respiratory mortality among the elderly (65 years and over) by 20% to 35% respectively (Paravantis *et al.*, 2017), and reported a 5.54% increase in natural mortality above the city-specific threshold (Baccini *et al.*, 2008). Last, a recent study of Zafeiratou et al.

investigated the intra-urban differentiation in the temperature–mortality effects of 42 Municipalities within the Greater Athens Area, showing an increase on all-cause, cardiovascular and respiratory mortality for increases in temperatures (Zafeiratou *et al.*, 2019).

As it has been made evident, the literature focuses almost entirely on Athens, with the rest of Greek urban agglomerations being under-represented. The recent study by Kouis et al. (Kouis *et al.*, 2019) is the first significant contribution for the greater area of Thessaloniki, on the association between high ambient air temperature and cardio-respiratory mortality from 1999 to 2012. The study shows significant effects of heat above the temperature threshold of 33 °C. Furthermore, cardiovascular and respiratory mortality risk increased by 4.4% and 5.9% above the threshold, respectively.

For such purposes, we investigate the association between daily maximum apparent temperature and daily all-cause (natural, non-accidental), cardiovascular, cerebrovascular and respiratory mortality and mortality concerning the elderly (all-causes, 65+ years) from 2006 to 2016 in the urban area of Thessaloniki, by describing the exposure-lag-response association with the use of a DLNM. We also examine the effect of time lag and non-optimum temperatures using measures such as relative risk and attributable fractions, as very little is known about the relative contribution of both heat and cold from moderate and extreme temperatures to the whole disease burden.

The present Chapter is based on recent developments in statistical modeling to account for the versatile temperature–mortality dependencies. This single-city analysis demonstrates significant advantages, taking into consideration the size of the examined area, the city population lasting exposure to high temperatures and the increasing proportion of elderly people among urban dwellers. The data and methodology used in this work are described in Sections 5.1 and 5.2 and contain detailed presentation of results, and Section 5.3 summarizes the major conclusions.

5.1 Data and Methods

5.1.1 Study area

The study focuses on the urban area of Thessaloniki, consisting of six Municipalities and one Municipal Unit. Thessaloniki, the second largest city of Greece and one of the largest urban agglomerations in the Balkan Peninsula, is located in the northern part of the country accommodating approximately 1,000,000 inhabitants (Poupkou *et al.*, 2011). As shown in Figure 5.1, it is built along the north-east coast of the Thermaikos Gulf and its Mediterranean climate, with hot and dry summers and mild and wet winters, and is directly affected by

the sea. The annual mean temperature is 15.9 °C, the annual mean relative humidity is 62.4%, the annual mean precipitation is 448.7 mm and the annual mean wind speed is 5.6 m/s (Giannaros and Melas, 2012).

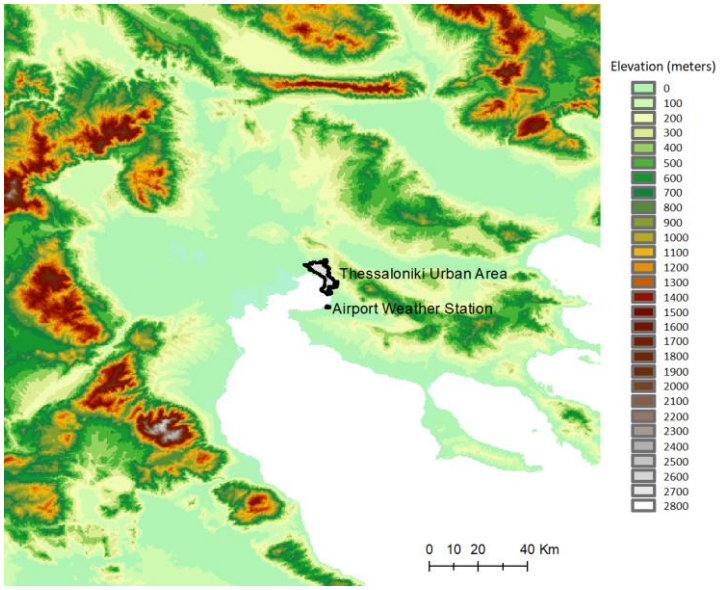


Figure 5.1. The study area. Topography is shaded with linear altitude (above sea level) scales. The locations of Thessaloniki centre and Airport weather station are shown.

5.1.2 Meteorological and Mortality Data

Hourly values of temperature and dew-point temperature for the period 2006–2016 were obtained from the Makedonia Airport weather station (Longitude 22.97, Latitude 40.53, Elevation 2m), which is operated by the Hellenic National Meteorological Service. Previous studies, e.g., (Ullah *et al.*, 2021), have shown that uniformity and stability tests are performed to achieve better results when using in-situ data. Nevertheless, the meteorological dataset used in this study is provided by HNMS, responsible for Greece's national weather forecast and certifier of the national weather network. Therefore, the evaluation performed on the data by the authors indicated no further assessment.

The exposure variable considered in the study is represented by Apparent Temperature, a thermal index that expresses thermal stress and comfort perceived by humans. To identify the most effective thermal predictor of heat-related mortality, we investigated daily mean temperature (Tmean, °C) and daily maximum Apparent Temperature (Tapp, °C). Tapp was computed from temperature and dew-point data as follows:

$$Tapp = -2.653 + 0.994*Ta + 0\ 0153*Td^2$$

where Ta = air temperature (°C) and Td= dew point temperature (°C). Then, the daily maximum value was extracted ($Tapp_{max}$), defined as the highest among hourly values.

Tapp is a discomfort index widely used in the literature (D'Ippoliti *et al.*, 2010; de' Donato *et al.*, 2015) and it is used operationally as the main thermal index in the Italian National Heat Health Watch Warning Systems (Michelozzi *et al.*, 2010). It is also found that Tapp is an optimal indicator for predicting all-cause mortality risk and for activating heat alerts and warnings (Lin *et al.*, 2012; Zhang *et al.*, 2014).

The Hellenic Statistical Authority (ELSTAT) provided the daily mortality data, including age and cause of death for all Municipalities in the urban area of Thessaloniki for the study period (2006–2016). The causes of death were classified to All causes (natural, non-accidental), Cardiovascular, Cerebrovascular and Respiratory, according to ICD-10 (International Classification of Diseases, 10th version). A focus on elderly total mortality was carried out, considering all total deaths among people aged 65 years and older.

5.1.3 Data analysis

When assessing the mortality–temperature relationship in a specific area, the most appropriate temperature-based index needs to be investigated (Analitis *et al.*, 2008). Various studies have been conducted on the matter but were unable to draw a decisive conclusion (Barnett, Tong and Clements, 2010; Kim *et al.*, 2011), whereas in order to adopt an appropriate temperature index, regional meteorological characteristics and the disease status of population should be considered.

In the present study, we investigate the effect of temperature-related variables on mortality for the urban area of Thessaloniki during the period 2006–2016, using Distributed Lag Non-linear Models in order to simultaneously account for the non-linear and lagged effect of temperatures on mortality, as previously presented in the literature (Gasparrini, 2014a, 2014b; Guo *et al.*, 2021). The main advantage of this method is that it provides a detailed representation of the time-course of the exposure–response relationship, which then estimates the overall effect in the presence of delayed contributions. This family of models is implemented in the package DLNM (Gasparrini *et al.*, 2017) within the statistical environment R (https://www.r-project.org/foundation/).

According to the Akaike information criterion (AIC) (Gasparrini, Armstrong and Kenward, 2010), we applied a generalized non-linear model with quasi-Poisson family, with the following choices regarding the control of confounders for the effect of temperature index: (i) natural cubic splines to describe the exposure–response function; (ii) natural cubic splines to describe the lag–response function; (iii) knots were placed at quantiles (10th, 75th, 90th) in the range of temperature

variables and at equal intervals in the logarithmic scale of lags; (iv) maximum lag was set to 20 days; (v) indicator variables were chosen for day of the week and 6 degrees of freedom per year were set to describe long-time trends and seasonality.

To evaluate the best model specification concerning the exposure variable, we compared the constructed models with T_{mean} and $Tapp_{max}$ using:

The Quasi Akaike Information Criterion (QAIC), a modified version of AIC to deal with the over-dispersed Poisson model, which can be used to assess the model fit of the quasi-Poisson regression model. It considers both the statistical fitness of the model and the number of parameters fitted (Peng, Dominici and Louis, 2006).

The partial autocorrelation function (PACF) criterion calculated as the absolute value of the sum of the partial autocorrelations of the residuals from lags 1 to 20 (Touloumi *et al.*, 2006). PACF investigates the remaining autocorrelation.

The best model is chosen when/if both QAIC and PACF are minimized at the same time. These two criteria are widely used in time series analysis to decide for the best fit (Peng and Dominici, 2008; Rodopoulou *et al.*, 2015; Yan *et al.*, 2019).

Table 5.1 reports QAIC and PACF values for the two models. Based on these, $Tapp_{max}$ can be uniformly chosen as the most representative exposure variable for Thessaloniki for our dataset.

Table 5.1. Model fit statistical criteria per exposure variable.

Temperature Index	**QAIC**	**PACF**
T_{mean}	23,125	3.918
$Tapp_{max}$	23,088	3.879

5.2 Results and Discussion

During the 11-year study period, we analyzed 73,990 deaths from all natural causes— 21,811 from cardiovascular diseases, 10,007 from cerebrovascular causes and 7134 from respiratory causes. Moreover, total mortality concerning the elderly counted 62,482 deaths. Table 5.2 provides the descriptive statistics on exposure variable $Tapp_{max}$ (bottom panel) and daily mortality (top panel) during the study period. Elderly mortality is distinctively noticeable, as Greece is among the countries with the highest proportion of elderly population in Europe (EUROSTAT, 2019). It is also evident that cardiovascular deaths account for an important part of cause-specific daily mortalities. This result is supported by

(European Observatory on Health Systems and Policies, 2019), which reported that stroke and ischemic heart disease is the leading causes of death in Greece.

Table 5.2. Summary statistics of daily mortality (number of deaths, bottom) and Tappmax (°C, top).

$Tapp_{max}$					
Median	**Range**	**Min**	**5th perc.**	**95th perc.**	**Max**
18.7	49.1	−5.6	2.5	35	43.5

Daily Mortality		
	Mean	**St. dev.**
All-cause	18.4	4.7
Cardiovascular	5.4	2.4
Cerebrovascular	2.5	1.6
Respiratory	1.8	1.4
Elderly	15.5	4.4

Figure 5.2 displays the bi-dimensional exposure-lag-response surface of the fitted RR in a three-dimensional diagram for maximum apparent temperature and lag values. The association between $Tapp_{max}$ and mortality is non-linear, suggesting an immediate increase in mortality for exposures to high levels of $Tapp_{max}$ at lag days 1–3, whereas for low levels the effect is delayed (day 10–15).

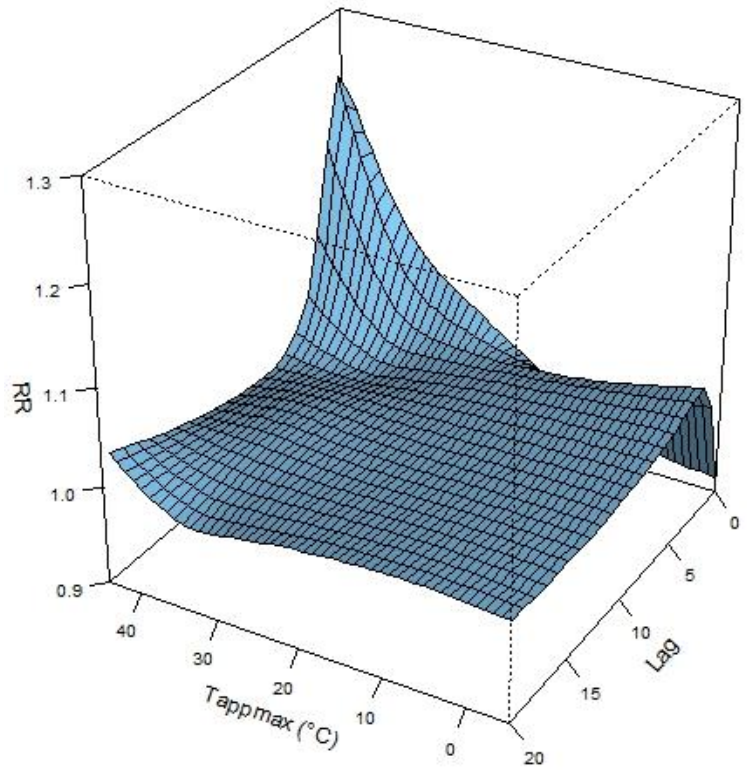


Figure 5.2. Exposure−lag-response risk surface demonstrating the nonlinear association between temperature and mortality, as calculated for the city of Thessaloniki for the period 2006−2016.

Figure 5.3 top panel shows an overall cumulative exposure–response curve (with 95% CI marked as grey areas), interpreted as the risk cumulated over the entire lag period of 20 days, and $Tapp_{max}$ range as a frequency histogram. Dashed lines define extreme temperatures (5^{th} and 95^{th} percentile, 2.5°C and 35°C respectively) and dotted line represents minimum mortality temperature (MMT) at 22°C.

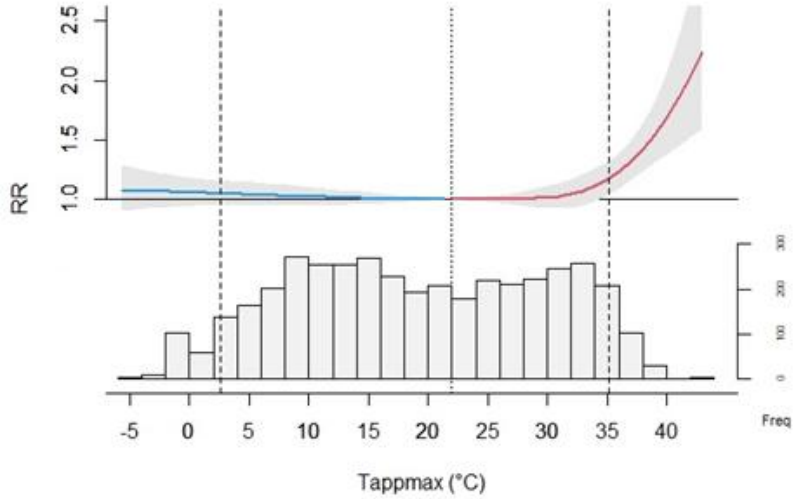


Figure 5.3. Overall cumulative exposure−response association (top panel) and $Tapp_{max}$ distribution (bottom panel), as calculated for the city of Thessaloniki for the period 2006−2016.

Identifying MMT has important practical implications for the investigation of the relationship between temperature and mortality and the definition of non-optimum temperatures, as mortality rates increase at temperatures outside local MMT (Yin *et al.*, 2019). Studies have shown that MMT varies from city to city, according to local climate and latitude (Tobías, Armstrong and Gasparrini, 2017). The values in the present work were anticipated for a Mediterranean city (Kouis *et al.*, 2019; Yin *et al.*, 2019), although for respiratory mortality, MMT was found to be lower. Generally, MMT levels are higher for Mediterranean cities than those in Northern Europe, indicating that residents of south-coastal cities are acclimatized to heat and risk conditions (Baccini *et al.*, 2008).

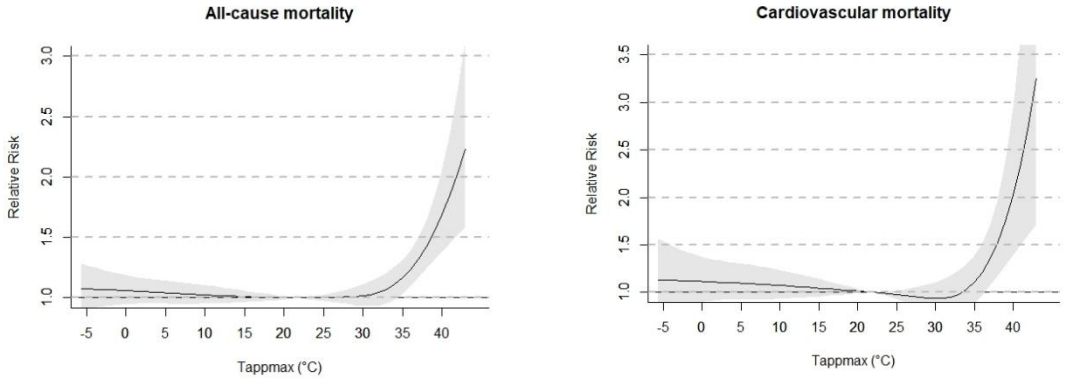
Risk increases rather slowly for cold temperatures below MMT and shows a more prominent exponential rise below the 5th percentile of $Tapp_{max}$, although it is not statistically significant for Thessaloniki. Similarly, hot temperatures between MMT and 95th percentile depict a slow, insignificant increase in RR, with a significant effect only for extreme values above 35 °C, reaching the highest RR values at 43 °C.

Table 5.3 summarizes the effect of heat and cold on cause-specific mortality and mortality of the elderly. Results show statistically significant effects of high temperatures on total and cause-specific mortality with a greater risk for respiratory deaths (RR 1.47, CI 95% 0.9–2.4), as shown in previous studies (Breitner *et al.*, 2014). In Thessaloniki, exposure to cold ($Tapp_{max}$ between 5^{th} percentile and MMT) did not show a significant effect on mortality.

Table 5.3. Relative risks of daily cause-specific mortality and elderly mortality associated with non-optimum ambient temperatures, for changes below and above MMT and the 95th and 5th percentile.

Cause of Death	MMT (°C)	Relative Risk (95% CI) Extreme Low, 2.5 °C	Relative Risk (95% CI) Extreme High, 35 °C
All-cause	22	1.05 (0.95–1.16)	1.17 (1.04–1.32)
Cardiovascular	30	1.18 (0.93–1.52)	1.20 (1.08–1.31)
Cerebrovascular	30	1.41 (0.97–2.04)	1.08 (0.93–1.24)
Elderly (65+)	19	1.09 (0.98–1.20)	1.25 (1.07–1.45)
Respiratory	14	1.13 (0.9–1.42)	1.47 (0.9–2.4)

Figure 5.4 illustrates the non-linear effects of $Tapp_{max}$ (lag 0–20) on cause-specific and elderly mortality. The exposure–response curves show the typical J-shape with an increase in the risk of mortality for high temperatures. U, J or V-shaped relationships between temperature (or temperature-based thermal indices) and mortality have been identified in many previous studies (Michelozzi *et al.*, 2006; Anderson and Bell, 2009; D'Ippoliti *et al.*, 2010; Breitner *et al.*, 2014; Ma, Chen and Kan, 2014; Zhang *et al.*, 2016), with optimum temperature corresponding to the lowest point in the curve; the shape of the curve may vary by geographic locations, climatic characteristics and demographic factors (Liu *et al.*, 2011; Breitner *et al.*, 2014; Nordio *et al.*, 2015). It is worth noting that respiratory mortality risk reaches very high values (RR > 10), as found in other studies (Zhang *et al.*, 2016).



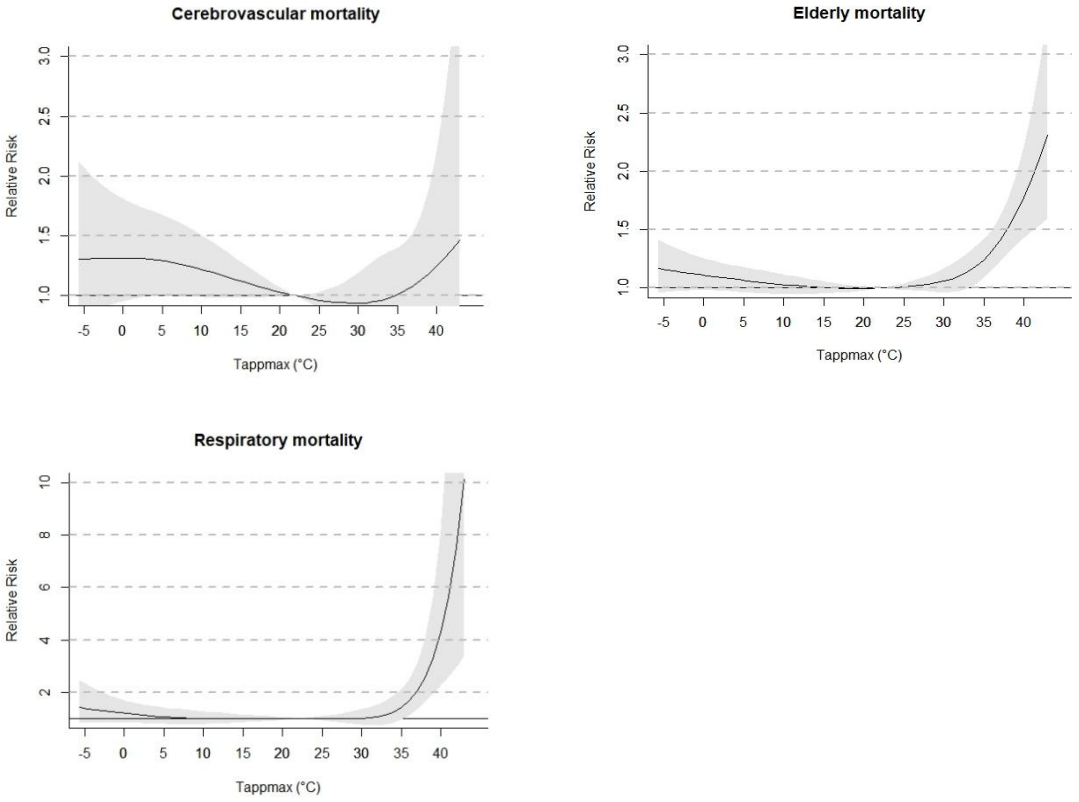
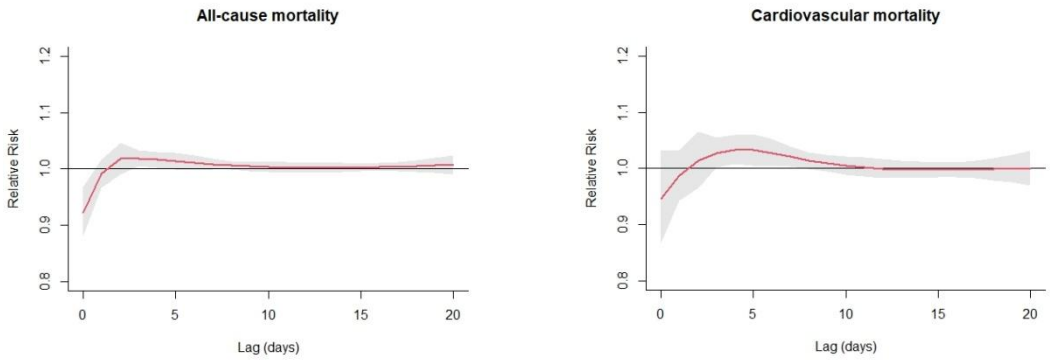


Figure 5.4. Cumulative exposure−response curves between daily $Tapp_{max}$ and cause−specific mortality and elderly mortality, over lag days 0−20, as calculated for the city of Thessaloniki for the period 2006−2016. 95% CI marked as grey areas.

As shown in Figure 5.5, the mortality risks of extreme cold $Tapp_{max}$, defined as the 5th percentile at 2.5 °C, reach maximum values on day 3 and subsequently decrease until day 10 (all-cause, cardiovascular, elderly) to 15 (cerebrovascular, respiratory).



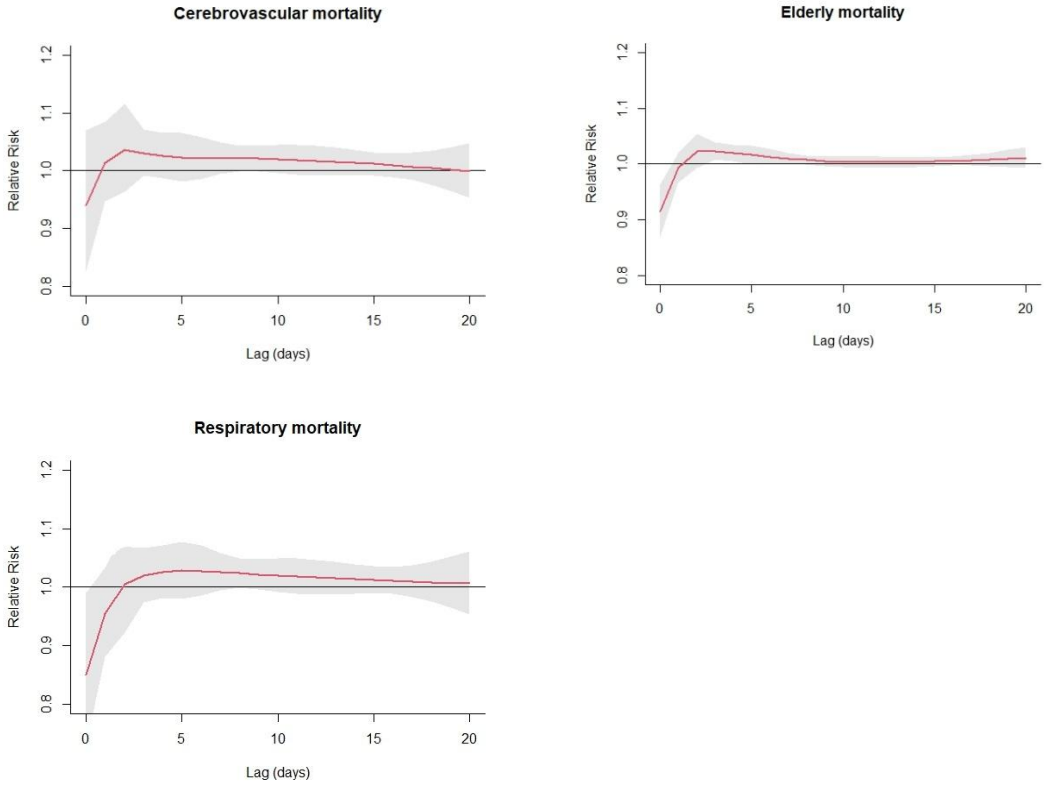


Figure 5.5. Non−linear effects of extreme cold $Tapp_{max}$ on daily cause−specific mortality and elderly mortality at lag 0−20, as calculated for the city of Thessaloniki for the period 2006−2016. Effects were defined as the risks at 5th percentile of $Tapp_{max}$ distribution compared with the estimated MMT.

Figure 5.6 shows the estimated lag–response curves at the 95th percentile of $Tapp_{max}$ (35 °C) for various causes of mortality and elderly mortality. The graphs indicate strong risk in the first days, followed by a protective association (RR < 1) at longer lags for All-cause, Cerebrovascular, Respiratory and Elderly mortality. For respiratory and cerebrovascular mortality, there is a suggestive mortality displacement, or a harvesting effect, as the initial increase caused by an event of extreme temperatures is followed by a negative risk in mortality (Baccini *et al.*, 2008; Gasparrini *et al.*, 2012; Kouis *et al.*, 2019). The overall shape of the curves is consistent with Kouis et al. who focused on Thessaloniki (Kouis *et al.*, 2019).

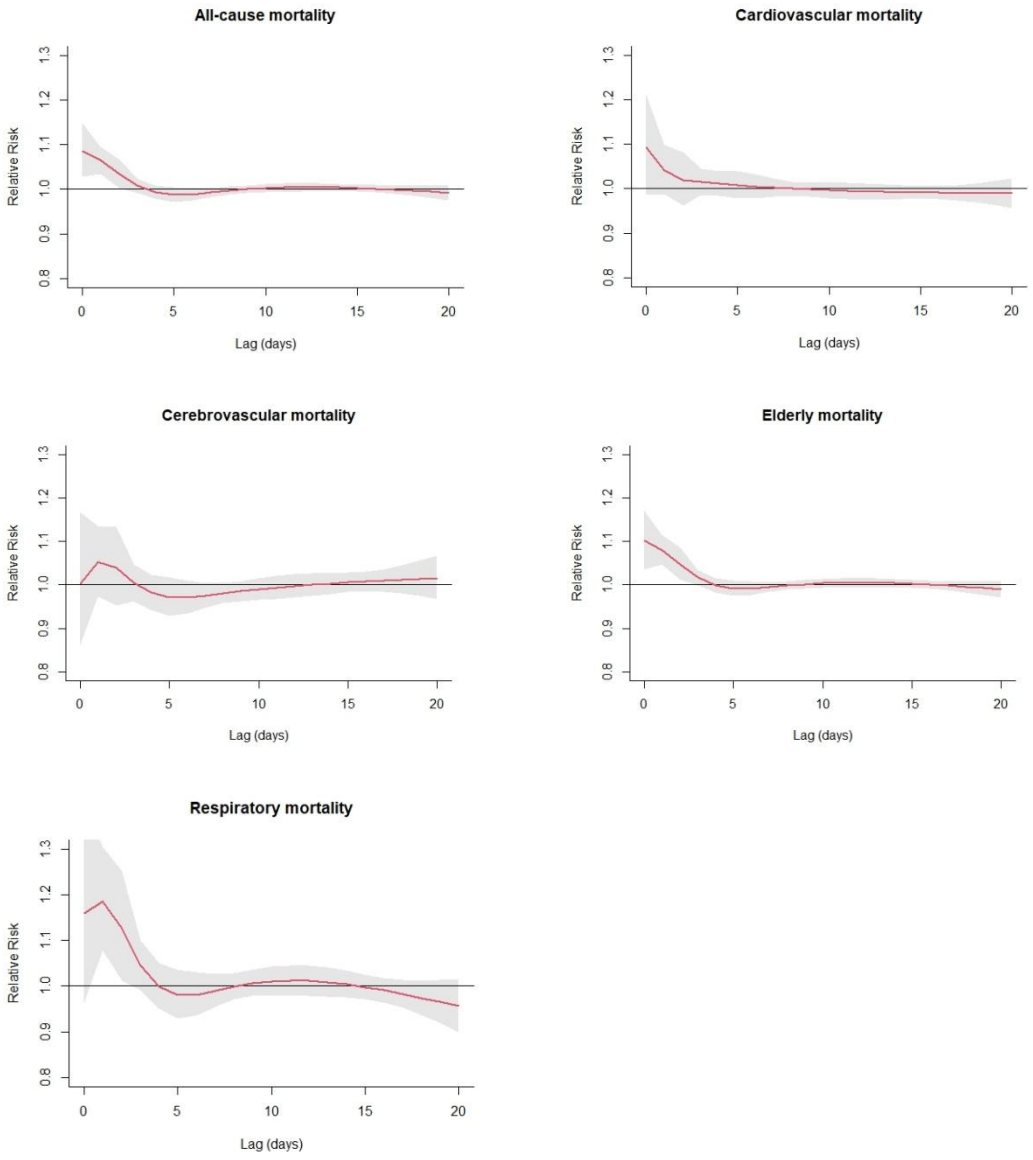


Figure 5.6. Non−linear effects of extreme hot $Tapp_{max}$ on daily cause−specific mortality and elderly mortality at lag 0−20, as calculated for the city of Thessaloniki for the period 2006−2016. Effects were defined as the risks at 95th percentile of $Tapp_{max}$ distribution compared with the estimated MMT.

Percent change in mortality per 1°C change above and below MMT (Table 5.4) shows a larger increase for all-cause mortality in heat (1.95%, 95% CI: 1.07–2.84), in contrast to smaller (insignificant) increases in cold (0.54%, 95% CI: 0–1.09). Cerebrovascular mortality is largely affected by cold (1.7%, 95% CI: 0.2–3.3), whereas the highest increase in mortality concerns respiratory causes in heat (5.07%, 95% CI: 2.1–8.1), followed by elderly mortality (2.36%, 95% CI: 1.34–3.34). Bunker et al. (Bunker *et al.*, 2016) reported that with 1 °C increase above

the heat-related threshold, respiratory mortality was the most affected category, depicting the largest risk increase, followed by cardiovascular and cerebrovascular causes. This pattern is also evident in the present study. It is interesting to notice that, although heat risk is often associated with effects on the cardiovascular system, relative risks for cardiovascular mortality are no higher than those of most other causes of death, and remarkably lower than respiratory causes, a result found also in Gasparrini et al. (Gasparrini *et al.*, 2012). Statistically insignificant results were obtained for cerebrovascular heat mortality (0.98%, 95% CI: –1.4–3.41), cardiovascular cold mortality (0.97%, 95% CI: −0.1–1.98), and respiratory cold mortality (1.48%, 95% CI: −0.3–3.24).

Table 5.4. Percentage change in mortality per 1°C change in $Tapp_{max}$ above and below MMT.

Cause of Death	Mortality Heat (% Change)	Mortality Cold (% Change)
All-cause	1.95 (1.07–2.84)	0.54 (0–1.09)
Cardiovascular	2.15 (0.52–3.81)	0.97 (−0.1–1.98)
Cerebrovascular	0.98 (−1.4–3.41)	1.7 (0.2–3.3)
Elderly (65+)	2.36 (1.34–3.34)	0.77 (0.18–1.37)
Respiratory	5.07 (2.1–8.1)	1.48 (−0.3–3.24)

The estimation of the overall attributable fraction categorized per cause of death is reported in Table 5.5. Regarding All-cause mortality, 3.51% of deaths are attributed to temperature. The total attributable risk is then separated into components due to cold and hot temperatures, defined as those below and above MMT, respectively (Gasparrini and Leone, 2014; R. Chen *et al.*, 2018). The comparison of the two contributions clearly indicates that heat is responsible for most of the all-cause mortality attributable to $Tapp_{max}$, with an value equal of 2.34% compared to 1.34% for cold.

Cardiovascular and cerebrovascular mortality is mostly attributed to cold temperatures, a result which is expected from the high MMTs of 30°C. Mortality concerning the elderly and mortality due to respiratory causes are mostly attributed to heat (3.75% and 5.6% respectively).

Table 5.5. Cause-specific mortality and elderly mortality fraction (%) attributable to high and low levels of $Tapp_{max}$.

Cause of Death	MMT (°C)	Overall (%)	Hot (%)	Cold (%)
All-cause	22	3.51	2.34	1.34
Cardiovascular	30	10.1	2.36	8.1
Cerebrovascular	30	14	1.07	13.12
Elderly (65+)	19	5.4	3.75	1.88
Respiratory	14	6.76	5.6	2.04

The analysis is extended by further separating the attributable components into contributions from mild and extreme $Tapp_{max}$ as follows:

- Extreme cold: minimum to 5th percentile.
- Mild cold: 5th percentile to MMT.
- Mild hot: MMT to 95th percentile.
- Extreme hot: 95th percentile to maximum.

As indicated in Figure 5.7, which illustrates the attributable fractions of causes of mortality and elderly mortality associated with different components of non-optimum $Tapp_{max}$, All-cause and Respiratory mortality are mainly attributed to extreme high values of $Tapp_{max}$ (1.35% and 3.3%, respectively). Mild cold $Tapp_{max}$ accounts for the majority of attributable mortality due to cardiovascular and cerebrovascular causes by far (7.21% and 11.6%, respectively). Lastly, Mild hot $Tapp_{max}$ is mostly responsible for Elderly mortality (2.22%).

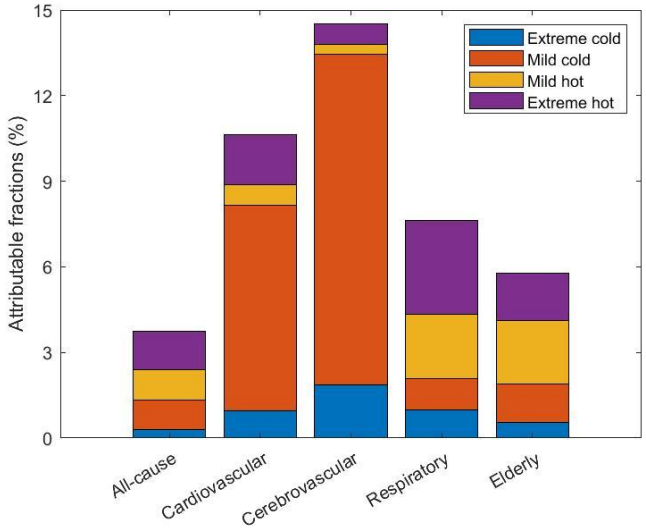


Figure 5.7. Fractions of mortality and elderly mortality attributable to non−optimum $Tapp_{max}$.

5.3 Conclusions

In the present study, the effects of $Tapp_{max}$ on daily mortality from 2006 to 2016 in the urban area of Thessaloniki, Greece, were assessed. DLNMs were used to examine the associations between thermal indicator $Tapp_{max}$ and cause-specific mortality, and to investigate the effect of time lag and non-optimum temperatures.

There is a documented association between high temperatures and mortality for Thessaloniki. The present results come to agreement with recent work (World Health Organization, 2022) and contribute further in increasing the knowledge concerning the effects of temperature on daily mortality in the urban area of Thessaloniki: (a) a wide range of mortality categories was investigated in the present study, covering the majority of deaths related to temperature with the use of a state-of-the-art statistical framework, (b) instead of choosing a single temperature parameter, we calculated $Tapp_{max}$ as a thermal index expressing thermal stress and comfort perceived by humans, and (c) we also examined the attributable fraction on non-optimum temperatures.

In Thessaloniki, extreme high temperatures strongly influence the risk in mortality. Strong exponential rise was evident over 35°C, with further and more prominent increase with $Tapp_{max}$ values over 40 °C. J-shaped relationships were found between temperature and mortalities. Heat was short lived with an immediate effect (mortality increase), whereas cold had a prolonged effect.

Percent change in mortality per 1 °C change above and below MMT showed large increase for all-cause, cardiovascular and respiratory mortality in heat. Similarly, elderly mortality was also affected by heat. Taking into consideration the attributable fraction of mortality assigned to the various causes investigated, it was noted that overall 3.51% deaths were attributable to $Tapp_{max}$. Deaths attributed to heat outnumbered deaths attributed to cold, with stronger impacts on respiratory mortality and among the elderly.

In conclusion, heat-attributable mortality in Thessaloniki was found to be mainly associated with high temperatures. Given the eminent vulnerability of the Mediterranean area to temperature rise due to climate change and the expected more frequent occurrence of heat wave episodes (Ullah *et al.*, 2022), these results could contribute to the decision-making process regarding extreme weather preparedness. The need to conduct heat health action plans for the implementation and coordination of extreme heat response activities that will reduce the negative impact of extreme heat is undeniable and requires high-resolution information on the association between temperature and mortality on the city-level.

The results of the present study can effectively contribute to this scope, whereas future work should be conducted to include not only major Greek cities but

additional environmental stressors such as air pollutants as well, in order to draw decisive conclusions on the national frame. Investigating mortality behavior under the influence of climate change could be a critical next step.

Chapter 6

Short-Term Effects of Air Pollution on Mortality in the Urban Area of Thessaloniki, Greece

In recent years, poor air quality, both ambient and indoor, has become a pressing issue, with more frequent and intense episodes of high pollution levels being prevalent in cities across the globe. Currently, it is considered the biggest environmental risk to human health and the second-greatest environmental concern among Europeans, second only to climate change (European Environmental Agency, 2020).

According to the WHO (WHO, 2016), 3 million deaths were solely attributable to outdoor air pollution globally in 2012, an estimation which Fuller et al. (Fuller *et al.*, 2022) has raised to 4.5 million, particularly for ambient particulate matter (4.14 million) and ambient ozone (0.37 million). This not only impacts mortality but morbidity as well. The most compelling evidence regarding the health consequences of air pollution relates to cardiovascular and respiratory ailments; nevertheless, studies exploring other health impacts are also increasing (WHO, 2022; WHO Regional Office for Europe, 2022). Older adults are more susceptible to the negative health impacts of air pollution due to their decreased ability to adapt to stressors on their physiological, metabolic, and compensatory processes, as well as their higher likelihood of having cardiovascular and respiratory diseases (Geller and Zenick, 2005; Shumake *et al.*, 2013). Elderly mortality has been found to be particularly affected by PM10 and O_3, with higher excess risks than other age groups (Cakmak, Dales and Vidal, 2007; Katsouyanni *et al.*, 2009; Liu *et al.*, 2022; Olstrup, Åström and Orru, 2022).

PM10 and O_3 are considered to represent a major part of the problem (Stanaway *et al.*, 2018). Ozone exposure has significantly increased worldwide, leading to a 46% increase in ozone-attributable mortality from 2000 to 2019 (Malashock *et al.*, 2022). PM10 and O_3 are linked to a rise in all-cause, cardiovascular, and respiratory mortalities (Biggeri *et al.*, 2004; Katsouyanni *et al.*, 2009; Garrett and Casimiro, 2011; Peng *et al.*, 2013; Olstrup *et al.*, 2019; Vicedo-Cabrera *et al.*, 2020). The WHO has also emphasized PM2.5 (World Health Organization, 2006) as they are found to be associated with the premature mortality of several age groups (Garrett and Casimiro, 2011; Pascal *et al.*, 2014; Lelieveld *et al.*, 2015). In 2020, approximately 238,000 premature deaths in the European population were caused by exposure to PM10 concentrations above the WHO's 2021 guideline level of 45 $\mu g/m^3$ (EEA, 2022a). Additionally, the European Environment Agency attributed 16,800 premature deaths to acute ozone exposure in 2019 (EEA, 2021). Despite EU and national policies, the pollutant levels in many areas exceed the recommended guidelines (European Council Directive 2008/50/EC), and although significant improvements are evident, the impacts of serious air pollution in Europe still persist. Approximately 11% and 12% of the EU urban population is exposed to PM10 and O_3 concentrations above EU standards, a percentage that rises to 71% and 95%, respectively, when taking into account the WHO guidelines of 2021 (EEA, 2022b).

Threshold violations take place at several locations throughout Europe (EEA, 2012). However, the problem appears to be more pronounced in Southern and Eastern Europe (EEA, 2018), especially with respect to the PM and ozone concentrations in Greece, Spain, and Italy (Pleijel, 2000; Karanasiou *et al.*, 2014; Sicard *et al.*, 2021). These areas are characterized as climate change hotspots; thus, the collective impacts of climate change and air pollution variables should be taken into consideration (Bytnerowicz, Omasa and Paoletti, 2007) under the specific topographical and meteorological conditions of each region (Valjarević *et al.*, 2021). With respect to the latter air pollutant, the ground-level ozone concentrations in Southern Mediterranean countries are often alarmingly high and are comparable to the highest levels of places that are located in the most contaminated parts of Central Europe (Moussiopoulos *et al.*, 2009).

When focusing on Greece, the country has been found to be in violation of the three most commonly exceeded EU air quality standards for PM10, O_3, and NO_2, according to (EEA, 2019). Using 2019 data, it was estimated that 75 deaths per 100,000 population in Greece could be attributed to air pollution, where the deaths were primarily caused by ischemic heart disease, stroke, and respiratory infections (WHO Regional Office for Europe, 2022); this corresponds to 1,101 attributable DALYS (Disability-adjusted life years) per 100,000 citizens (WHO, no date a), or 104,000 YLLs (Years of life lost) for the entire Greek population (WHO, no date b). As expected, the two largest cities of the country suffer the most from the acute air quality problems because of the dense population and build-up of air pollutants caused by the topography and adverse meteorological conditions, e.g.,

the urban heat island effect (Poupkou *et al.*, 2011). The EU air quality standards are significantly surpassed by the PM10 concentrations observed in Athens and Thessaloniki (Kalabokas, Adamopoulos and Viras, 2010), and the YLLs are primarily affected by PM10 exposure as well as O_3 to a lesser extent (Kassomenos, Dimitriou and Paschalidou, 2013).

Thessaloniki in particular is one of the most polluted cities in Europe, especially with respect to the PM level (Vlachokostas *et al.*, 2012) but also with respect to the O_3, VOCs, and noise pollution levels (Vlachokostas *et al.*, 2013). O_3 limit values are mostly exceeded during the summer months, while winter is the most favorable season for PM10 violations (Moussiopoulos *et al.*, 2009). Nevertheless, Thessaloniki's major air quality problem consists of PM10 concentration levels. As a result, in December 2020, the European Commission decided to take legal action against Greece by referring the country to the European Court of Justice for the substandard PM_{10} air quality of Thessaloniki (European Commission, 2020).

To address the issue, effective and enduring air pollution mitigation plans must be identified and put into action (Miranda *et al.*, 2015; Silveira *et al.*, 2016). Such measures and policies to combat particulate air pollution were tested in a recent study (Progiou *et al.*, 2023), which resulted in a more than 20% reduction in the PM10 concentrations in Thessaloniki, Greece. Moreover, it is necessary to assess the health benefits of the abatement measures by quantifying the impact of air pollution on human health.

However, majority of the literature focuses almost entirely on Athens (e.g., (Gryparis *et al.*, 2004; Touloumi *et al.*, 2006; Kassomenos, Dimitriou and Paschalidou, 2013)); only recently has a study by (Psistaki *et al.*, 2022) discovered that brief exposure to PM2.5 and PM10 in Thessaloniki is connected to an amplified risk of all-cause and cardiovascular mortality. In addition to the above, there is a significant lack of studies specifically examining the suitability of mitigation measures in terms of health benefits for the area of Thessaloniki.

In this Chapter, we utilize advanced statistical tools to investigate the associations between short-term exposure to PM10 and O_3 and daily all-cause (natural, non-accidental), cardiorespiratory, and cerebrovascular mortality from 2006 to 2016 in the urban area of Thessaloniki. We also examine the effect of air pollution on the elderly (all-causes, 65+ years) as it is crucial to understand the specified response of frail subgroups to environmental stressors.

Most importantly, to assist air quality planning, we estimate for the first time the impact of the modification of PM10 levels on Thessaloniki's population mortality under two air pollution abatement scenarios: (1) full compliance to EU levels, thus eliminating the exceedances of PM10 daily values; and (2) a 20% horizontal reduction in the PM10 concentration in order to assist air quality planning. These scenarios are based on the most cost-efficient measures identified by the recent study of (Progiou *et al.*, 2023) to combat PM10 pollution in the urban area of Thessaloniki.

Thus, the main goal of the current Chapter is to present evidence on the air pollution–mortality relationship in the Thessaloniki urban area, accounting for the cause-specific deaths, lag structure, elderly mortality, and potential mitigation measures that can be of utmost importance for environmental stakeholders and local policy makers

6.1 Data and Methods

6.1.1 Study area

This research centered on the urban area of Thessaloniki (Figure 6.1), which includes seven municipalities. Thessaloniki, the second largest city in Greece and an important economic and industrial center in the Balkans, is situated in the northern part of the country and has a population of about 1,000,000, representing 20% of the country's industrial activity (Moussiopoulos *et al.*, 2009). The city is located on the northeastern coast of the Thermaikos Gulf and is close to Hortiatis mountain (1200 m) on the eastern side. The western side is characterized by a large flat area, which houses the industrial zone of Sindos. The city's location to the south means that it is greatly affected by the nearby sea, which contributes to its Mediterranean climate (Giannaros and Melas, 2012). Vehicular traffic, residential heating (Progiou *et al.*, 2023), biomass burning (Diapouli *et al.*, 2017), and industrial emissions (Moussiopoulos *et al.*, 2009) are the main origins of air pollutants in Thessaloniki (Melas *et al.*, 2017), resulting in the deteriorated air quality in the area, especially during years of economic crisis (Zyrichidou *et al.*, 2019). Dust storms originating from North Africa also significantly contribute to particle pollution in the area (Achilleos *et al.*, 2020; Psistaki *et al.*, 2022; Rizos *et al.*, 2022).

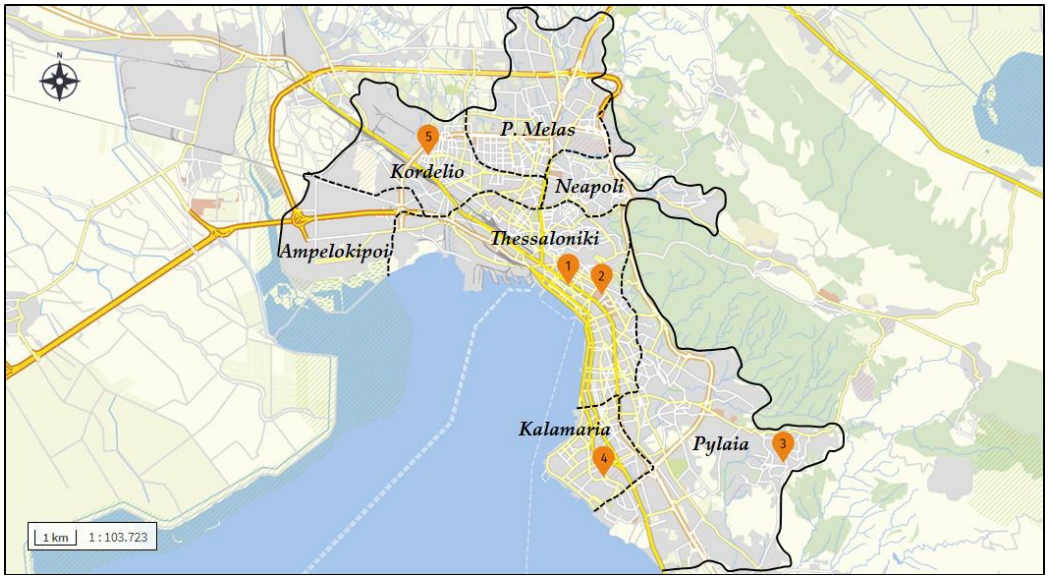


Figure 6.1. The study area with the locations of air quality stations (1: Agias Sofias, 40.63° N 22.94° E; 2: AUTh, 40.63° N 22.95° E; 3: Panorama, 40.58° N 23.03° E; 4: Kalamaria, 40.57° N 22.96° E; 5: Kordelio, 40.67° N 22.89° E). Dotted lines represent municipalities.

6.1.2 Air Quality and Mortality Data

The hourly values of PM10 and O_3 concentrations ($\mu g/m^3$) for the period of 2006–2016 were acquired by 5 air quality monitoring stations that cover the urban area of Thessaloniki and are operated by the Ministry of the Environment and Energy. The highest PM10 value and maximum 8-hour moving average for O_3 over each station were used in the present study, which represented the daily concentrations for the datasets.

The Hellenic Statistical Authority (ELSTAT) provided the daily mortality data, consisting of age and cause of death, for all municipalities in the urban region of Thessaloniki (2006–2016); the causes of death were categorized into all-cause (natural, non-accidental), cardiorespiratory, and cerebrovascular according to the ICD-10. Emphasis was placed on studying the overall mortality rate among the elderly, specifically for deaths that occurred among individuals aged 65 years and older.

6.1.3 Data analysis

We applied a DLNM to our data in order to show the impact of air pollution on mortality with delay in time, in accordance to previous studies (Gu *et al.*, 2020; Vicedo-Cabrera *et al.*, 2020; Kriit *et al.*, 2022). DLNMs are a powerful modeling tool that are capable of simultaneously capturing both non-linear exposure–

response dependencies and delayed effects. Unlike conventional distributed lag models, which struggle with non-linear relationships, the DLNM methodology utilizes a 'cross-basis', a two-dimensional function space that depicts the connection between predictor variables and the lag dimension of their occurrence. This approach offers a comprehensive portrayal of the exposure–response relationship's time course, making it possible to estimate the overall effect with precision, even in the presence of delayed contributions. In order to describe the air pollution–mortality associations in the present study, we applied generalized non-linear models with a quasi-Poisson family based on the quasi Akaike information criterion. The DLNM package (Gasparrini *et al.*, 2017) in R programming language (R version 4.1.1; R Foundation for Statistical Computing) was used to implement the family of applied models.

There are differences in the literature regarding the lag structure used to best describe the association between air pollution and mortality; in some cases, short lags of 0–1 days (Katsouyanni *et al.*, 2001; Ballester *et al.*, 2002; Analitis *et al.*, 2006; Lelieveld *et al.*, 2015; Khaniabadi *et al.*, 2017; Liu *et al.*, 2019) or up to 3 days (Garrett and Casimiro, 2011) are deemed to be the most appropriate, while in other studies, a week is chosen (Samoli *et al.*, 2009; Stafoggia *et al.*, 2010; Gariazzo *et al.*, 2023). There are also examples in the literature suggesting that the adverse response to pollution persists for more than a month (Zanobetti *et al.*, 2002, 2003; Stojić *et al.*, 2016). To this end, we investigated the correlation between short-term exposure to PM10 and O_3 and specific causes of death at various lags in order to decide the effect estimates for the present analysis.

In order to investigate the efficiency of mitigation measures in terms of health benefits, we not only applied the DLNM analysis for the original PM10 dataset, but also for 2 mitigation scenarios:

- Complete compliance with the EU limits (daily PM10 value < 50 μg/m^3),
- 20% reduction in the PM10 concentration.

Table 6.1 shows the percentage of days in which the daily EU limits were exceeded during the range of 2006–2016. The EU air quality guidelines were surpassed on 1894 (47%) days of the 4018-day study period for PM10 (>50 μg/m^3) and on 1124 (28%) days for O_3 (>120 μg/m^3). Under the 20% PM10 reduction scenario, only 27% of days surpassed EU limits, resulting in 1119 exceedances.

Year	**O_3 Mean Annual Value (%—Days Over 120 μg/m^3)**	**PM10 Mean Annual Value (%—Days Over 50 μg/m^3)**	**PM10 20% Reduction Scenario (%—Days Over 50 μg/m^3)**

2006	85.8 (6.5%)	58.9 (53%)	47.1 (34%)
2007	95.3 (18%)	70.5 (79%)	56.4 (53%)
2008	118.7 (48%)	66.9 (76%)	53.5 (51%)
2009	112.7 (45%)	56.1 (57%)	44.9 (28%)
2010	99.1 (26%)	51.2 (39%)	41 (20%)
2011	114 (50%)	56.8 (45%)	45.5 (25%)
2012	115.2 (47%)	52.6 (43%)	42 (24%)
2013	101 (30%)	48.7 (35%)	39 (21%)
2014	82.2 (2.5%)	46.6 (30%)	37.3 (14%)
2015	99.5 (25%)	49.7 (33%)	39.8 (17%)
2016	92.3 (9%)	47 (31%)	37.6 (15%)

Table 6.1. Mean annual values of pollutants ($\mu g/m^3$) during the study period and during PM10 reduction scenario 2. Numbers in parentheses denote the percentage of annual violations of the EU daily limits.

6.2 Results

6.2.1 Mortality Data analysis

During the study period, we analyzed 73,990 natural deaths that occurred from all causes, 28,945 from cardiorespiratory diseases, and 10,007 from cerebrovascular causes. The number of deaths among the elderly population amounted to 62,482. The descriptive statistics of the pollution and daily mortality for the reference period are provided in Table 6.2.

Table 6.2. Statistics of the daily mortality (number of deaths, top) and pollution ($\mu g/m^3$, bottom).

	Daily Mortality	
	Mean	**St. dev.**
All-cause	18.4	4.7
Cardiorespiratory	7.2	2.9
Cerebrovascular	2.5	1.6
Elderly	15.5	4.4

PM10					
Median	**Mean**	**Min**	**25th perc.**	**75th perc.**	**Max**
49	55	11.6	38	65	256.6
O_3					
Median	**Mean**	**Min**	**25th perc.**	**75th perc.**	**Max**
99	101	14	76	123	232

The data on deaths show that cardiorespiratory mortality accounts for over 40% of all natural deaths, making it a crucial group to examine in terms of susceptibility; the authors of (European Observatory on Health Systems and Policies, 2019) have reported that stroke and ischemic heart disease are the primary causes of mortality in Greece, which supports the claim. Elderly mortality reflects 84% of all-cause mortality for all ages, as Greece has one of the highest percentages of individuals aged over 65 years in Europe (EUROSTAT, 2020). The daily mean and median pollutant concentrations are generally higher in Thessaloniki than those reported in other metropolitan areas (Garrett and Casimiro, 2011; Samoli *et al.*, 2014) and resemble the values of large cities with important air quality issues (Samoli *et al.*, 2009; Stafoggia *et al.*, 2010; Wang *et al.*, 2018). Similar values of mean daily mortality and summary statistics of PM10 in Thessaloniki are also verified in (Samoli *et al.*, 2013).

6.2.2 Lag Effect analysis

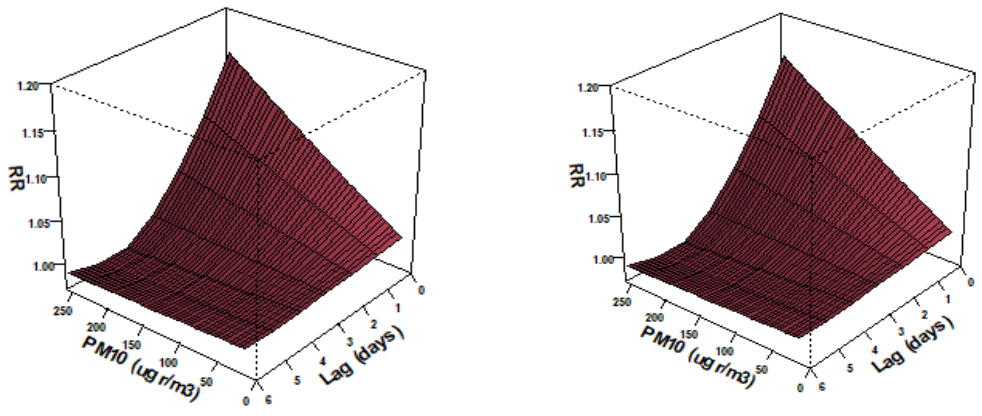
Table 6.3 displays the correlation between short-term exposure to PM10 and O_3 and specific causes of death at various lags. The lag structure here yields a prolonged effect of PM10 and O_3 on all mortalities from the current day to day 6 in Thessaloniki. As a result, the relative risk per 10 μg/m^3 increase in PM10 and O_3 concentrations over lag 0–6 is used hereinafter as the effect estimates.

Table 6.3. Associations between cause-specific mortality and short-term exposure to PM10 and O_3 at various time intervals (0–1, 1–6, and 0–6 days). Results are presented as a percentage increase of risk (RR%) and as 95% confidence intervals (95% CI) per 10 μg/m^3.

PM10			
Mortality	**RR%, Lag 0–1**	**RR%, Lag 1–6**	**RR%, Lag 0–6**

All-cause	2.2 (0.6–3.3)	0.8 (−1.9–3.2)	2.3 (0.8–3.8)
Cardiorespiratory	1.9 (0.5–3.6)	0.7 (−2–3.5)	2 (0.1–4.5)
Cerebrovascular	1.5 (−1.8–5.2)	1.1 (−1.9–4.9)	1.8 (−2–6.1)
Elderly	2.7 (1–3.5)	1.5 (−0.4–2.9)	3.2 (1.5–5)
		O_3	
Mortality	**RR%, Lag 0–1**	**RR%, Lag 1–6**	**RR%, Lag 0–6**
All-cause	1.9 (0.9–3)	2.7 (0.2–5.3)	3.9 (2.5–5.3)
Cardiorespiratory	2.8 (1.06–4.5)	3.5 (−0.54–4)	5.3 (3.1–7.7)
Cerebrovascular	−0.7 (−3.5–2.23)	2.8 (−4–9.9)	3 (−7–11)
Elderly	2.2 (1.55–3.4)	3 (0–5.86)	4.4 (2.9–6)

The estimated associations between the PM10, O_3, and mortality in Thessaloniki are illustrated in Figure 6.2. The diagrams show the relationship among the air pollutants concentrations, excess risk, and lag values as a three-dimensional surface. The associations of PM10, all-cause, and cardiorespiratory mortalities are non-linear. An immediate increase in deaths is evident for exposures to high levels of pollutants at lag days 0–2; however, for cardiorespiratory causes, a secondary maximum is present at lag 6. Concerning O_3, a lag of up to 3 days depicts a large increase in excess risk, which results in higher values of cardiorespiratory deaths. At days 5–6, a smaller increase is evident for both causes of death, indicating a prolonged impact.



(a) (b)

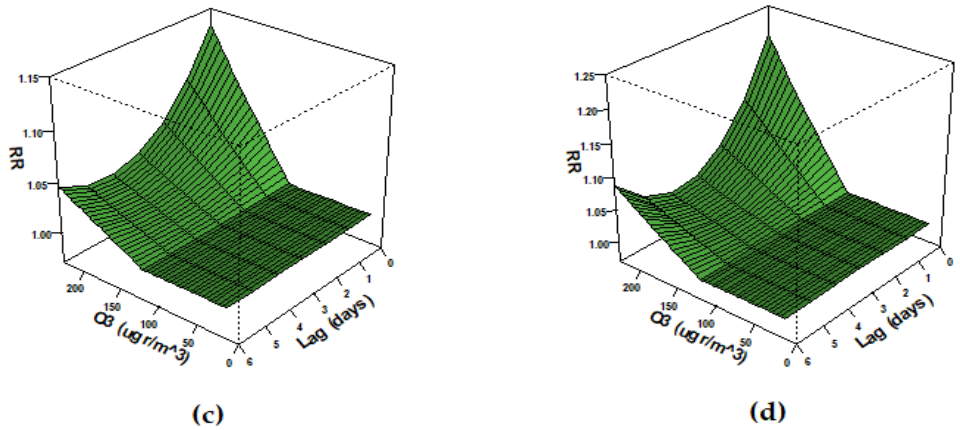


Figure 6.2. Overall effect of PM10 on all-cause mortality (**a**) and cardiorespiratory mortality (**b**); overall effect of O_3 on all-cause mortality (**c**) and cardiorespiratory mortality (**d**) for Thessaloniki in the years 2006–2016.

The dose–response relationships for the natural and cardiorespiratory mortalities for PM10 and O_3 (not shown here) were found to be linear, as noted in previous studies (Gryparis *et al.*, 2004; Ortiz *et al.*, 2017; Psistaki *et al.*, 2022).

6.2.3 Total effect analysis

We present the evidence of the positive association of natural all-cause and cardiorespiratory deaths with PM10 and O_3 in Table 6.3.

A 10 unit increase in PM10 is associated with a 2.3% (95% CI: 0.8–3.8) increase in natural all-cause mortality and a 2% (95% CI: 0.1–4.5) increase in cardiorespiratory mortality; O_3 causes a 3.9% (95% CI: 2.5–5.3) increase in all-cause mortality and a 5.4% (95% CI: 3.1–7.7) increase in cardiorespiratory mortality. Neither of the two air pollutants are associated with cerebrovascular outcomes, as confirmed in similar studies (Stafoggia *et al.*, 2010; Samoli *et al.*, 2014).

Due to the significant differentiation of the lag selection, there is no uniformed way to compare our results with other studies. PM10 levels are generally associated with increases of 0.8–4.3% in all-cause mortality, 0.12–6.6% in cardiovascular mortality, and 0.47–4.2% in respiratory mortality, respectively (Kunzli *et al.*, 2000; Katsouyanni *et al.*, 2001; Ballester *et al.*, 2002; Zanobetti *et al.*, 2002, 2003; Analitis *et al.*, 2006; Pascal *et al.*, 2014; Khaniabadi *et al.*, 2017); the RR estimations in the present study are found to be within the range demonstrated above. Thessaloniki is underrepresented in similar publications; ref. (Psistaki *et al.*, 2022) linked exposure to PM10 to a 1.75% increase in cardiovascular deaths (lag 0–6) but found no link to respiratory mortality.

Many studies (Gryparis *et al.*, 2004; Samoli *et al.*, 2008, 2009; Stafoggia *et al.*, 2010; Garrett and Casimiro, 2011; Khaniabadi *et al.*, 2017; Olstrup *et al.*, 2019)

have reported positive associations between O_3 and increases in all-cause (0.33–2%), cardiovascular (0.45–2.5%), and respiratory mortalities (0.6–2.8%.), and correlations are evident in the present analysis. In particular, ref. (Stafoggia *et al.*, 2010) indicated higher impacts of O_3 on respiratory and cardiac mortality than on all-cause mortality, which is also confirmed by our results. However, the excess risks estimated here are higher compared with those obtained in other studies.

It is worth noticing, however, that the estimates from single-city studies tend to be higher compared with pooled multi-city results as the model specification utilized in the studies focused on individual cities could result in an overestimation of the outcome (Katsouyanni *et al.*, 2001; Samoli *et al.*, 2008).

When comparing the effect of O_3 and PM10 on different causes of mortality, we document more severe impacts from the former than the latter. This consistent behavior is evident in similar studies covering various areas worldwide and various time spans, e.g., South Africa (2006–2015) (Christina Adebayo-Ojo *et al.*, 2006), Russia (2003–2005) (Revich and Shaposhnikov, 2010), and China (Shang *et al.*, 2013).

Susceptible population subgroups are often separately considered in order to account for the specified behavior of these groups to environmental stressors. In the present work, we developed a dedicated DLNM model for assessing the impact of PM10 and O_3 on the elderly.

Elderly mortality is affected by both PM10 and ozone; a 3.2% RR increase (95% CI: 1.5–5) per 10 unit increase of PM10 and a 4.4% raise (95% CI: 2.9–6) per 10 unit increase of O_3 are evident. Similar results are verified in (Katsouyanni *et al.*, 2009; Stafoggia *et al.*, 2010; Garrett and Casimiro, 2011; Shang *et al.*, 2013). The air pollution in Thessaloniki has been found to demonstrate a more intense impact on elderly mortality than on the all-cause mortality for all ages, as found in (Revich and Shaposhnikov, 2010).

Additionally, 5% of elderly deaths are attributed to PM10 and 2.6% are attributed to O_3 (a total of 4,750 deaths out of 62,482). This corresponds to 284 and 146 annual deaths due to PM10 and O_3, respectively, for people aged 65 years and older.

Table 6.4 presents the attributable mortality and attributable fraction of mortality based on the PM10–mortality and O_3–mortality relationships. We estimate that 3.6% of total mortalities and 3.2% of cardiorespiratory causes were attributed to PM10, while the respective percentages for O_3 are 2.3% and 3%. These estimates correspond to 242 annual premature all-cause mortalities from PM10 and 170 from O_3, respectively. On an annual basis, 82 cardiorespiratory deaths are related to elevated PM10 levels, and another 80 cardiorespiratory deaths are related to O_3 levels. Overall, in Thessaloniki, 412 deaths are recorded annually due to PM10 and O_3 pollution, out of which 162 are attributed to cardiorespiratory causes.

Table 6.4. Attributable mortality (AM, number of deaths) and attributable mortality fraction (AF, %) for different causes of mortality.

	PM10			O_3		
Mortality	**AM**	**AF**	**Average Annual Deaths**	**AM**	**AF**	**Average Annual Deaths**
All-cause	2664	3.6	242	1865	2.3	170
Cardiorespiratory	914	3.2	82	876	3	80
Elderly	3146	5	284	1604	2.6	146

Our results are similar to previous studies, where the attributable fraction of natural mortality fluctuated between 1.35% and 6% and cardiovascular mortality fluctuated between 1.63% and 6.89% due to PM10 pollution (Christina Adebayo-Ojo *et al.*, 2006; Wang *et al.*, 2018). Ref. (Khaniabadi *et al.*, 2017) reported that 1.96% of cardiovascular mortality is attributed to O_3 and 6.6% to PM10, while (Goudarzi *et al.*, 2015) found that 3.2% of cardiovascular and 6.2% of respiratory mortality is attributed to O_3. According to (Fattore *et al.*, 2011), 2% of cardiovascular mortality, 5.6% of respiratory, and 1.5% of total mortality is attributed to O_3 levels.

6.2.4 Suitability of Studied Scenarios in Terms of Health Benefits

We present an examination of the suitability of two mitigation measures in terms of their health benefits for the urban area of Thessaloniki. The first case study (scenario 1) corresponds to a full abidance to EU limits concerning daily PM10 values (<50 μg/m^3), whereas the second case study (scenario 2) horizontally reduces PM10 concentrations by 20%, a case that is more realistically applicable as shown in (Progiou *et al.*, 2023).

Table 6.5 displays the RR, AF, and AM for scenarios 1 and 2, respectively. Reducing PM10 concentrations by 20% would result in 2368 deaths and a 3.2% AF value with respect to total mortality. Full compliance with EU environmental legislation leads to a 1.8% attributable all-cause mortality, which corresponds to 710 deaths. When comparing the scenarios, the RR increases from 1.7% (scenario 1) to 2.1% (scenario 2). It is obvious that radical measures positively affect human health to a larger degree than moderate ones.

Table 6.5. RR (%), AM (number of deaths), and AF (%) of total mortality for different PM10 scenarios.

Scenarios	RR	AM	AF
1—Full EU compliance	1.7	710	1.8
2—20% reduction	2.1	2368	3.2

When comparing the results of Table 6.3 and 6.4, the mortality burden decreases when mitigation measures are implemented. The AF is reduced by 0.4% and 1.8% compared with the original PM10 dataset for the 20% reduction and full compliance scenarios, respectively. Thessaloniki would count 27 less deaths on an annual basis if the PM10 concentration were reduced by 20% and 177 less annual deaths if under full EU compliance.

Thus, even with the more moderate abatement scenario, the health impact of PM10 concentration on the local population could be significantly lower.

6.3 Discussion

In the international literature, the interaction between human health and air quality is well-defined (WHO Regional Office for Europe, 2013) with respect to morbidity and mortality (Héroux *et al.*, 2015). The adverse impact of deteriorated air quality has also raised international concern with respect to the natural environment (Bytnerowicz, Omasa and Paoletti, 2007) and economy (Font-Ribera *et al.*, 2023). Cities in the Mediterranean area are frequently experiencing elevated levels of air pollution (Pleijel, 2000) under the additional pressure of the climate crisis. Thessaloniki, Greece, is particularly impaired with respect to the air pollution, especially due to PM10 and O_3 levels (Vlachokostas *et al.*, 2012; Karanasiou *et al.*, 2014). Although some recent studies have quantified the impact of temperature on mortality (Orellano *et al.*, 2020; Parliari *et al.*, 2022), there is insufficient evidence concerning air quality, thus pointing a gap in relevant knowledge.

The present study aimed to address this vacancy by presenting an evaluation of the short-term changes in daily mortality counts as associated with the concentrations of daily air pollutants from 2006 to 2016 in the urban area of Thessaloniki. We analyzed the associations between the daily maximum values of PM10 and O_3 levels and cause-specific mortality, and we investigated this effect on the susceptible elderly subgroup with the use of DLNMs. To quantify the mortality burden, we used relative risk changes for every 10 $\mu g/m^3$ increase in air

pollution concentrations as the primary effect estimates (Braga, Zanobetti and Schwartz, 2001; Orellano *et al.*, 2020). After conducting a specific analysis using a lag structure, which has great heterogeneity among literature, we determined the most suitable lag for this work to be defined at days 0–6, similar to other studies (Stafoggia *et al.*, 2010; Gariazzo *et al.*, 2023).

Based on our results, a 10 unit increase ($\mu g/m^3$) in PM10 concentration is associated with a 2.3% (95% CI: 0.8–3.8) increase in natural all-cause mortality and 2% (95% CI: 0.1–4.5) increase in cardiorespiratory mortality. O_3 causes increases of 3.9% (95% CI: 2.5–5.3) in all-cause mortality and increases of 5.4% (95% CI: 3.1–7.7) in cardiorespiratory mortality. Meanwhile, neither of the two air pollutants is associated with cerebrovascular outcomes. Considering the assigned attributable fraction of mortality for the various investigated causes, it is noted that overall, 3.6% of total mortalities are attributable to PM10 and 2.3% are attributable to O_3. PM10 levels are responsible for 3.2% of cardiorespiratory mortality (3% for O_3). These estimations correspond to 242 annual premature all-cause casualties due to PM10 and 170 due to O_3.

The direct comparison of our findings with similar studies in this field is particularly challenging due to the differentiation of the lag selection and underrepresentation of the specific area. Nevertheless, both RR estimates and attributable mortalities are in agreement with comparable research (Kunzli *et al.*, 2000; Zanobetti *et al.*, 2003; Stafoggia *et al.*, 2010; Garrett and Casimiro, 2011). It is worth noting that (Psistaki *et al.*, 2022) linked exposure to PM10 to a 1.75% increase in cardiovascular deaths (lag 0–6) but found no link to respiratory mortality in the Thessaloniki area.

Elderly mortality is also affected by the 10 unit increase in the air pollutants to an even larger degree than the mortality accounting for all ages, which was also confirmed in (Revich and Shaposhnikov, 2010). We report that excess risks increase by 4.4% and 3.2% due to O_3 and PM10, respectively, while 284 annual deaths are attributed to PM10 and 146 are attributed to O_3, corresponding to a 5% and 2.6% attributable mortality, respectively. Studies on elderly people, such as (Katsouyanni *et al.*, 2009; Garrett and Casimiro, 2011), report similar results.

The need to abide by EU environmental legislation is crucial for reducing the negative impact of air pollutants on public health (Progiou *et al.*, 2023); thus, high-resolution, location-specific information on the association of human morbidity and mortality to environmental stressors is of utter importance. Appropriate mitigation actions should be taken to decrease the population's exposure to pollutants and to further explore how location-specific factors contribute to this vulnerability. An innovative aspect of this work is the quantification of the health benefits as a result of two PM10 abatement scenarios, which was conducted for the first time in the study's urban area. The first case study (scenario 1—full abidance to EU limits, 50 $\mu g/m^3$) yields 177 less annual

deaths, and the second case study (scenario 2—horizontal reduction by 20%) results in 27 less casualties compared with the baseline.

The above findings of the present study clearly indicate that local residents are at risk from the current levels of PM10 and ozone. O_3 is found to have a more severe impact than PM10, and the elderly are particularly frail to poor air quality in the area. If the two proposed mitigation measures were implemented, the attributed mortality fraction would decrease by 0.4% and 1.8%, respectively.

It should be noted that this study is limited by the fact that no confounding effects (e.g., temperature and humidity) were considered during the modeling process.

Future work should be conducted to include more air pollutants such as PM2.5 and to further study the synergy between thermal stress and air pollution on health so as to draw decisive conclusions. Examining the impact of climate change and projected air quality conditions on mortality patterns could be a crucial next step.

6.4 Conclusions

While there is considerable literature on the impact of air pollution on human health, the case of Thessaloniki, Greece, is considerably under-studied, despite it being a city with significantly deteriorated air quality. By exploring the link between short-term exposure to air pollutants and cause-specific mortality, the current study offers proof of a positive association between daily mortality from natural and cardiorespiratory causes and exposure to PM10 and O_3. However, no connections were identified between these pollutants and cerebrovascular mortality. The study indicates that the elderly population is particularly vulnerable to the effects of PM10 and O_3. To further contribute to policy-making-associated knowledge for a sustainable environment for humans, the study quantified the health benefits that resulted from two air pollution abatement scenarios and found a significant reduction in total excess mortality. The respective results demonstrate significant decreases in air quality-related mortality, highlighting the importance of appropriate civil protection actions based on scientific expertise tailored to local populations for the development of proper health and air quality plans.

Chapter 7

Synergistic impact of air quality and thermal conditions on human mortality

Rapid urbanization rate has caused cities to face increasing pressure from growing populations, limited resources and escalating impacts of climate change (World Health Organization, 2017). The degradation of air quality has become so prominent in cities that the term urban pollution island (UPI) was recently introduced, to describe the spatial and temporal variations in pollution concentrations between urban and rural areas (Ulpiani, 2021). The synergistic interactions of urban heat islands (UHIs) and UPIs lead to increased pollutant concentrations via mechanisms, such as accelerated atmospheric chemistry cycles due to high temperatures and increased emissions of precursor species (Ulpiani, 2021).

The Mediterranean region faces poor air quality conditions, associated with a range of health challenges. In 10 Mediterranean cities, an increase in PM2.5 was linked to higher all-cause and respiratory mortality, particularly among those aged 75 years and above (Samoli *et al.*, 2013). PM10 was associated with increased mortality from various causes such as diabetes, cardiac, cerebrovascular, and chronic obstructive pulmonary disease (Samoli *et al.*, 2014). Rising temperatures in the area contribute to increased pollutant production, mostly ozone (Pyrgou, Hadjinicolaou and Santamouris, 2018). Climate change projections suggest that the Mediterranean will become a prominent "hot spot," with scorching summers becoming more common (Lelieveld *et al.*, 2012). The region will experience a temperature increase of 2°C to 5°C and a 40% decrease in precipitation, especially

in southern Europe (Lelieveld *et al.*, 2012; Zanis *et al.*, 2015). Greece is particularly susceptible to climate change, and is projected to experience a 4.3°C increase in temperature as well as reduced precipitation (Gao, Pal and Giorgi, 2006; Georgoulias *et al.*, 2022).

Thessaloniki, one of Europe's most polluted cities (Ministry of the Environment and Energy, 2023), faces unfavorable meteorological and air quality conditions. For instance, heat was associated with increased cardiovascular and respiratory mortality risk (Kouis *et al.*, 2019). The city also struggles with air pollution, primarily from O_3 in summer and PM10 in winter (Moussiopoulos *et al.*, 2009; Kalabokas, Adamopoulos and Viras, 2010). PM10 has consistently exceeded EU limits, resulting in legal consequences (Case C-70/21). Exposure to such pollution levels has negative health impacts, including increased hospital admissions and mortality rates for cardiac and respiratory diseases (Giannaros *et al.*, 2011; Psistaki *et al.*, 2022; Parliari, Giannaros, *et al.*, 2023). The interaction between air quality and thermal stress is crucial in Thessaloniki (Zoumakis *et al.*, 2011), which also experiences a strong Urban Heat Island Effect (Giannaros and Melas, 2012). The combination of air pollution and heat-discomfort conditions during heat waves leads to high discomfort levels in the city (Papanastasiou, Melas and Kambezidis, 2015).

The available evidence concerning the potential interactive effects of heat and ambient air pollution remains largely inconclusive. Previous studies mostly focused on the individual impact of environmental stressors on human health (Bao *et al.*, 2016; Kriit *et al.*, 2022), with only a few examining the combined influence of temperature and daily air pollution levels (Stafoggia *et al.*, 2008; Cheng and Kan, 2012; Meng *et al.*, 2012; Turner *et al.*, 2012; Breitner *et al.*, 2014; Jhun *et al.*, 2014). Different publications present varying perspectives, with some suggesting synergistic effects (Baccini *et al.*, 2008; Cheng and Kan, 2012; Meng *et al.*, 2012), others finding no combined impact (Samet *et al.*, 1998; Hales *et al.*, 2000; Basu, Feng and Ostro, 2008), and some reporting effect modifications for only one of the pollutants under study (Breitner *et al.*, 2014).

The diverse perspectives on this matter continue to be a subject of debate within academic literature. Moreover, there has been relatively limited investigation into the simultaneous interactive effects of temperature and air pollution as predictors of mortality. Recent research investigating synergy has shown increased death numbers at high temperatures and high levels of O_3 or PM10, but changes in cold effects with increasing air pollution levels were not reported (Burkart *et al.*, 2013a; Scortichini *et al.*, 2018; Rai *et al.*, 2023).

The present study investigates the interactive effects between daily maximum Apparent Temperature ($Tapp_{max}$) and air pollution (NO_2, O_3 and PM10) in cause-specific mortality (non-accidental, cardiovascular, respiratory), by developing a Distributed Lag Non-linear Model using the framework of Generalized Additive

Models. A separate analysis is conducted for the Elderly citizens (> 65 years old), as well as evaluation of the lag structure.

The synergy is estimated by introducing a tensor product between $Tapp_{max}$ and either PM10 (lag 0–6), NO_2 (lag 0–6) or O_3 (lag 0–8). Temperature estimates were extrapolated at low, medium, and high levels of pollutants defined as the 5^{th}, 50^{th}, and 95^{th} percentile of pollutant-specific distribution; heat and cold effects were estimated as the percentage change in mortality between the 75^{th} and 99^{th}, and the 1^{st} and 25^{th} percentiles of $Tapp_{max}$, respectively. This is the first application of the proposed GAM-based approach and the first analysis to explore this complex association for Thessaloniki, Greece.

7.1 Data and Methods

7.1.1 Study area

The second largest city in Greece and an important economic and industrial center in the Balkans, Thessaloniki is home to more than 1,000,000 inhabitants (Hellenic Statistical Authority, 2023). The city is notable for its aging population, with 21.3% of the population older than 64 (Kouis *et al.*, 2019).

Its Mediterranean climate is significantly affected by the adjacent Thermaikos Gulf in the south; the mean annual temperature of Thessaloniki is ~16 °C and the mean annual relative humidity is ~62%. The city is affected by a prominent UHI effect with an intensity of between 1 °C and 3 °C in winter and 2°C and 4°C in summer (Giannaros and Melas, 2012).

The primary sources of air pollution in the greater Thessaloniki area are road traffic, residential heating (Progiou *et al.*, 2023), biomass burning (Diapouli *et al.*, 2017), and industrial emissions (Moussiopoulos *et al.*, 2009). These activities have generally increased, leading to a decline in air quality (AQ) (Melas *et al.*, 2017), particularly during the economic crisis when unregulated fuel burning for domestic energy use was notorious (Zyrichidou *et al.*, 2019). In addition, particle pollution in the area is also substantially impacted by dust storms that originate in North Africa (Achilleos *et al.*, 2020; Psistaki *et al.*, 2022; Rizos *et al.*, 2022).

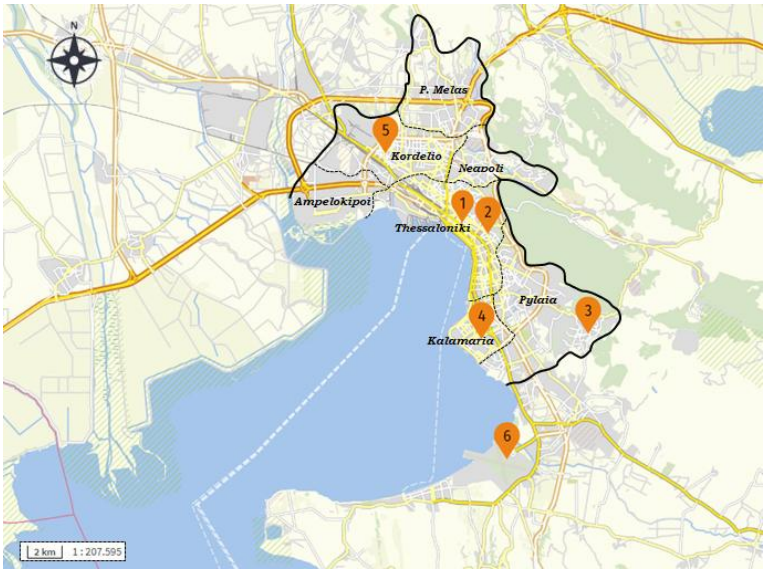


Figure 7.1. The study area with the locations of monitoring stations (1: Agias Sofias, 2: AUTh, 3: Panorama, 4: Kalamaria, 5: Kordelio, 6: Makedonia airport). Dashed lines represent municipal borders.

7.1.2 Data description

Hourly values of PM_{10}, O_3, and NO_2 concentrations ($\mu g/m^3$) for the period 2006–2016 were obtained from five air quality monitoring stations covering the urban area of Thessaloniki, operated by the Ministry of the Environment and Energy (Table 7.1). The highest PM_{10} and NO_2 values and the maximum 8-hour moving average for O_3 over each station were used, representing the daily concentrations for the datasets.

Data regarding temperature and dew-point temperature on an hourly basis from 2006 to 2016 were acquired from the Makedonia Airport weather station, operated and certified by the Hellenic National Meteorological Service (Table 7.1).

The study focused on the Apparent Temperature, a thermal index that gauges the perceived thermal stress and comfort levels experienced by humans. Hourly Tapp was computed as follows:

$$Tapp = -2.653 + 0.994*Ta+0.0153*Td^2$$

where Ta is air temperature (°C) and Td the dew point temperature (°C). Subsequently, the daily maximum value ($Tapp_{max}$) was computed as the highest among the hourly values. Tapp is an optimal indicator for predicting all-cause mortality risk and for issuing heat alerts and warnings (Michelozzi *et al.*, 2010;

Lin *et al.*, 2012; Zhang *et al.*, 2014) and has been previously used to study mortality in Thessaloniki (Parliari *et al.*, 2022; Parliari, Giannaros, *et al.*, 2023).

Table 7.1. Description of the monitoring stations

Station	Description	Coordinates
1. Agias Sofias	Urban-traffic	40.63°N 22.94°E
2. AUTh	Urban-background	40.63°N 22.95°E
3. Panorama	Exurban-background	40.58°N 23.03°E
4. Kalamaria	Exurban-background	40.57°N 22.96°E
5. Kordelio	Urban-industrial	40.67°N 22.89°E
6. Makedonia Airport	Meteorological	40.52°N 22.97°E

Daily mortality data were obtained from the Hellenic Statistical Authority (ELSTAT), including age and cause of death for all Municipalities in the urban area of Thessaloniki for the study period (2006-2016). The data are stratified by causes of death: All-cause (natural, non-accidental), Cardiovascular and Respiratory, according to ICD-10 (International Classification of Diseases, 10th version). Emphasis was placed on studying the overall mortality rate among the elderly, specifically aged 65 and higher.

7.1.3 Statistical analysis

To quantify the association between the various exposures and attributed mortality we use the general framework of distributed lag models (DLMs). The DLM is a regression modelling framework that can capture the distributed effect of an exposure across temporal lags (Gasparrini, Armstrong and Kenward, 2010). Here, we implement DLMs as GAMs with objective penalization to guard against over-fitting, while also allowing for a straightforward quantification of interactions across exposures.

Let M_t and AT_t denote the mortality count and Tappmax for day t. A DLM is defined as

$$M_t \sim NegBin(\mu_t, \theta) \quad (1)$$

$$\log(\mu_t) = \alpha + \beta_0 AT_t + \beta_1 AT_{t-1} + \cdots + \beta_L AT_{t-L} \quad (2)$$

where L days is the maximum temporal lag. The use of the negative binomial (NegBin) distribution is a conventional choice in epidemiological analyses. It extends the Poisson distribution to allow for over-dispersion (extra variance). The linear "effects" β_l act multiplicatively on the mean mortality count μ_t (and

additively on $\log(\mu_t)$. The framework can be extended to DLNMs to allow for non-linear effects by extending the formulation of μ_t via:

$$\log(\mu_t) = \alpha + h(0, AT_t) + h(1, AT_{t-1}) + \cdots + h(L, AT_{t-L}) \qquad (3)$$

where $h(l, AT_{t-l})$ is an unknown 2D function of Tapp_{max} and lag l. Assuming that $h(l, AT_{t-l})$ is smooth, then this is a GAM which can be implemented in the R package mgcv (Wood, 2011, 2017) to optimally estimate $h(l, AT_{t-l})$ by penalising its flexibility. An example of an estimated $h(l, AT_{t-l})$ is shown in Figure 7.2.

Penalization in non-linear regression models is important to avoid over-fitting (over-explaining) the data, and in this case, to also reduce sensitivity to the choice of L (as long as this is large enough). More importantly, it is straightforward to define interactions of the Tappmax-lag effect with other exposures (e.g., with PM10), via

$$\log(\mu_t) = \alpha + h\left(0, AT_t, PM_{10,t}\right) + h\left(1, AT_{t-1}, PM_{10,t-1}\right) + \cdots + h\left(L, AT_{t-L}, PM_{10,t-L}\right). \qquad (4)$$

Function $h(\cdot)$ can be defined using tensor product interactions of regression splines (Wood, 2017), a robust and flexible approach to defining smooth functions across many dimensions. The models presented in what follows were implemented in the R package *mgcv*, which makes use of penalised maximum likelihood to estimate the smooth functions.

In *mgcv*, the "effects" (i.e., the smooth functions) are constructed such that they are centered at zero, i.e., their sum is zero. As such, the term $\exp\{\alpha\}$ is interpreted as the overall (across all time and exposure values) mean mortality count. Function $\rho(\cdot) = (\exp\{h(\cdot)\})$ is therefore the multiplicative increase or decrease of the mean mortality count. $\rho(\cdot) > 1$ implies greater than average mortality risk, whereas $\rho(\cdot) < 1$ means lower-than-average risk. Thus $\rho(\cdot)$ is the relative risk or RR (relative to the overall mean death count). Moreover, a quantity to summarise the "marginal" risk due to the exposure is based on the sum of $h(\cdot)$ over the lags. For instance,

$$CR(AT) = \exp\left\{\sum_{l=0}^{L} h(l, AT)\right\} \qquad (5)$$

is the cumulative risk (CR) for Tappmax from model (3).

Moreover, GAMs implemented in mgcv can be interpreted in a Bayesian way (Wood, 2017) and Monte Carlo simulation can be used to quantify the associated uncertainty in estimating the smooth function $h(\cdot)$. This in turn enables the assessment of "significance" in the RR estimated, which here is determined by checking whether the value 1 lies within the 95% credible interval of $\rho(\cdot)$. If it is not, then we can say that with probability 0.95 the value of the RR is not 1 and that the weight of evidence supporting this is strong.

The surface that graphically explains the concept of the present work is demonstrated in Figure 7.2, where the cumulative risk plot results from summing across the lag dimension and along the pollutant and Tappmax ranges.

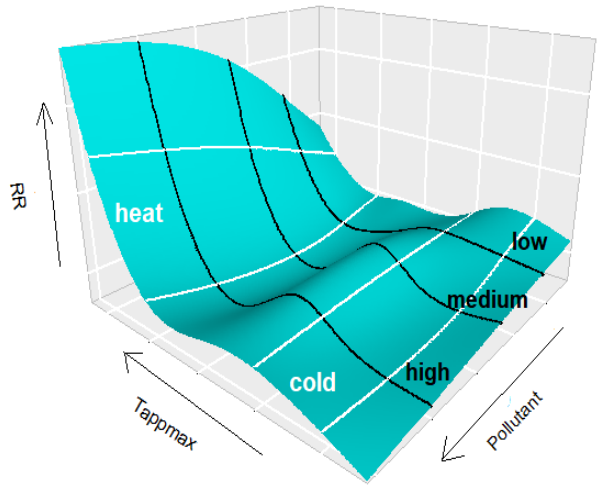


Figure 7.2. Representation of the tri-dimensional surface depicting the non-linear association between Tappmax and pollutant on mortality. Effect estimates of heat (75th and 99th percentiles of $Tapp_{max}$ distribution) and cold (1st and 25th percentiles) are shown, along with sections corresponding to low, medium and high pollution values (5th, 50th and 95th percentiles).

7.1.4 Data analysis

Figure S1 shows the violations of EU Air Quality Guidelines for PM10, NO_2 (annual, 40 μgr/m^3) and O_3 (daily, 120 μgr/m^3) during study period 2006-2016. EU annual limits were surpassed every year for PM10 and 6 out of 11 years for NO_2, while 28% of total days (4018) recorded O_3 daily values above threshold.

We calculated the mean monthly values of the environmental stressors for Thessaloniki across the 11-year period, to get a picture of their seasonal variability. PM10 and NO_2 display peaks during winter months and troughs at

summertime. O_3 exhibits reverse seasonality and follows the pattern of $Tapp_{max}$ behavior, with summertime maxima due to enhanced photochemical processes (Figure S2).

During the study period, there were 73,990 natural deaths from all-causes, 21,811 from cardiovascular (CVD) diseases, and 7,134 from respiratory (RD) causes. Mortality among the elderly was 62,482 representing more than 80% of the total number of deaths. Table 7.2 provides the descriptive statistics of pollution, $Tapp_{max}$ and daily mortality for the reference period.

The mortality data indicates that 30% of all natural deaths are attributed to cardiovascular diseases, highlighting the significance of this health condition for investigating susceptibility, noting that stroke and ischaemic heart disease are the leading causes of death in Greece (European Observatory on Health Systems and Policies, 2019). In addition, Greece is among the countries with the highest population rates in the age group of over 65 in Europe (EUROSTAT, 2020); in our dataset elderly mortality reflects 84% of all-cause mortality. Pollutant concentrations are generally higher in Thessaloniki than those reported in Greece (Rai *et al.*, 2023) and other metropolitan areas (Garrett and Casimiro, 2011; Samoli *et al.*, 2014), comparable to values of other large cities with substantial air quality issues (Samoli *et al.*, 2009; Stafoggia *et al.*, 2010; Wang *et al.*, 2018). Similar values of mean daily mortality and summary statistics of PM10 in Thessaloniki are verified also in (Samoli *et al.*, 2013).

Table 7.2. Descriptive statistics of mortality (number of deaths, top), $Tapp_{max}$ (°C, middle) and pollution (μgr/m^3, bottom).

Daily Mortality (number of deaths)				
	Mean	**St. dev.**		
All-cause	18.4	4.7		
Cardiovascular	5.4	2.4		
Respiratory	1.8	1.4		
Elderly	15.5	4.4		
$Tapp_{max}$ (°C)				
Mean	**1st perc.**	**25th perc.**	**75th perc.**	**99th perc.**
19	0.5	10	28	38
PM10 (μg/m^3)				
Mean	**5th perc.**	**50th perc.**	**95th perc.**	

55	28	49	104

O_3 (µg/m^3)			
Mean	**5th perc.**	**50th perc.**	**95th perc.**
101	54	99	160

NO_2 (µg/m^3)			
Mean	**5th perc.**	**50th perc.**	**95th perc.**
40.3	17	37	74

7.2 Results

7.2.1. Application of GAM for thermal stress

A model defined by equations (1) and (3) is fitted to quantify the effect of $Tapp_{max}$ along its lags with L= 21 days. The estimated RR surface is given in Figure 7.3 left panel, indicating elevated risk for high Tappmax at short lags (0-3). The surface is comparable to the one shown in (Parliari *et al.*, 2022), who studied the same data set using a DLNM from the *dlnm* package in R. Moreover, Figure 7.3 right panel shows the associated CR (cumulative risk as defined in equation 5) for Tappmax, which shows that risk grows exponentially above 33 °C.

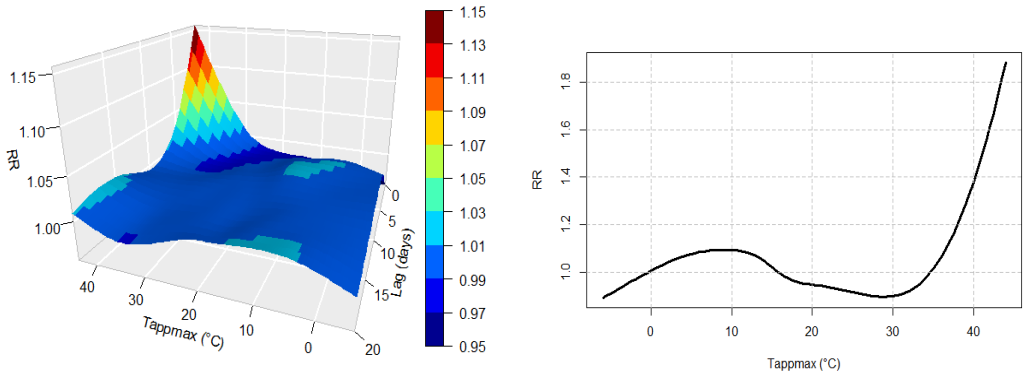


Figure 7.3. Exposure-lag-response risk surface demonstrating the nonlinear association between $Tapp_{max}$ and mortality (left panel); Cumulative exposure-response curve between daily $Tapp_{max}$ and all-cause mortality over lag days 0-20 (right panel).

Using the estimated CR, we can quantify the percentage change in risk when $Tapp_{max}$ changes. Specifically, we define as "heat effect" the percentage change in risk when $Tapp_{max}$ increases from its 75th to its 99th percentile. Similarly, the "cold effect" is the change occurring from the 25th to the 1st percentile. A single model was fitted for each cause of death. The estimates of the heat and cold effects as defined above show that the impact from heat is considerable across all causes, with RD recording the largest increase (54.8%), while the age group of > 65 years exhibits the smallest (28.4%) increase. Lower (but still positive) changes are evident for the cold effects, with RD being the health condition with the most pronounced effect (30.2%), roughly three times larger than the others (Figure S3).

Generally, Thessaloniki's population is more severely impacted by high temperatures than low ones with respect to all types of mortality. For comparison, Rai et al. (2023) reported a 17% increase in CVD and 19% increase in RD mortality between the 75th and the 99th percentile of temperature distribution, pooled from five cities in Greece. Concerning lag effects, there is an immediate increase in RR upon exposure to high temperatures (lag 0–3), whereas for low temperatures the effect is delayed (lag > 3). This finding is in agreement with previous studies concluding that heat has an almost immediate effect on human health, while impacts from cold take longer to manifest (Guo *et al.*, 2011; Burkart *et al.*, 2013a; Bao *et al.*, 2016; Parliari *et al.*, 2022).

7.2.2 Synergy between PM10 and $Tapp_{max}$

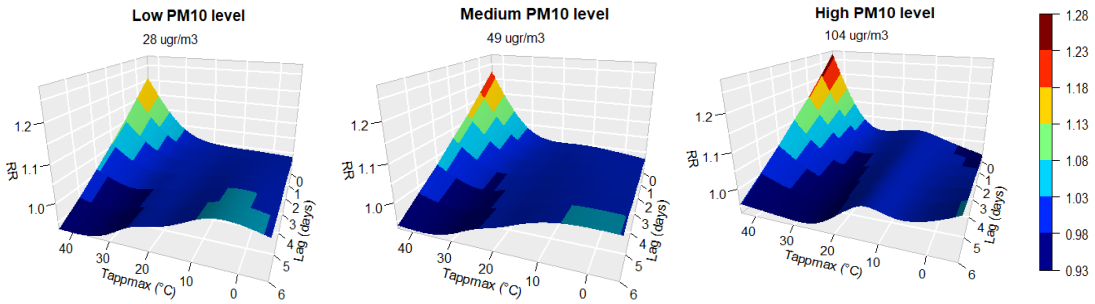


Figure 7.4. Combined effect of PM10 and $Tapp_{max}$ on all-cause mortality stratified by levels of pollutant (defined as "low", "medium", and "high" based on 5th, 50th, and 95th percentiles of PM10 distribution).

A model defined by equations (1) and (4) is implemented to study the joint effects of $Tapp_{max}$ and PM10. The estimated RR surfaces $h(l, AT, PM_{10})$ for the 5th, 50th and 95th percentiles of PM10 (29, 49, 104 μg/m^3) are given in Figure 7.4. Clearly,

the most harmful combination of outdoor conditions for human health is high $Tapp_{max}$ and high pollution levels (RR up to 1.28), while at low and medium levels of pollution, risk is lower (RR up to 1.18 and 1.23, respectively).

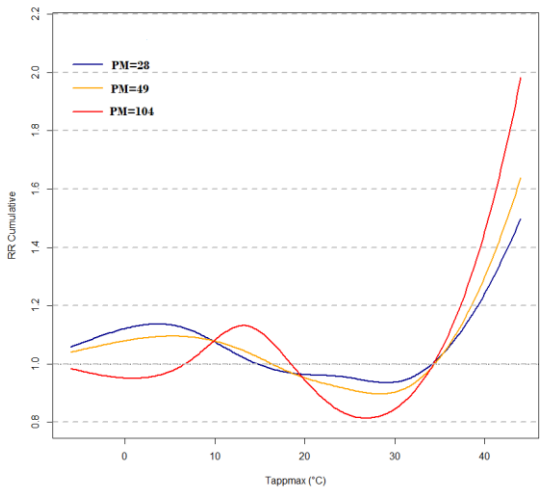


Figure 7.5. Cumulative exposure–response association across lags 0-6 for different levels of PM10 (blue denotes "low", yellow denotes "medium", and red denotes "high").

Figure 7.5 shows the corresponding CR plots for each PM10 level. For $Tapp_{max}$ < 7 °C, low PM_{10} levels result in higher mortality risk than medium and high pollutant concentrations. In the region [7 °C, 20 °C], the effects of low and medium pollution levels decrease with temperature, while at high levels of pollution there is a ceiling of impact at 13 °C, above which, risk decreases. This could be related to data availability in the region, rather than physical behavior of the system. In warmer conditions below 33 °C, all RR values are lower than 1, indicating that these conditions are favorable. In extremely hot conditions ($Tapp_{max}$ > 33 °C), there is a sharp increase in mortality risk, which becomes more marked with increasing PM_{10} levels. The highest RR value of around 2 occurs when air quality is at its poorest under conditions of extreme thermal discomfort of 43°C. These conditions, high $Tapp_{max}$ values and high airborne PM levels, are quite frequent in Thessaloniki.

7.2.2.1 Weight of evidence

As discussed in section 7.1.3, uncertainty in the estimated risk can be quantified in a Bayesian manner and produce probabilistic statements regarding the weight-of-evidence (or statistical significance) behind the estimates. We produce the 3D RR surface plots as 2D raster images of RR in Figure S4. Grid points for which RR=1 is outside the 95% credible interval are marked with grey shading (circles). Grey

regions indicate statistically significant areas where the RR is either greater (red) or smaller (blue) than 1 (the mean mortality count).

In general, many of the regions (particularly for heat effects at Tappmax > 20 °C) are statistically significant, and therefore the conclusions drawn are robust. However, the areas below 30 °C for low and medium PM10 levels and the area 5 °C–30 °C for the high level at lags 0–3 define regions where the RR is not different from 1. This could either be because there are very few Tappmax-PM10 values there, or because the association between mortality and stressors is weak at short lags.

To further assess the robustness of the findings, sensitivity analyses were performed to investigate confounding effects with other pollutants. Specifically, we fitted a model where data points corresponding to high (> 90th percentile) NO2 values were excluded (Figure S4). This resulted in extended grey regions suggesting some degree of synergy between high PM10 and high NO2 concentrations. The same procedure is repeated for O3 values and again, the significance increased, implying confounding effects among the three pollutants at high concentrations. Nevertheless, the differences were not pronounced enough to justify using the cropped dataset for the rest of the analysis.

For the corresponding CR plots, uncertainty is presented via 95% intervals (dashed lines) in Figure 7.6. Risk is “significant”, where the value of 1 is not included in the intervals. There is little confidence for Tappmax < 0 °C at low and medium PM10 levels and below 8 °C at a high PM10 level. A possible explanation might be the relatively lower exposure of the population to outdoor conditions during winter. The wider breadth of the intervals at extremely low and extremely high Tappmax is due to the very small sample size of temperature values in those regions.

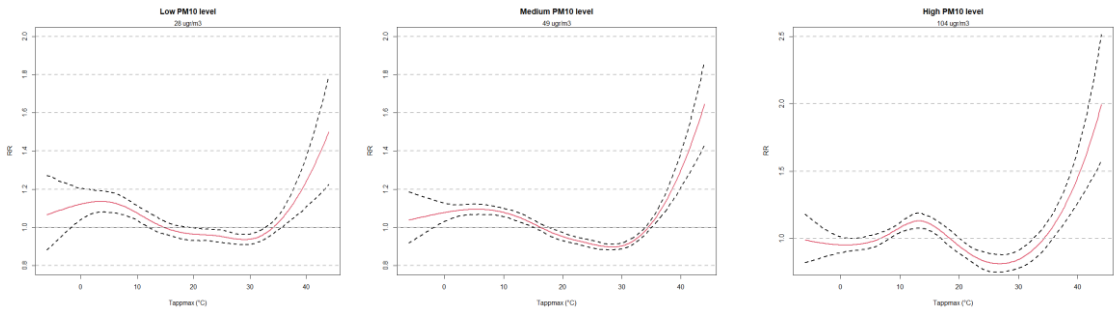


Figure 7.6. Cumulative exposure−response associations across lags 0-6 for Low, Medium and High PM10 levels. Dashed lines represent 95% CI.

7.2.3 Synergy between NO_2 and $Tapp_{max}$

To study the NO_2 effect, the same model as in section 7.2.2 was implemented, but with NO_2 rather than PM10. Similar to PM_{10}, 3D plots in Figure S5 reveal consistent synergy between $Tapp_{max}$ and NO_2 concentrations in all pollution ranges (low, medium and high defined at 17, 37 and 74 $\mu g/m^3$). With increasing temperature, mortality risk increases, exhibiting maxima at short lags (0–2). For all three levels, a second peak is present below 10 °C for longer lags. An increased mortality risk of about 20% is evident at the high NO_2 level for $Tapp_{max}$ > 40 °C, confirming that intense thermal stress and poor air quality pose major threats to human health.

The pattern of cumulative RR for NO_2 over the entire lag period (0–6) for the three levels of pollution is similar to PM_{10}, highlighting the similarity between the two pollutants (Figure S6).

The peaks are statistically significant as indicated by the grey shading areas (Figure S7), and this remained largely unchanged when investigating the possible confounding of NO_2 with high (>90^{th} percentile) values of PM_{10} and O_3 (results not shown). The top right region (high $Tapp_{max}$ and long lags) remains insignificant, indicating that those values may not be supported by adequate data or a strong relationship between exposure and mortality. Finally, there is high statistical significance below 0 °C (at low and medium NO_2 levels) and below 8 °C (at a high NO_2 level) (Figure S8).

7.2.4 Synergy between O_3 and $Tapp_{max}$

The analysis for O_3 is analogous to that of PM_{10} and NO_2. The three pollution levels in this case are defined as 54 $\mu g/m^3$ (low), 99 $\mu g/m^3$ (medium), and 160 $\mu g/m^3$ (high pollution). The highest mortality risk occurs for high $Tapp_{max}$ over short lags (0–2), with a second peak appearing at 10 °C, for all pollution levels over longer lags. O_3 concentrations of 160 $\mu g/m^3$ are associated with the most adverse human health impacts at $Tapp_{max}$ > 40 °C (Figure S9).

Cumulative risk is slightly elevated for $Tapp_{max}$ between 0 °C and 10 °C in conditions of medium O_3 pollution. At low and high levels of ozone, there are insignificant relationships for specific segments of temperature ($Tapp_{max}$ < 8 °C and $Tapp_{max}$ > 15 °C for low, and $Tapp_{max}$ >17 °C, for high ozone concentrations).

The weight of evidence for high O_3 concentrations and low $Tapp_{max}$ is low (Figure S11). Indeed, no such combination exists in our dataset (i.e., the estimates are statistical extrapolations) given the opposite seasonal behavior of these components. An additional hiatus is found at low O_3 levels for $Tapp_{max}$ between 10 °C and 20 °C. After omitting high PM_{10} and NO_2 values, the 95% CI did not increase: therefore, we assume that confounding does not occur.

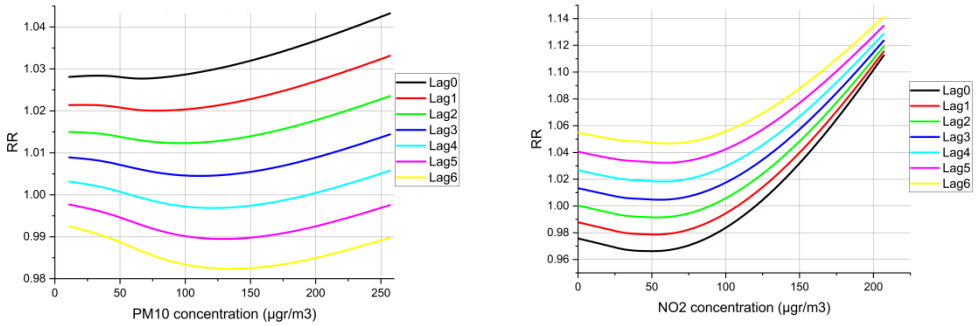
7.2.5 Lag structure analysis

In order to better understand the temporal dimension of the complex exposure-lag-response association, an appropriate representation of the temporal pattern of risk is needed. In what follows, we cumulate the $Tapp_{max}$-Pollutant-Lag surface across the $Tapp_{max}$ space (i.e., sum the RR at the log scale) to "integrate out" $Tapp_{max}$. We then present "slices" of the resulting Pollutant-Lag surface for different lags in Figure 7.7.

The top left panel of the plot relates to PM10 where it is evident that the highest mortality risk is on the day of exposure (lag 0), and this diminishes as the lag increases. This behavior shows that there is no threshold in the PM10 dose–response relationship, and even a small increase in this pollutant has health impacts, in agreement with previous studies (Psistaki *et al.*, 2022; Parliari, Giannaros, *et al.*, 2023).

In contrast, the impact of NO2 on mortality (right panel) is more pronounced several days after the exposure and reaches a maximum on the last day (lag 6). This indicates that the health impacts of NO2 may be cumulative.

The temporal pattern of O3 (bottom left) is different from PM10 and NO2. Up to a certain threshold (~ 170 μg/m3), the risk increases with lag. On lag 8 the risk is greater than on lag 7 and the smallest RR values occur at lag 0. For very high O3 concentrations (> 170 μg/m3) this pattern is reversed: the effect on mortality is immediate (lag 0). Interestingly, this convergence point for O3 concentrations is partly evident in other studies focusing on the impact of O3 on human health (Parliari, Giannaros, *et al.*, 2023), showing that the lag structure is different depending on the pollutant concentration under study.



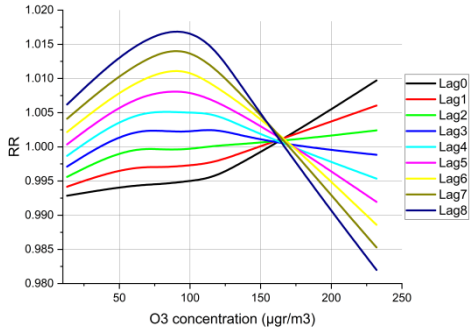
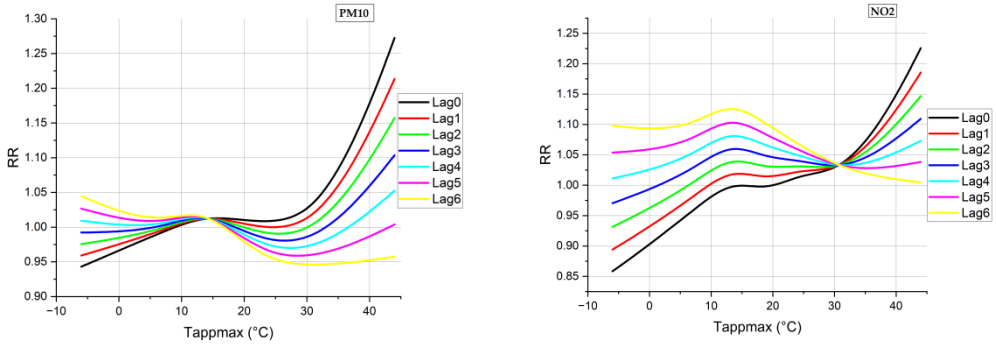


Figure 7.7. Dose-response curves of cumulative RR across $Tapp_{max}$ range, demonstrating the lag structure for PM10 (top left, lags 0-6), NO_2 (top right, lags 0-6) and O_3 (bottom left, lags 0-8).

We then looked at the lag structure of RR as a function of $Tapp_{max}$, by cumulating the risk across the pollutants. Figure 7.8 shows the associated curves relating to PM10 (top left), NO_2 (top right) and O_3 (bottom left). In all cases, the following temporal structure of the exposure-response relationship is evident: heat effects are immediate while the ones from cold become predominant at longer time lags. These results are in line with previous studies (Liu *et al.*, 2011; Lubczyńska, Christophi and Lelieveld, 2015; Schnell and Prather, 2017; Rodrigues, Santana and Rocha, 2019).

For PM10, the RR for $Tapp_{max}$ < 15 °C is higher 7 days after the exposure (lag 6) than present day (lag 0). Conversely, the RR for $Tapp_{max}$ > 15 °C increases exponentially and reaches its peak at lag 0. The same applies for NO_2 beyond the convergence point of 31°C, and O_3 at 27°C.



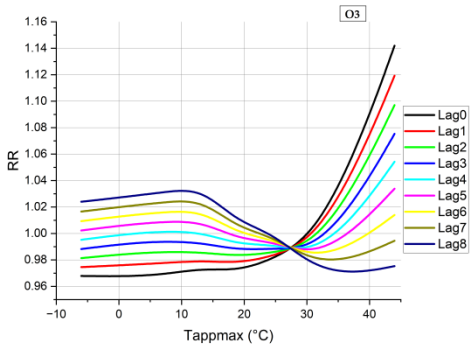


Figure 7.8. Dose-response curves of cumulative RR across pollutants concentration ranges, demonstrating the lag structure for PM10 (top left), NO_2 (top right) and O_3 (bottom left).

7.2.6 Heat effect by pollutant levels (all- and specific-cause mortality)

Heat effects on all-cause mortality stratified by pollutant levels are shown in Figure S13. The exposure of the population to outdoor conditions is higher in summer than in winter; therefore, the percentage change in mortality for all pollutants is greater for heat compared to cold. Figure 7.9 shows that mortality rises with increasing concentrations of PM_{10}, NO_2, and O_3. Overall, PM_{10} accounts for the largest health burden, expanding to 47.7% mortality increases for high levels, compared with 37.7% for NO_2 and 32% for O_3. Similarly, in the cold part of the range, the highest pollutant concentrations exert the greatest impact on mortality, but the respective increases are significantly lower (Figure S14).

Figure 7. 9 shows the heat effects on mortality across the various causes for the whole population and the elderly (> 65 years) – stratified by levels of PM_{10}, NO_2, and O_3. A consistent rise in the impact of heat on mortality due to all causes and CVD diseases is observed. The highest percentages occur at high pollutant levels. All-cause mortality is primarily affected by all levels of PM_{10} (20%, 27.5%, and 47.7%, respectively), secondly by NO_2 and lastly, by O_3. A very large effect of heat on CVD mortality is found at the high level of PM_{10} (58.9%), followed by O_3 (45.3%). Interestingly, CVD mortality is not affected by varying levels of NO_2 and its levels remained high (37.2%). It is worth noting the respiratory (RD) decrease with increasing PM_{10} and NO_2 levels.

The elderly population is primarily affected by PM_{10} at all levels, followed by NO_2, and O_3. For all pollutants, the elderly estimates qualitatively follow the ones

for all-cause mortality for the respective species, but with much higher values compared to the general population.

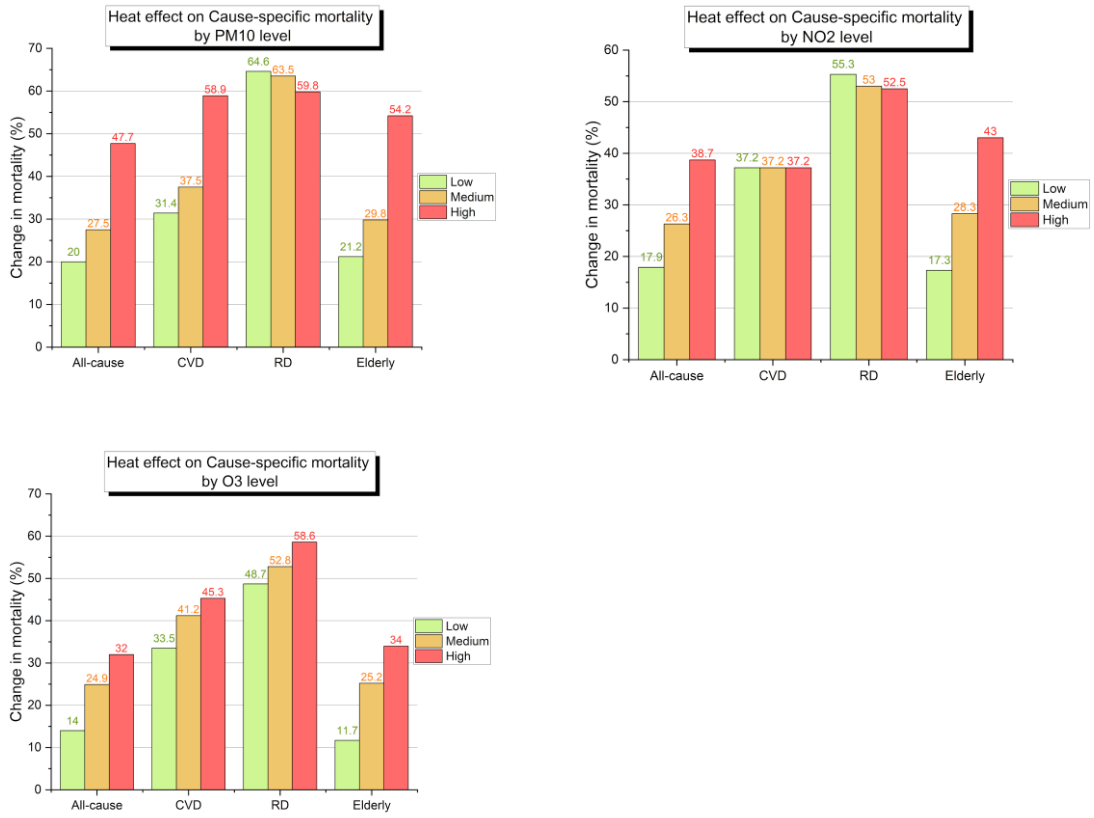


Figure 7.9. Estimates of heat effects as % change in cause-specific mortality for $Tapp_{max}$ increases between the 75th and 99th percentile by levels of pollutants (defined as "low", "medium", and "high" based on 5th, 50th, and 95th percentiles of pollutants distributions).

7.2.7 Attributable Mortality Fraction (all- and specific-cause mortality) for non-optimum $Tapp_{max}$ ranges

The approach presented in this paper is extended to encompass the mortality burden (Attributable Fraction, AF). In contrast to RR, which is evaluated at potentially counterfactual situations and which does not allow for the likelihood of stressor values, AF is a more rigorous metric which quantifies the effect on the population, taking into consideration the observed number of deaths and also the frequency of extreme $Tapp_{max}$ occurrence (Kim, Kim and Liu, 2014; de' Donato *et al.*, 2015).

Like RR, the AF is computed using the estimated functions (e.g., $h(l, AT)$) but using the actual $Tapp_{max}$ values in the data to attribute the number of deaths on any given day to the distributed effect of $Tapp_{max}$.

Figure 7.10 shows the AF for non-optimum $Tapp_{max}$ (extreme cold, mild cold, mild heat, and extreme heat) stratified by pollutant level as follows:

(a) Extreme cold: minimum to 5th percentile

(b) Mild cold: 5th percentile to MMT

(c) Mild heat: MMT to 95th percentile

(d) Extreme heat: 95th percentile to maximum

It is apparent that in the vast majority of cases, extreme heat has the biggest influence on the AF. Two exceptions are noted, specifically at low levels of PM_{10} and NO_2, where extreme cold is more prominent. Very frequently, extreme cold is the second most harmful temperature range.

Although in articles studying the impact of temperature on mortality, optimum temperatures (mild cold, mild heat) are associated with most of the attributable deaths (Parliari *et al.*, 2022; Psistaki, Dokas and Paschalidou, 2023), in our synergistic analysis, extreme heat results not only in the highest RR values, but highest AF as well, compared to other optimum and non-optimum ranges. This confirms our previous inference that extremely high $Tapp_{max}$ values are most harmful to health when combined with increased levels of pollutants.

PM_{10} has the largest mortality burden among the three pollutants at the medium and high levels, while NO_2 is mostly prominent when levels of pollution are low. It is also worth noting that the AF decreases (overall) from medium to high O_3 levels, probably due to the limited exposure of the population to extremely high temperatures in the summer months.

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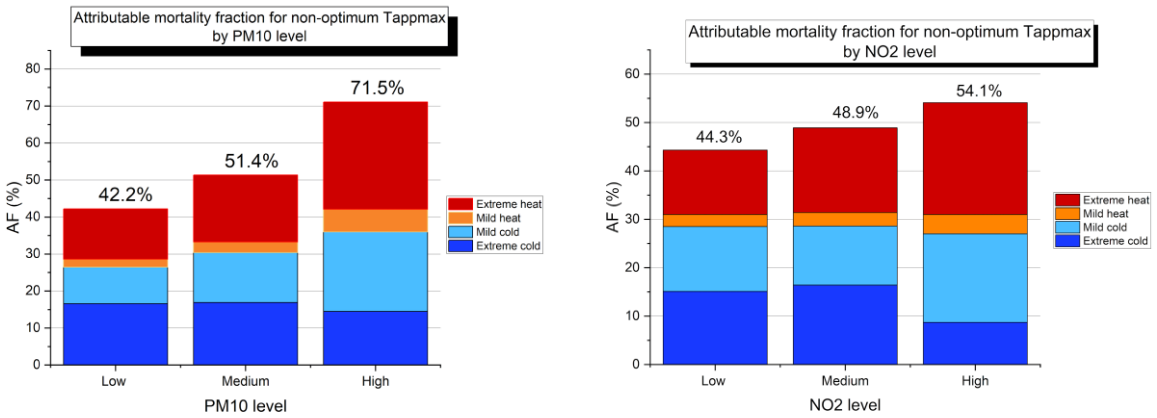


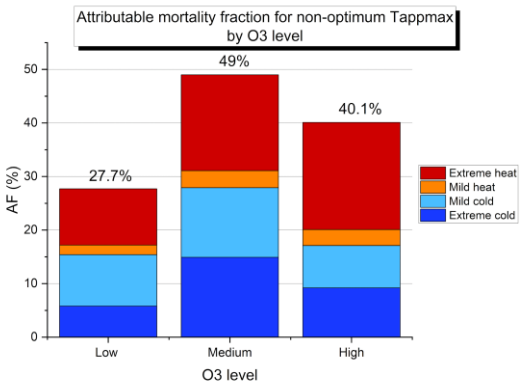
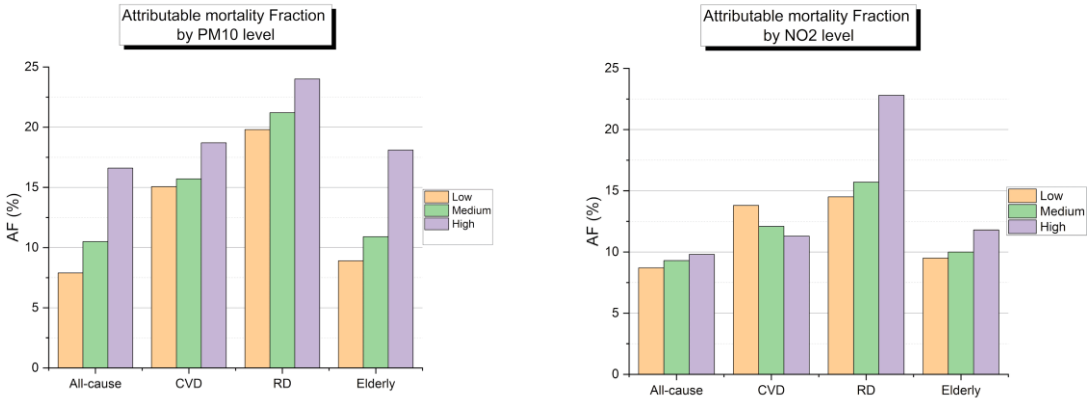


Figure 7.10. Fractions of all-cause mortality attributable to non−optimum $Tapp_{max}$ by levels of pollutants (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of pollutants distributions).

Stratifying AF by the various diseases confirms that heat impact on cause-specific mortality burden is strongly modified by pollutant levels (Figure 7.11). Mortality fraction from all- and respiratory causes is primarily affected by PM10 levels and then by NO_2. AF related to CVD mortality, although increasing with rising O_3 concentrations, decreases for PM10 and NO_2.

The estimates of the AF for the Elderly follow the all-cause distribution for all pollutants but are exhibit much higher numbers compared to the general population. Effect modification is higher for PM10, followed by NO_2 and O_3. .



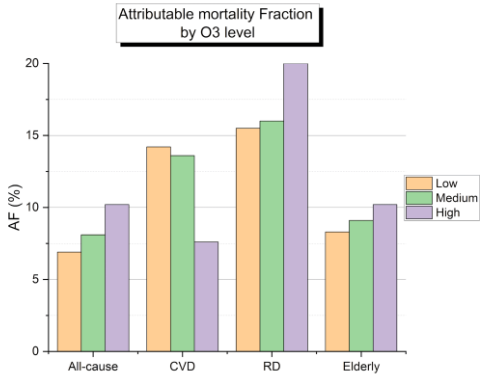


Figure 7.11. Fractions of cause-specific mortality attributable to levels of pollutants (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of pollutants distributions).

7.3. Discussion

To our knowledge, this study is the first to use a GAM-based approach to assess the synergistic impacts of thermal conditions and air quality for the urban area of Thessaloniki.

We used an advanced statistical approach that captures the complex non-linear and lagged dependencies in both the exposure-response and lag-response associations. This approach is flexible and can be adjusted to account for other synergies as well. Our results are statistically significant based on high-quality data spanning a period of 11 years.

The research holds significant potential for applications in various fields such as atmospheric sciences, biometeorology, and environmental epidemiology as our findings can shed light on the impacts of climate and weather on human health. This interdisciplinary significance can inform evidence-based policies, adaptation strategies, and targeted public health interventions in the vulnerable Southern European region facing climate change challenges.

We provide compelling evidence for the compounded effects of air pollution (PM_{10}, NO_2, and O_3) and the maximum apparent temperature, with particularly pronounced adverse impacts on the elderly. We show that deterioration in air quality renders the population more susceptible to the effects of temperature variability, and *vice versa* that extreme temperatures influence susceptibility to air pollution. We also examine the effects of temporal lag and non-optimum $Tapp_{max}$, as very little is known about the relative contribution of both heat and cold from moderate and extreme temperatures to the disease burden. In this study, we identified $Tapp_{max}$ as the most appropriate thermal predictor, based on previous

investigations of the dataset (Parliari *et al.*, 2022; Parliari, Giannaros, *et al.*, 2023).

Relationships between deaths and temperature are frequently expressed in the literature with the use of V, U, J, and reverse J-shaped structures (Baccini *et al.*, 2008; Zhang *et al.*, 2016; Psistaki, Dokas and Paschalidou, 2022). Our analysis produced J-shaped $Tapp_{max}$-mortality curves stratified by air pollution levels, with RR values increasing sharply over 33 °C. This specific threshold is demonstrated in Kouis et al. (2019) for Thessaloniki, indicating that it is typical. We found that low temperatures are associated with increased mortality as well, but not to the same extent.

The exposure–response associations between $Tapp_{max}$ and RR cumulated over all lags shows consistent patterns for the three studied pollutants:

- Winter temperatures ($Tapp_{max}$ < 10 °C), probably affected by limited exposure to outdoor conditions and confounded by the transmission of diseases such as influenza, increase the mortality risk up to 1.18, 1.17, and 1.15 for PM_{10}, NO_2, and O_3, respectively. As temperatures rise (10–20 °C), people spend more time outdoors or increasingly ventilate with ambient air, increasing exposure and the RR.
- In view of excess deaths, a prominent "harvesting effect" or mortality displacement (RR < 1) is evident between 20 °C and 33 °C. This indicates the existence of subgroups of vulnerable individuals, for whom exposure to cold and high pollution levels leads to a subsequent decrease in deaths, as reported also in Breitner et al. (2014). It is worth mentioning that this $Tapp_{max}$ range is in force during months when dust events are more frequent in Thessaloniki, with recommendations to avoid outdoor activity, which in turn may safeguard the local population (Psistaki *et al.*, 2022). Another explanation of the RR < 1 area of the graph (particularly at around 25 °C) could be the "September phenomenon" (Falagas *et al.*, 2009), which proposes reduced numbers of deaths in the late summer to early fall months in the Mediterranean countries due to human behavioral patterns, socio-economic factors, and environmental parameters.
- From 33 °C upwards, cumulative mortality risk rises exponentially for all pollutants. The most adverse impact is reported for the combination of very high $Tapp_{max}$ (> 40 °C) and high pollution levels (RR = 1.95 for PM_{10}, 2.0 for NO_2, and 1.82 for O_3). The same result arises from the three-fold lag–exposure–response surfaces, where the death risk reaches +26%, 20% and +15% for PM_{10}, NO_2 and O_3, respectively, at lag 0. The findings of Chen et al. (2018) support the idea that high air pollution enhances temperature effects on daily mortality, while associations between high temperatures and mortality seem to be generally stronger at high pollution levels. Significant heat impact (expressed by UTCI) was evident for the medium-high and high O_3 categories of Lisbon and Berlin and high PM_{10}

pollution in Lisbon (Burkart *et al.*, 2013b). Breitner et al. (2014) also showed that correlations between high temperatures and mortality were most pronounced at elevated levels of PM_{10} and O_3.

Generally, heat effects are found to be more harmful than cold in this study. High levels of PM_{10}, NO_2, and O_3 are associated with increases in mortality of 47.7%, 38.7%, and 32%, respectively, whereas the respective increases for cold are 13.6%, 19.2%, and 2.1%. Similar results are reported in Burkart et al. (2013a), noting that the cold impact was mostly unaffected by air pollution.

We found that in Thessaloniki, EU air pollution limits are regularly exceeded for the studied pollutants. By reducing the concentration of these harmful substances, especially during heat waves when vulnerable populations are at a greater risk, it will be possible to significantly reduce the numbers of fatalities caused by various ailments. Strict compliance with EU limits represents a proactive approach to improving public health and mitigating the adverse effects of extreme heat events.

In view of the mortality burden, we show that extremely high temperatures ($Tapp_{max}$ > 35 °C) are responsible for the majority of deaths at all three levels of PM_{10}, NO_2, and O_3. For all pollutants, extreme heat, extreme cold, mild cold, and mild heat are responsible for 60.7%, 48%, 45% and 11% of attributable mortality, respectively. These findings confirm our previous results regarding mortality risk, indicating that non-optimum $Tapp_{max}$ values in Thessaloniki (hot more so than cold) are responsible for the majority of the detrimental impacts on health when coincident with enhanced concentrations of ambient air pollution.

The assessment of percentage increases in cause-specific deaths across pollution levels shows that all-cause mortality is strongly affected by enhanced PM_{10} levels (20%, 27.5%, 47.7%), whereas both PM_{10} (31.4%, 37.5%, 58.9%) and O_3 (33.5%, 41.2%, 45.3%) affect cardiovascular disease (CVD). Interestingly, the death rate from respiratory disease (RD) marginally decreases as NO_2 and PM_{10} concentrations increase, possibly due to behavioral patterns of the population. Nevertheless, consistently higher increases in RD mortality were found for all pollutants compared to all-cause and CVD, also evident in Rai et al. (2023). Lastly, in our study, CVD has a higher death toll than all causes, also demonstrated by Chen et al. (2018).

Our analysis shows that elderly citizens (65 years and older) are particularly vulnerable to the adverse combination of thermal conditions and poor air quality. Many studies report that older people are susceptible to extreme meteorological conditions and air pollution (Barnett, 2007; Cakmak, Dales and Vidal, 2007; Oudin Åström, Bertil and Joacim, 2011; Gasparrini *et al.*, 2012; Shim, Byun and Lee, 2023), due to the prevalence of pre-existing chronic conditions and because they may be subject to physiological changes in thermoregulation and homeostasis. In addition, the limited care and social support for this age category may also render them more susceptible (Breitner *et al.*, 2014).

The lag structure analysis across the $Tapp_{max}$ range revealed varying influence of the three pollutants: PM_{10} showed the highest mortality risk at lag 0 with no threshold in PM_{10} dose-response relationship, as in previous studies (Psistaki *et al.*, 2022; Parliari, Giannaros, *et al.*, 2023). However, for NO_2 the health impacts were delayed by several days. O_3 had an immediate effect at high concentrations, even at day 0, while below 170 $\mu g/m^3$ the situation was reversed. This "threshold" in O_3 emerges in other studies as well (Parliari, Giannaros, *et al.*, 2023). Further, the dose–response relationships of cumulative RR across pollutant concentrations showed that the impacts of high temperatures are immediate (days 0–3), whereas the cold effects became more pronounced with longer time lags (lag > 3). In general, heat effects tend to occur on a short-term, typically a few days, whereas cold effects evolve and persist over a longer duration, ranging from several days to weeks (Burkart *et al.*, 2013b; Breitner *et al.*, 2014; K. Chen *et al.*, 2018).

While the biological mechanisms responsible for the combined impact of air pollution and thermal conditions on mortality are not well known, several hypotheses have been put forward. Hot days induce physiological stress which may modify the response to air pollution, potentially increasing the susceptibility to adverse effects. Similarly, air pollution can render individuals more susceptible to thermal stress, as exposure impacts heart rate variability, the autonomic nervous system, and inflammatory parameters, for example (Gordon, 2003).

The limitations of this study include the following. Given the location-specific character of our and similar studies (Samoli *et al.*, 2014; Ma, Zhou and Chen, 2020), generalizing the findings and directly comparing with assessments of health impacts in other regions with possibly distinct basic health and air pollution conditions may be problematic. Furthermore, using air quality data from fixed stations instead of exposure data may result in bias from exposure misclassification, as individual exposure does not necessarily coincide with measured atmospheric parameters.

Our findings emphasize the need to mitigate the health burdens associated with ambient air pollution and thermal conditions. Additional research is necessary to explore air pollution and air temperature inter-relationships using morbidity data, such as hospitalization and emergency room visits, in order to gain a more comprehensive understanding of the interaction between thermal stress and air pollution.

7.4. Conclusions

We investigated the interactive effects of meteorological conditions (i.e., thermal conditions) and air pollution, using PM_{10}, NO_2, and O_3 as predictors. We found that air pollution strongly modifies thermal effects, especially heat, and *vice versa*, in varying degrees across different lags. Our results underscore that low

temperatures have delayed effects on mortality, whereas high temperatures have immediate effects. We studied the compounded effects of air pollutants and the maximum apparent temperature and found that mortality strongly increases at high temperatures and high levels of air pollution. The elderly (65 years and older) are particularly vulnerable to heat stress and impaired air quality. These findings have important implications for the development of public health interventions aimed at controlling and preventing health consequences of exposure to extreme temperatures and poor air.

7.5. Supplementary material

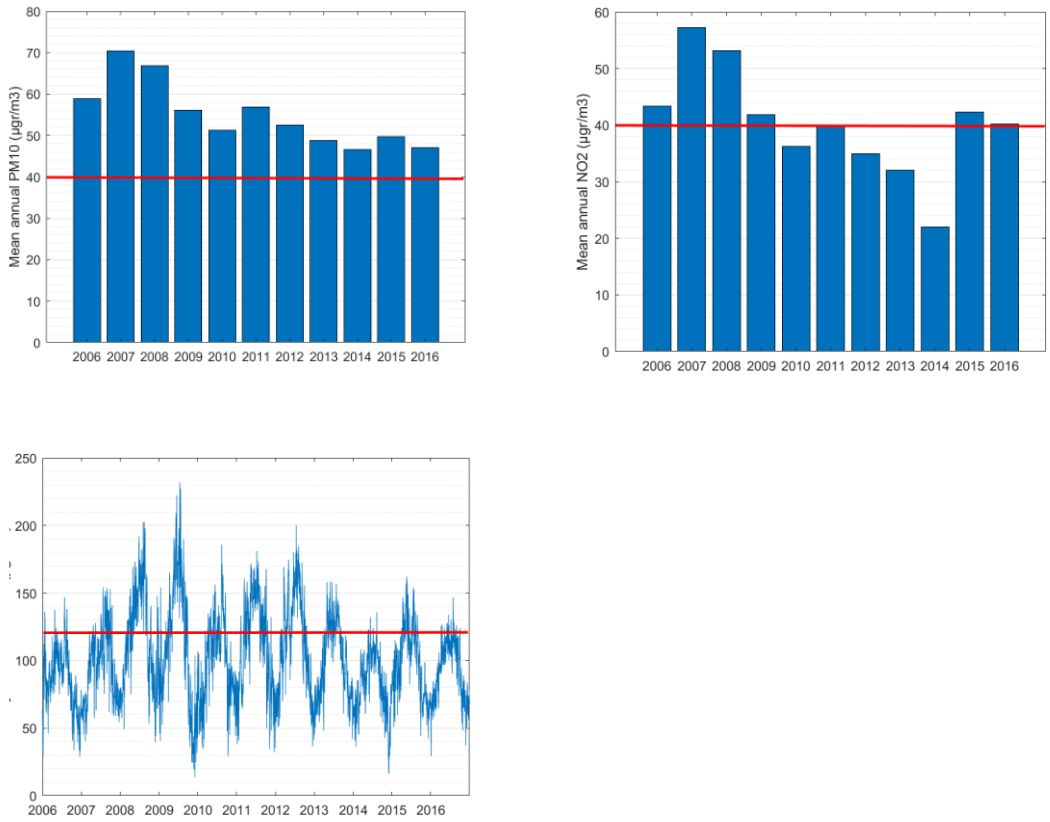


Figure S1. Exceedances of the EU thresholds denoted by red lines (PM_{10}, NO_2: annual mean 40 µgr/m^3) (O_3: maximum daily 8-hour mean 120 µgr/m^3) during study period.

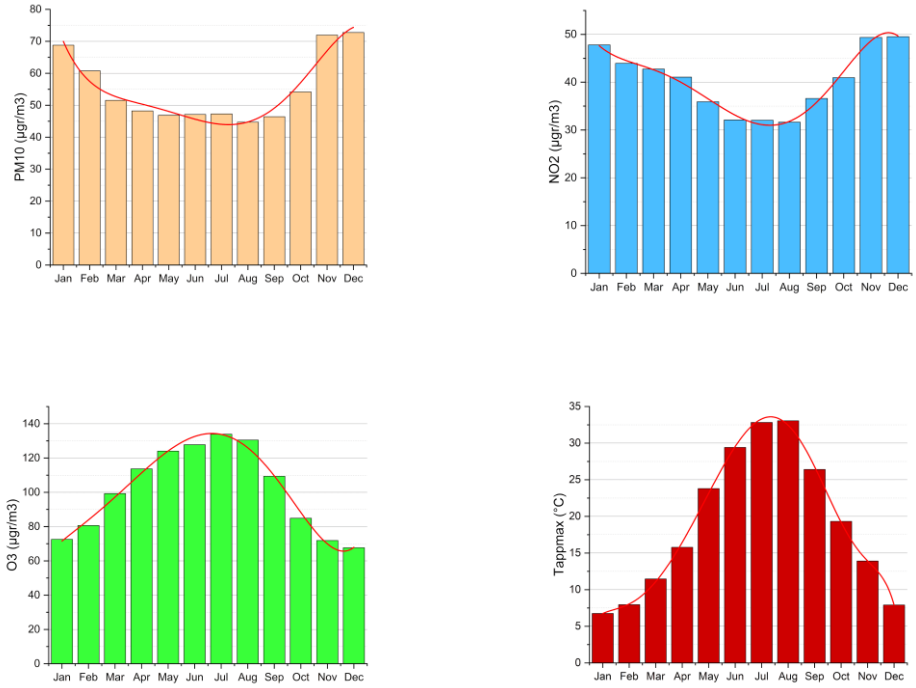


Figure S2. Seasonal distribution of PM_{10} (top left), NO_2 (top right), O_3 (bottom left) and $Tapp_{max}$ (bottom right).

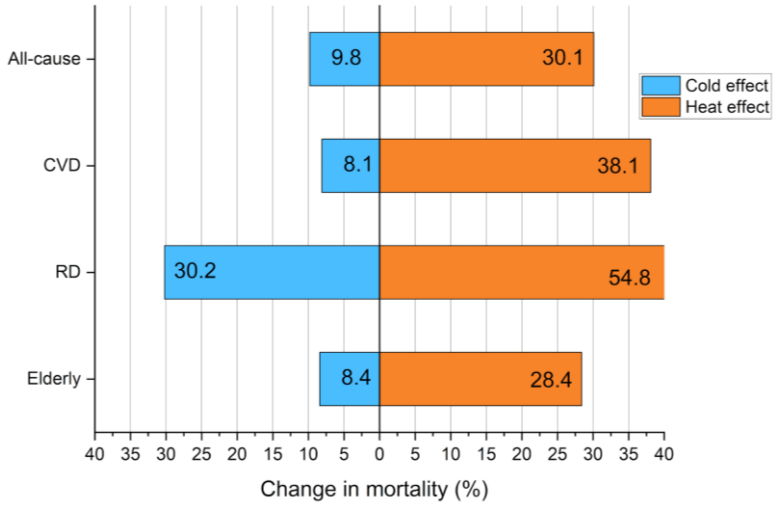


Figure S3. Estimates of heat and cold effects on cause-specific mortality and elderly mortality.

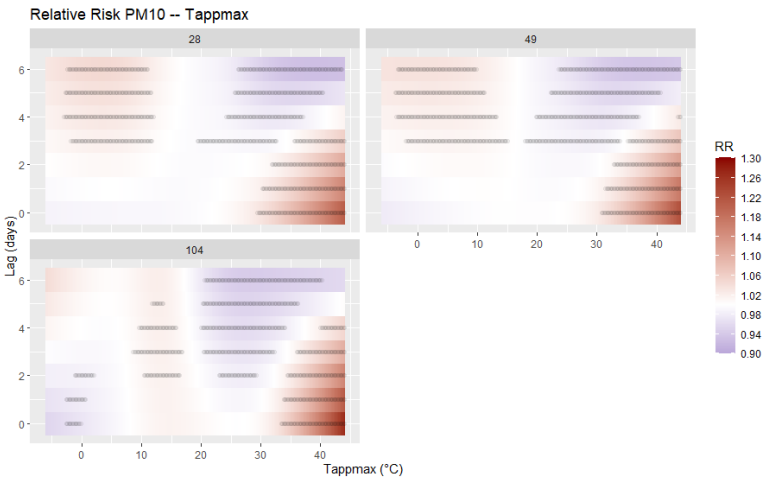


Figure S4. Contour plot of the joint association of PM_{10} and $Tapp_{max}$. Statistical significance (95% CI) is indicated by grey points.

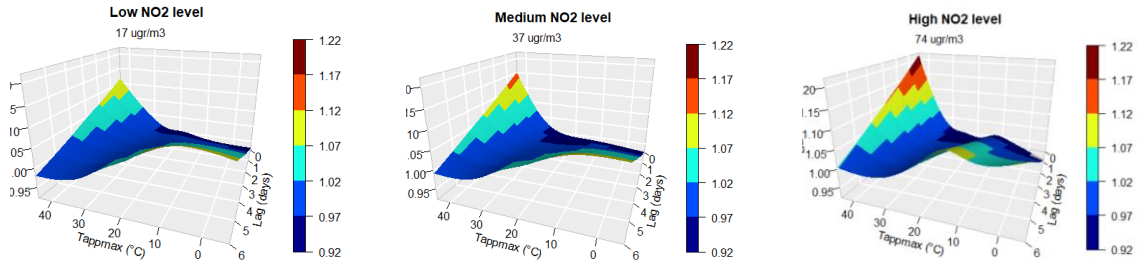


Figure S5. Combined effect of NO_2 and $Tapp_{max}$ on all-cause mortality stratified by levels of pollutant (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of NO_2 distribution).

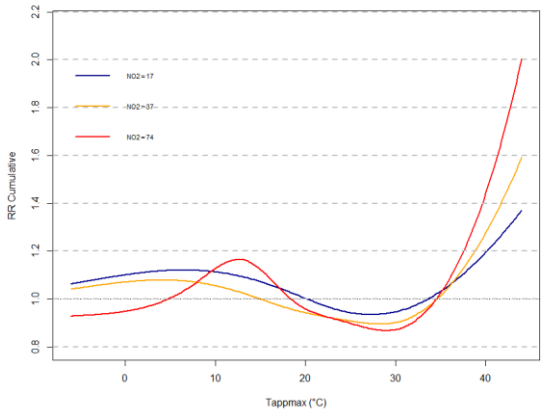


Figure S6. Cumulative exposure–response association across lags 0-6, the temperature range and different levels of NO_2 (blue denotes “low”, yellow denotes “medium”, and red denotes “high” levels).

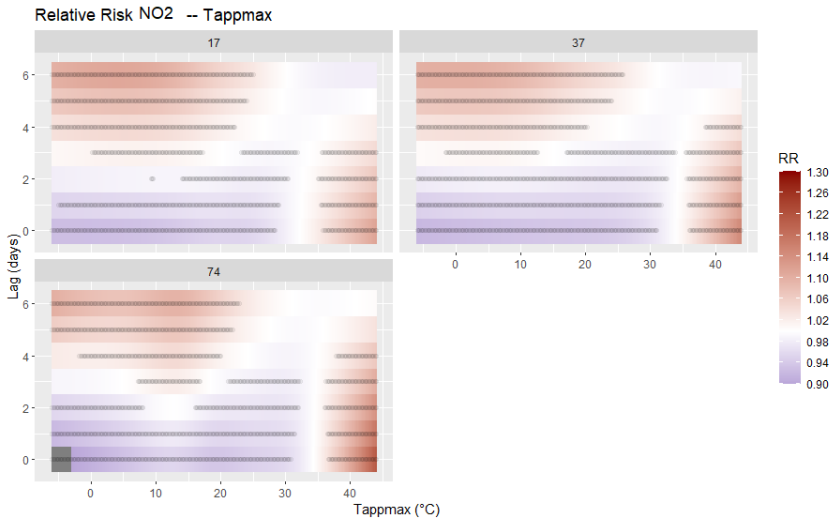


Figure S7. Contour plot of the joint association of NO_2 and $Tapp_{max}$. Statistical significance (95% CI) is indicated by grey points.

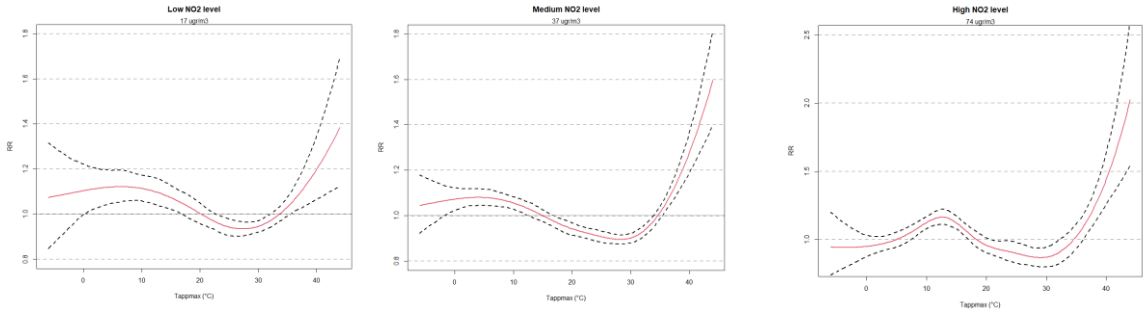


Figure S8. Cumulative exposure–response associations across lags 0-6 for Low, Medium and High NO_2 levels. Dashed lines represent 95% CI.

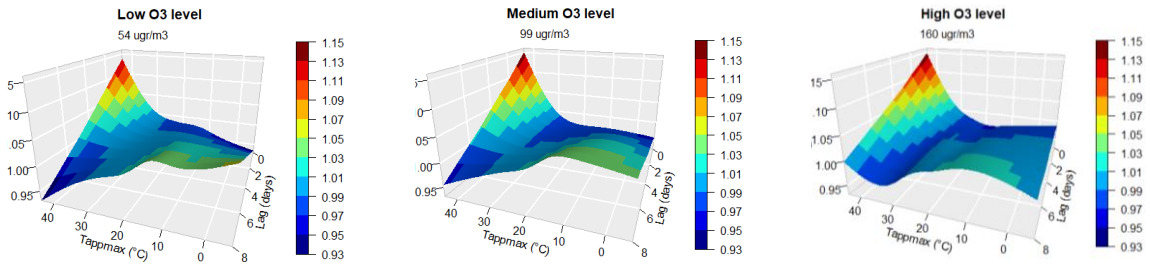


Figure S9. Combined effect of O_3 and $Tapp_{max}$ on all-cause mortality stratified by levels of pollutant (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of O_3 distribution).

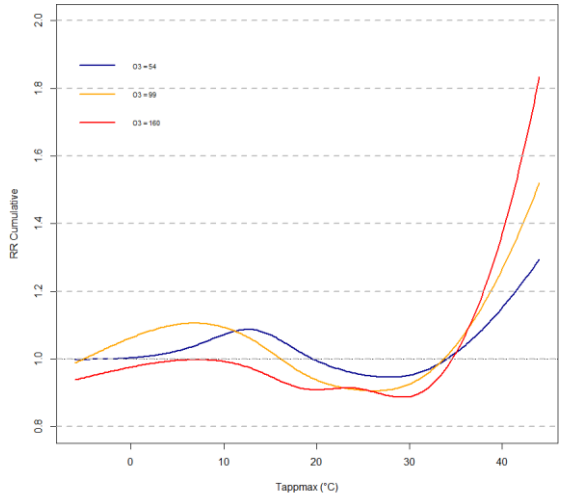


Figure S10. Cumulative exposure–response association across lags 0-8, the temperature range and different levels of O_3 (blue denotes “low”, yellow denotes “medium”, and red denotes “high” levels).

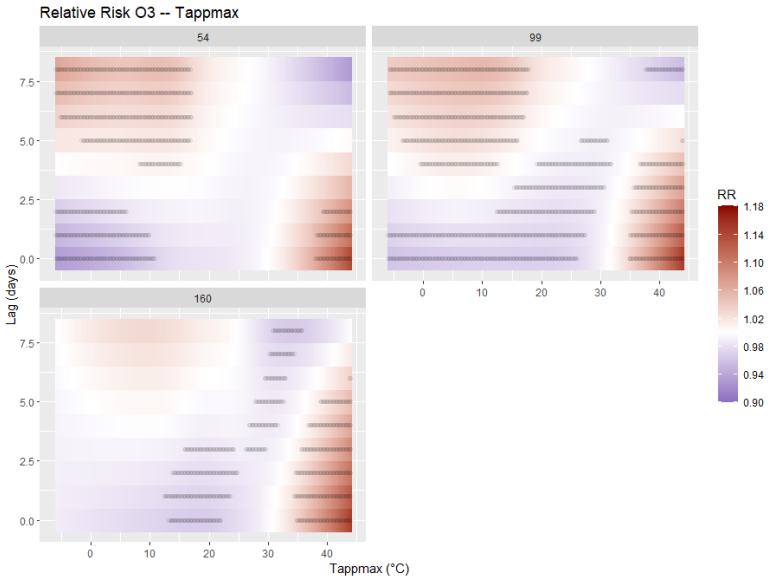


Figure S11. Contour plot of the joint association of O_3 and $Tapp_{max}$. Statistical significance (95% CI) is indicated by grey points.

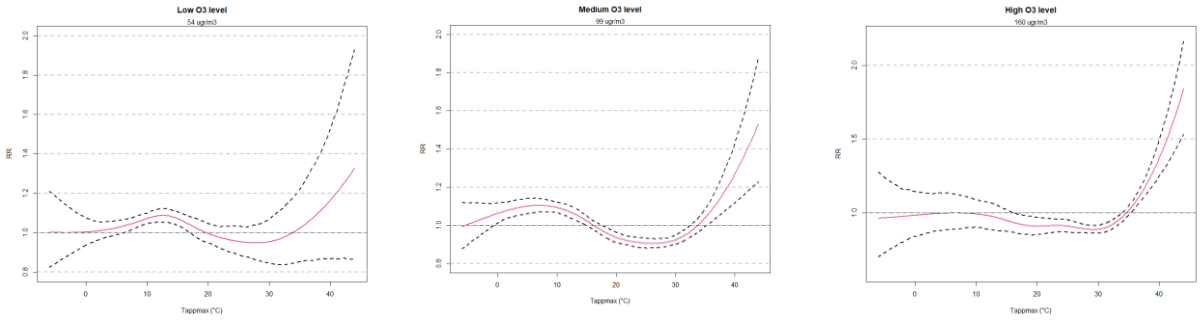


Figure S12. Cumulative exposure–response associations across lags 0-8 for Low, Medium and High O_3 levels. Dashed lines represent 95% CI.

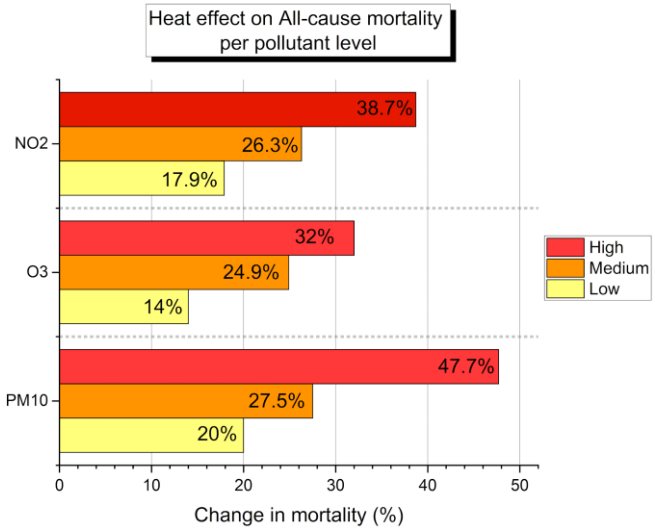


Figure S13. Estimates of heat effects as % change in all-cause mortality for $Tapp_{max}$ increases between the 75th and 99th percentile by levels of pollutants (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of pollutants distributions).

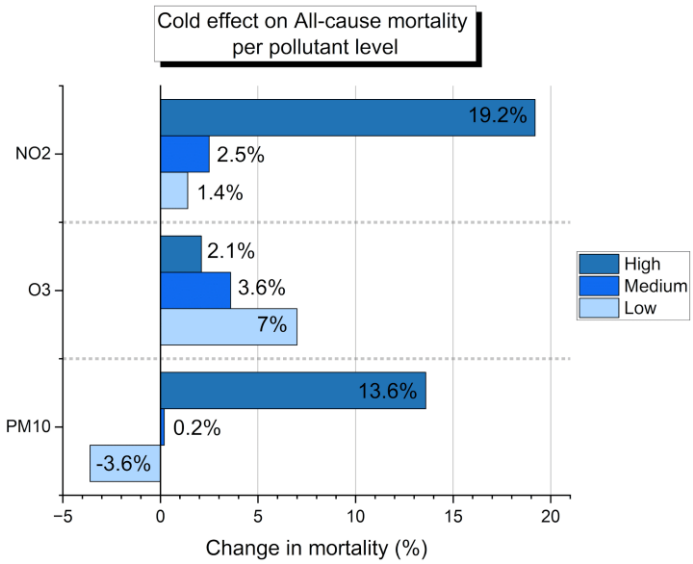


Figure S14. Estimates of cold effects as % change in all-cause mortality for $Tapp_{max}$ increases between the 1st and 25th percentile by levels of pollutants (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of pollutants distributions).

Chapter 8

Conclusions

Although the health effects of air pollution and heat stress pose a growing concern in today's world, there has been relatively limited investigation into the simultaneous interactive effects of temperature and air pollution as predictors of mortality. Thessaloniki, the second largest city in Greece, faces unfavorable air quality and meteorological conditions, exacerbating the relating health risks for the local citizens. The impact of climate change in the area is expected to further compound these challenges, increasing the frequency and intensity of heatwaves and pollution episodes. Unfortunately, the understanding of Thessaloniki's specific vulnerability to these issues remains understudied, hindering effective mitigation strategies. The current dissertation has introduced a Distributed Lag Non-linear Model using the framework of Generalized Additive Models to investigate the interactive effects between daily maximum Apparent Temperature and air pollution in cause-specific mortality from 2006 to 2016, in the urban area of Thessaloniki. This is the first application of the proposed GAM-based approach and the first analysis to explore this complex association for Thessaloniki, Greece.

The first study (Chapter 5) investigated the association between daily maximum Apparent Temperature and daily all-cause (natural, non-accidental), cardiovascular, cerebrovascular and respiratory mortality, by describing the exposure-lag-response association with the use of a DLNM. The effect of time lag and non-optimum temperatures, as well as specific analysis of the Elderly (+65 years), were also examined.

This study concluded that heat-attributable mortality in Thessaloniki was mainly associated with high temperatures. Significant implications that derived from this work include:

- ✓ Extreme high temperatures strongly influenced the risk in mortality with strong exponential rise over 35°C, with further and more prominent increase with Tappmax values over 40 °C.
- ✓ J-shaped relationships were found between temperature and cause-specific mortalities. Heat was short lived with an immediate effect, whereas cold was prolonged.
- ✓ The Elderly were more vulnerable to heat than general population.
- ✓ Deaths attributed to heat outnumbered deaths attributed to cold, with stronger impacts on respiratory mortality.

The second study (Chapter 6) investigated the associations between short-term exposure to PM10 and O_3 and daily all-cause (natural, non-accidental), cardiorespiratory, and cerebrovascular mortality on the general population and the Elderly. To assist air quality planning, the impact of the modification of PM10 levels on Thessaloniki's population mortality under two air pollution abatement scenarios was estimated: (1) full compliance to EU levels, thus eliminating the exceedances of PM10 daily values; and (2) a 20% horizontal reduction in the PM10 concentration.

The key conclusions of this study are summarized as follows:

- ✓ Local population was at risk from the current levels of PM10 and ozone. O_3 was found to have an even more severe impact than PM10, and the elderly were particularly vulnerable to poor air quality in the area.
- ✓ Mortality risk and mortality burden of O_3 were more acute for cardiorespiratory mortality than all-cause; the opposite result was evident concerning PM10.
- ✓ Neither of the two air pollutants was associated with cerebrovascular outcomes.
- ✓ If the two proposed mitigation measures were implemented, the attributed mortality fraction would decrease significantly in both cases.

The objective of the final study (Chapter 7) was to analyze the interactive effects between daily maximum Apparent Temperature and air pollution (NO_2, O_3, PM10) in cause-specific mortality (non-accidental, cardiovascular, respiratory), by developing a Distributed Lag Non-linear Model using the framework of Generalized Additive Models. Separate analysis was conducted for the Elderly citizens, as well as evaluation of the lag structure. The synergy was estimated by introducing a tensor product between Tappmax and either PM10 (lag 0–6), NO_2 (lag 0–6) or O_3 (lag 0–8). Temperature estimates were extrapolated at low, medium, and high levels of pollutants defined as the 5th, 50th, and 95th percentile of pollutant-specific distribution; heat and cold effects were estimated as the percentage change in mortality between the 75th and 99th, and the 25th and 1st percentiles of Tappmax, respectively. This study found that deteriorated air

quality rendered the local population more susceptible to the effects of temperature variability, and vice versa.

The following conclusions were drawn:

- ✓ Heat effect on mortality was more harmful than cold, in this study.
- ✓ Tappmax-mortality relationships, stratified by air pollution levels, demonstrated J-shaped curves with RR values increasing sharply over 33°C. Low temperatures were associated with increased mortality as well, but not to the same extent.
- ✓ High air pollution enhanced temperature effects on daily mortality, while associations between high temperatures and mortality were generally stronger at high pollution levels. Moreover, impacts of high temperatures were immediate, whereas the prevalence of cold effects became more pronounced as longer time lags were considered.
- ✓ Non-optimum Tappmax values (Extreme High Tappmax > 35 °C, in particular) had the greatest mortality burden on health when coupled with increased concentrations of pollutants.
- ✓ All-cause and respiratory mortalities were heavily affected by PM10 levels, whereas PM10, NO_2 and O_3 affected cardiovascular causes of death.
- ✓ Based on this analysis, the elderly citizens were particularly vulnerable to the adverse combination of thermal conditions and poor air quality.
- ✓ PM10 depicted immediate mortality risk increase, while NO_2 needed more days to exhibit the negative impact on human health. O_3 had prompt effect for large concentrations, and prolonged for decreased values.

To our knowledge, this study was the first application of the proposed GAM-based approach to assess the synergistic impact of thermal conditions and air quality for the urban area of Thessaloniki, by using an advanced statistical approach that captured the complex non-linear and lagged dependencies in both the exposure-response and lag-response associations, and flexible enough to be modified for other synergies. Given the vulnerability of the Southern European region, our work contributed significantly to various research fields such as atmospheric sciences, biometeorology and environmental epidemiology. 11 years of good quality data were available, resulting in satisfactory statistical significance of the produced results.

To sum up, the findings of this research made a substantial impact on the scientific efforts of better understanding the synergies with which environmental factors effect human health. They also concluded to a robust statistical technique that can be implemented to other epidemiological studies. Thus, the principal objective of this dissertation has been met with a great deal of success providing evidence of the combined impact of air quality and biometeorological factors on

human mortality. The present results carry important implications for the development of public health interventions aimed at controlling and preventing the health consequences of exposure to adverse thermal and air quality conditions.

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Appendix A: List of Figures

Figure 7.11 Fractions of cause-specific mortality attributable to levels of pollutants (defined as “low”, “medium”, and “high” based on 5th, 50th, and 95th percentiles of pollutants distributions). Page 87

Appendix B: List of Tables