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Understanding the role of urban green space impact on extreme temperatures and cardiopulmonary mortality in Oslo

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Master in Public Health Science

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Foreword

This master thesis is the end of two very instructive, and interesting years at the program of public health science, at the Norwegian University of Life Sciences (NMBU). I have enjoyed my time at NMBU very much, and I cannot believe it is already ending. From before I started my studies, I have been concerned on how climate change will affect the human health. It has been very satisfying to gain more knowledge on this field, and it has been inspirational meet other students and researchers sharing my interest and concern on how climate changes affect us both on an individual level and the public health in general. I have been very fortunate to join a team at the Norwegian Institute of Public Health when writing my master thesis, it has been very motivating and interesting.

I would like to thank my main supervisor Shilpa Rao-Skirbekk, senior researcher at NIPH for including me in this project and as a member in the team at NIPH. It has been very important and valuable for my work, and I have learned much of this experience. I have felt very inclusive during this period of time. Thank you for sharing your knowledge and giving me good and constructive feedback on my thesis. My supervisor at NMBU, Suleman Atique, thank you for your precise feedback on my text along the way. I also would like to thank Norun Hjertager Krog, senior researcher at NIPH, with great knowledge on greenspace and health, for very good discussions, contribution, and feedback on my thesis along the way. I am very thankful for that. With good help from Bente Margaret Oftedal, senior researcher at NIPH, the statistical method became clearer, thank you for all the guidance, and all encouraging words along the way. Terese Bekkevold, research coordinator at NIPH have been very helpful with all the practical details and challenges, thank you for your patience and help along the way. I would like to send a special thanks to Dr Siqi Zhang, in the EXHAUSTION project, who helped create a script in RStudio to be used in this study. Thanks to Alfonso Diz-Lois Palomares, researcher NIPH, for all the GIS effort, and answering questions along the way. Thank you Meizhu Chen and Christian Rikter-Ydse, also at EXHAUSTION project and NIPH, for help with interpreting and using the RScript and answering questions along the way. At NMBU, professor Geir Aamodt have been at great help understanding the method and results, thank you very much.

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I hope you will find this thesis interesting.

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Kicki Svensson

Abstract

Background: The climate change contributes to increasing temperature and causes severe heatwaves; at the same time, we see increased urbanization worldwide. Every year many people die from cardiovascular disease (CVD) and respiratory disease (RD), in some places there is increased mortality due to extreme temperatures. The cities must adapt to climate change and prevent the health issues following. In many places nature-based solutions are implemented as climate adaption strategy, where green vegetation contributes to lower temperatures. In Norway we can expect more extreme temperatures in the future.

Objective: The aim with this study is to investigate if people living near urban green areas are protected against premature cardiopulmonary mortality in Norway's capital and biggest city, Oslo.

Method: This study has used data from HUBRO cohort (Oslo Health survey), merged with temperature data and NDVI values at individual level. The study period is 1st January 2000 till 31st December 2018. Persons who died from all-cause mortality, ICD-10 code A00-R99 was extracted, it was created groups for CVD and RD mortality for the analysis. The method of case crossover using conditional logistic regression to estimate the effect of daily mean air temperature on cardiopulmonary mortality was used as statistical method. With use of lag days delayed outcome was captured. NDVI was used as an effect modifier, divided by the median, 0.43, in two categories. Both warm and cold effect was measured. Measures of association was produced in odds ratio (OR).

Main findings: The total number of participants was 3527 people from the HUBRO cohort who died in Oslo due to natural causes, 1070 people died due to CVD, and 302 due to RD. The analyze gave two statistically significant results: use of 3 lag days on warm effect the OR was 4.92 (95%CI: 1.48-16.4) for RD mortality, and in the interaction analysis CVD mortality had OR 4.82 (95%CI:1.6-14.43) on cold effect in areas with high NDVI. The other results in the interaction analysis indicate people living in areas with high NDVI have reduced risk of premature mortality due to CPD, none of those results showed statistical significance.

Conclusion: There was too few participants to get results with good precision. But the result indicates surrounding greenness have impact on CPD mortality in Oslo. There is need for further investigations on the health issues due to climate change in Oslo, and to investigate the use of nature-based solutions as climate adaption strategies to improve the public health in Oslo.

Sammendrag

Bakgrunn: Som følge av klimaendringene øker temperaturene og forårsaker alvorlige hetebølger, samtidig er det økt urbanisering globalt. Hvert år dør mange av kardiovaskulær sykdom (CVD) og respiratoriske sykdommer (RD), noen steder ser man økt dødelighet som følge av ekstreme temperaturer. Byene må tilpasse seg klimaendringene, og forebygge helseutfordringer som følge av klimaendringer. Mange plasser har iverksatt natur-baserte løsninger som klimatilpasningsstrategier, grønn vegetasjon bidrar til å senke omkringliggende temperaturer. I Norge kan vi forvente mer ekstreme temperaturer i fremtiden.

Formål: Målet med denne studien er undersøke om mennesker som bor nære grøntområder i byene er bedre beskyttet mot for tidlig død som følge av hjerte- og lungesykdommer.

Metode: I denne studien er det brukt data fra Osloundersøkelsen, HUBRO kohorten, det er slått sammen med temperatur data og NDVI verdier på individ nivå. Studieperioden er fra 1 januar 2000 til 31 desember 2018. Folk som døde av naturlige årsaker, ICD-10 koden A00-R99 ble trukket ut fra datasettet, det ble laget egne grupper med kardiovaskulær og respiratorisk mortalitet for å bli analysert. Den statistiske metoden som ble brukt var case crossover med betinget logistisk regresjon for å måle effekten av daglig gjennomsnittstemperatur på kardiovaskulær og respiratorisk mortalitet. Ved bruk av ulike lag dager kunne man fange opp forsinkede effekter av temperatur. NDVI ble brukt som effekt modifikator, den ble delt i 2 grupper ved bruk av medianen, 0.43. Både varme og kalde temperatureffekter ble målt. Effekten ble målt i odds ratio (OR).

Hovedfunn: Totalt antall deltakere var 3527 personer fra HUBRO kohorten som døde i Oslo av naturlige årsaker, 1070 døde av CVD og 302 av RD. Fra analysen var det 2 resultat som viste statistisk signifikans; ved bruk av 3 lag dager på varm effekt hadde RD mortalitet en OR på 4.92 (95%CI: 1.48-16.4), i interaksjonsanalysen hadde CVD mortalitet en OR på 4.82 (95%CI:1.6-14.43) på kald effekt i områder med høy NDVI. De andre resultatene i interaksjonsanalysene indikerer at det er mindre dødelighet som følge av hjerte- og lungesykdommer i områder med høy NDVI, ingen av de resultatene var statisk signifikante.

Konklusjon: Det var for få deltakere til å få resultater med god presisjon. Men resultatene indikerer at grøntområder i nærheten av bostedsadresse påvirker dødeligheten av hjerte- og lungesykdommer i Oslo. Det er behov for mer forskning på helseutfordringer i Oslo som følge av klimaendringene, og bruk av natur baserte løsninger som klimatilpasningsstrategi for å bedre folkehelsen i Oslo.

Abbreviations

ART	Attention Restoration Theory
CI	Confidence interval
CO_2	Carbon dioxide
CONOR	Cohort of Norway
COPD	Chronic Obstructive Pulmonary Disease
CPD	Cardiopulmonary Disease
CVD	Cardiovascular Disease
DLNM	Distributed Lag Non-linear Model
DÅR	Cause of Death Register, Dødsårsaksregisteret
GIS	Geographic Information System
HUBRO	Oslo health study, Helseundersøkelsen i Oslo
IPCC	Intergovernmental Panel on Climate Change
OR	Odds Ratio
$PM_{2.5}$	Fine particulate matter
PM_{10}	Particulate matter
MMT	Minimum Mortality Temperature
NCD	Non-communicable diseases
NDVI	Normalized Difference Vegetation Index
NIPH	Norwegian Institute of Public Health
NO_3	Nitrogen dioxide
RD	Respiratory Disease
REK	Regional ethical committee (regional etisk kommittè)
SRT	Stress Reduction Theory

TSD	Service for sensitive data (Tjenester for sensitive data)
UHI	Urban Heat Island
WHO	World health organization

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1 Introduction

Climate change is rapidly affecting the planet and its ecosystems. There are more extreme weather events such as heatwaves, flood, hurricanes, and drought where the exposure and intensity vary across residential locations. In some places this forces the population to adapt in a new way of living (Leichenko et al., 2019). The impact of extreme temperatures on health of the population is a topic of recent interest. Some populations are more vulnerable to rising temperatures and heatwaves in particular children, outdoor workers, elderly, and people with pre-existing medical conditions, for example cardiovascular and respiratory diseases (Cissè et al., 2022). Taking everything into account the most vulnerable region to heat exposure is Europe because of its ageing population, high urbanization, and high prevalence of diabetes, cardiovascular, and respiratory diseases (Watts et al., 2019). Drought, storm, and flood are extreme climate events that have caused most deaths through years. Lately there has been an increase in extreme temperature related deaths worldwide. Globally extreme temperature is contributing to many deaths yearly (World Meteorological Organization, 2021).

Urbanization has a large impact on the heat-related impacts of climate change (WHO, 2016). Numbers from 2015 show that 54% of the world's population live in urban areas. It is estimated that 66% of the world's population will be urbanized by 2050. In Europe 74% of the population already live in urban areas (Urbanet, 2022). The combination of climate change, urbanization, aging population, temperature rise, and air pollution present a threat to the public health of the urban residents. Temperature rise increases the risk of urban heat islands which again can lead to worsening of air pollution and that people risk exposure to high temperatures. In a global context, research show that exposure to high temperature increases the risk of illness, hospitalization, and mortality. In cities people are more vulnerable to mortality and morbidity because of the increased risk of urban heat islands (Heaviside et al., 2017). This makes investigating the issue of extreme temperatures on health in urban areas a topic of current interest concerning public at large.

Adaption to climate change is of particular interest. There are many aspects and ways to understand and work on adaption. Biagini et al. (2014) have categorized types of adaption activities, among common categories mentioned in literature are capacity building, management and planning, policy, behavior, and green infrastructure. Much of this is dependent on the quality and location of physical infrastructure. IPCC have several definitions on adaption, one of them is about adaption capacity, defined as "*The ability of systems, institutions,*

humans, and other organisms to adjust to potential damage, to take advantage of opportunities, or to respond to consequences." (IPCC, 2018, p. 542). Within urban planning for climate adaption there is increased interest and use of nature-based solutions. There are several approaches within nature-based solutions like green infrastructure planning, ecosystem services, and water sensitive planning, being of current interest for urban environments as climate adaption planning (Cilliers et al., 2022). Especially during warm temperatures in cities, vegetation provide shade, and reduce temperature through evaporation from soil (Son et al., 2016). When using nature-based solutions like green roofs and walls it gives a cooling effect on buildings. Urban green space is beneficial for health as it increases participation in physical and social activity, reduces stress and improve well-being (Demuzere et al., 2014). Based on this, research stakeholders are responsible to implement climate adaption strategies that protect the population from health risks caused by increased temperatures in the future (Cissè et al., 2022).

In this thesis, I explore the role of green areas as an adaptive measure in the association of temperature exposure and mortality in Oslo. I will focus on short-term temperature exposure and mortality due to cardiovascular and respiratory diseases.

This master thesis is written as monography divided into 7 chapters. In chapter 2, updated information, guidelines, and prevalence of disease on the theme will be introduced. In chapter 3 the research question is presented. Chapter 4 explain the sample, study design, methods, and statistical analysis. In chapter 5 the results of the analysis are presented. In chapter 6 I discuss the results of the analyses in light of the background and looking at other studies with similar research questions. In the last chapter, 7 I will conclude the analysis, results, and implications for further research.

2 Background

In this chapter, necessary background will be presented and explained to get a better understanding of the research questions. First health is defined, then cardiopulmonary diseases will be presented. Temperature which is the exposure is explained, the focus is extreme high and low temperature that are affecting the health most. The availability of urban green areas is an effect modifier in this study relevant background information and research will be presented. Since this concern Oslo, relevant plans and strategies are presented last in the chapter.

2.1 Defining health

There are several definitions of health, the World Health Organization (WHO) have a definition on health from their foundation often mentioned in public health literature (Naidoo & Wills, 2016). In 1946 WHO defined health as "a state of complete physical, mental, and social well-being, not merely the absence of disease or infirmity" (WHO, 1946). They expanded it in 1986, to emphasize the meaning of what individuals and groups have of resources to cope everyday life (Salazar et al., 2019). Peter Hjort were one of several who were critical to the definition of WHO, he defined health in 1982 to have energy to tackle everyday life (Fugelli & Ingstad, 2001). With this definition of health, it is up to oneself to decide what is health for oneself. When it comes to health definitions within the biomedical domain, Boorse (1977, p. 555) defines it as "Health in a member of the reference class is normal, functional, ability; The readiness of each internal part to perform all its normal functions on typical occasions with at least typical efficiency". This definition is presented since this thesis will concern mortality and, in some way, also morbidity, therefore it is of interest how biomedicals define health. It is written more than 45 years ago but is still relevant when measuring health in health services where it is often measured with grades of disease or being healthy, having no diseases (Fugelli & Ingstad, 2001).

Measuring health as the aspect of having no disease in the population is often done by using epidemiological methods measuring the prevalence of certain diseases, and observing the development of it, e.g. adverse measure of health (Naidoo & Wills, 2016). Another way of measuring health in the population is to calculate the average life expectancy. This is an indicator on how good living conditions people have, it is also a good way to observe the development over a certain period of time (Salazar et al., 2019).

In the study to Fugelli and Ingstad (2001) health was understood mainly as something positive. Health defined by Hjort is probably a definition well adapted to Norwegian society and how people in general perceive the concept of health. Nature was also an important part of the

definition, many said they longed for being in nature when they were sick, it helped them feel better, and they experience better health. Adaption to disease was also something mentioned by many as a way of improving their health (Fugelli & Ingstad, 2001). In this thesis, where the outcome is mortality, it is natural to use an epidemiological approach to health. Though many of the participants might have experienced improved health and benefitted from being in nature while alive. The aim is adaption to climate change reducing extreme temperature related mortality, the aspects of nature will be explained and discussed to some extent in this thesis.

2.2 Urbanization and health

There is an increase in the number of people living in cities worldwide and it is estimated to continue, in Europe the majority of the population lives in cities (Urbanet, 2022). Places where people live crowded have through history been linked with increased risk of disease. John Snow was an important person for epidemiology and urban planning when he in 1854 in London investigated and found out what caused the repeating outbreaks of cholera (Webb et al., 2020). Nowadays the non-communicable diseases (NCD) are more common than infectious disease, but we should be aware how the urban environment can lead to increase in infections like COVID-19 and tuberculosis. Urbanization is an important health issue in the 21th century, while it is related to several things causing obesity, stress, and mental ill health (WHO, 2021b). The number of NCD is increasing, mainly because of wrong diet, inactivity, smoking, and alcohol (O'Flaherty et al., 2013). Contact with nature show decline in all-cause and CVD mortality, stress reduction, reduction of RD and better mental health. Less contact with nature when living in a city can contribute to increase of these outcomes (Cox et al., 2018). In many cities and small villages in Scandinavia there is an agreement on protecting area outside the city for food production and conserving nature, it is preferable to build new houses within the city (Nordh & Olafsson, 2021). With more dense cities studies show that it invites to more active transportation, and there is less stressful commuting (Stefansdottir et al., 2019; Stevenson et al., 2016). But with more dense cities there are increasing health issues in areas densely populated, more stress, and air and noise pollution can contribute to more morbidity (Beenackers et al., 2018). When it is built more dense the risk of losing urban green areas increase, which is important to reduce stress, contribute to more physical activity, and is an important place for recreation and restore new energy (see figure 1) (Markevych et al., 2017).

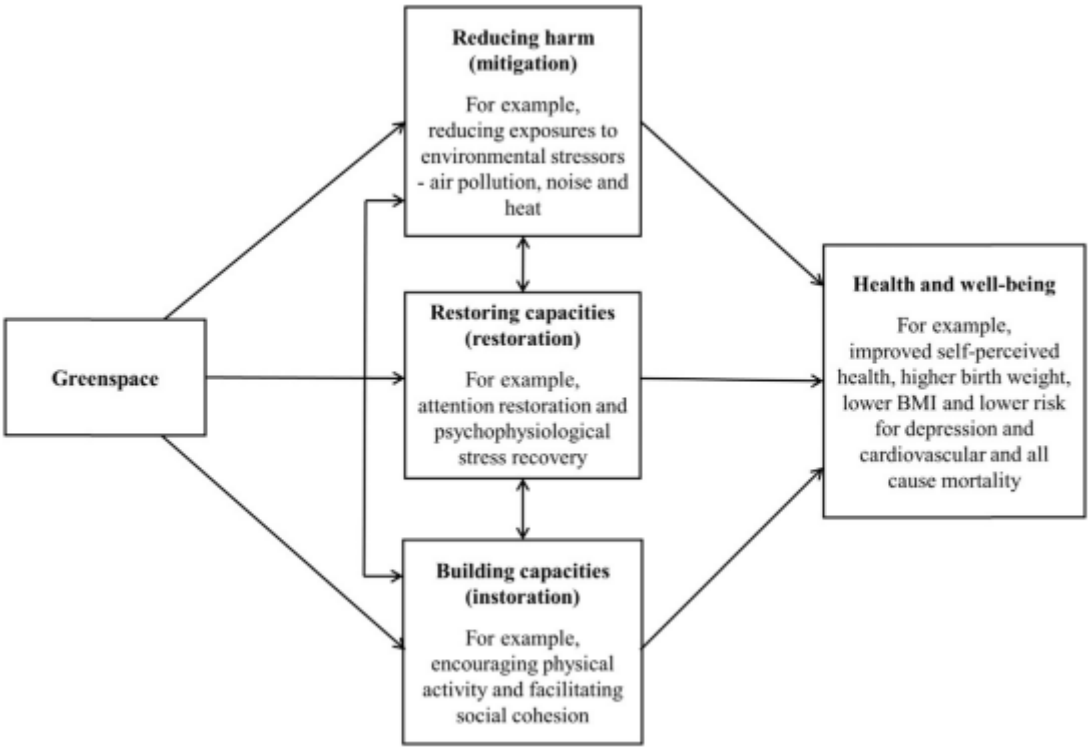

Figure 1 Three domains of pathways linking greenspace to positive health outcomes.

The arrows represent hypothetical patterns of influence, with specific pathways in each domain potentially influencing one or more specific pathways in the other domains.(Markevych et al., 2017, p. 302).

2.3 Cardiopulmonary diseases

The effects of temperature will be investigated on heart and lung diseases separately, but they are mentioned together as CPD in the text where it is natural. Therefore, the term cardiopulmonary disease (CPD) is used in the paper when referring to both heart and lung diseases. CVD will be used for cardiovascular diseases and RD is the abbreviation of respiratory diseases.

2.3.1 Cardiovascular disease

One of the leading cause of deaths in the world is cardiovascular diseases (CVD), and the death toll is increasing. Obesity, high blood pressure and diabetes are well known risk factors (WHO, 2021a). In Europe there is an increase of cardiovascular diseases, while the mortality due to CVD is decreasing, this can be explained by better preventive measures and treatment. Looking into the occurrence there is a difference between high-income countries and middle-income countries. In the high-income countries there is a decrease in CVD mortality and morbidity, while in middle-income countries there is an increase (Timmis et al., 2018). Diet, smoking,

alcohol, and inactivity are important risk factors for developing CVD. Mortality rates of CVD can change rapidly and unexpected, but it does not mean the decrease is set to continue. Changes in lifestyle and environment can affect the incidence of CVD. Therefore it is important to pay attention to trends in CVD mortality (O'Flaherty et al., 2013). According to the Intergovernmental panel on Climate Change (IPCC), heatwaves and extreme changes in temperature increase the risk of worsening the health for elderly and people with chronic diseases. Heatwaves, wildfires, and air pollution are factors contributing to increased cardiovascular and pulmonary distress (Pörtner et al., 2022). Several studies show an increased risk of cardiovascular mortality due to heat exposure and heatwaves (Masselot et al., 2023). For respiratory diseases there is also increased mortality, as for respiratory morbidity there is need to further research to see if there is any association between extreme temperatures and respiratory morbidity (Song et al., 2017). When there is a heatwave and at the same time high air pollution there is higher mortality and hospital admissions increase due to cardiovascular and pulmonary disease (Exhaustion, 2020).

The numbers on CVD in Norway have decreased in recent years due to better treatment, less people smoke and a reduction in blood pressure and cholesterol in the population. However, there is still one-fifth of the population suffer from a CVD or take preventive medicine. Increase in the population and the proportion of elder people and better survival rate after CVD are reasons for the increased use of medicines (Holtermann Ariansen, 2021).

2.3.2 Respiratory diseases

Chronic diseases in the lower respiratory tract were the third leading cause of death in Norway after CVD and cancer in 2016. Emphysema, asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD) are diseases that affect the lower respiratory tract. Smoking is a common cause for COPD, but people working in structural engineering who are exposed to silica dust or people working in tunnels and mines also have a higher risk of developing lung diseases (Folkhelseinstittutet, 2018). Asthma is a lung disease among adults occurring when being exposed for pollutants in working environments, e.g. gases, dust, or particles. This can contribute to worsen asthma or develop asthma among people who did not have it before. Air pollution and physical activity can also trigger asthma. It is a chronical inflammation in the airways giving symptoms like intense cough, shortness of breath, and thickness in the chest. Normally asthma is not fatal, but it can be worse of other infections, air pollution, cold temperatures, and weather changes. Among adults the symptoms can be like those with COPD.

Asthma is caused by both genetic and environmental factors, in Norway asthma is equally common in the cities as in rural areas (Amdal et al., 2020).

2.4 Temperature changes in urban areas

In this thesis, temperature is understood as ambient temperature. Heat waves will be mentioned since it is much literature on the subject and it is a consequence of climate changes, but the study focus is mainly on extreme temperatures, both warm and cold effects are measured. The analysis and results will focus on the warm and cold effects of temperature.

The average temperature has increased by 1ºC in the world. Areas close to the polar regions have experienced higher increase due to the melting ice and warmer sea. For example, northwestern Canada have experienced on average 3ºC warming (Watts et al., 2019). With the limitation of 1.5 degrees warming that have been agreed upon it is expected to be even warmer at other places. In Norway there has been 1ºC increase since 1900, but for the last 15 years there has been 0.5ºC warmer. If the greenhouse gas emissions continue as now there will be 4.5ºC warmer in year 2100 (The Norwegian Meteorological Institute, 2017). In Oslo it is estimated the average temperature will rise 3-6ºC if the emissions continue to rise. The precipitation is estimated to increase with 5-30% towards 2100. Episodes with extreme precipitation will occur more often, especially during winter (Oslo Kommune, 2020a).

There are different definitions of heatwaves in different countries, in Norway the meteorological institute is trying a new definition of heatwaves from 2022. A heatwave is when it is at least 5 days continuous with average maximum temperature of 28ºC or higher during daytime and minimum 16ºC during nighttime. At the 5th day with these temperatures, it is registered as a heatwaves event. If it lasts for more than 5 days a new heatwave will be registered. During the warm summer of 2018, 19 heatwave events were registered in total with this definition in Norway (Tajet et al., 2022). Oslo is the part of Norway which is experiencing most heatwaves. In the last 30 years the number of heatwaves has increased by four time in Oslo. In the period 1961-1990 Oslo had average 0.5 heatwaves a year, in the years 1990-2020 the average of heatwaves was 2.2 events per year in Oslo (The Norwegian Meteorological Institute, 2022).

In the cities, it gets warmer than rural areas where there are less buildings, especially during the summer. The heat in cities is absorbed in unshaded roads and buildings which then re-emit the solar heat in the air leading to rise in the urban temperature. In dense city areas where there is little or no vegetation the temperature gradient can get much higher than in the areas with

vegetation, creating *urban heat islands*. National Integrated Heat Health Information System (NIHHIS) shows that the temperature between a road in direct sunlight without any shadow during the day and grass in the shadow can differ up to 24^{o} C (NIHHIS, no year). Except the high temperatures in urban heat islands (UHI), it can affect rainfall patterns, increase air pollution, and affect water quality which are also determinants affecting the health of the population (Heaviside et al., 2017).

There is more heat effect among people in urban areas than rural areas. It might be because the urban heat islands contribute to temperature increase, during the night there is no time for temperature decrease cooling down surrounding environment. This contributes to increase the night temperatures (Kovats & Hajat, 2008; Macintyre et al., 2018). During heatwaves there is increased risk of adverse health effects, and severity depend on the prior health condition. Heat stroke is rarely the main cause of death but might contribute to worsen already existing disease such as CVD or RD. During urban heatwaves there is an increased risk of hospitalization and death in UK (Heaviside et al., 2017). IPCC predicts increased morbidity and mortality in the future due to increasing temperatures globally. Older people and people with preexisting health conditions are more vulnerable to getting ill due to high ambient temperatures (Cissè et al., 2022). A study from Sweden, which is comparable to Norwegian climate and society conditions, showed increases in all-cause and CVD mortality during heatwaves. Sweden is a wide country with difference in average temperature in north and south. These results are not interpreted to be valid in the whole country, but is statistically significant in Stockholm the largest, and Malmö the 3rd largest cities in Sweden (Astrom et al., 2020). In Finland, there is also conducted a study on mortality during heatwaves, showing increased mortality in urban areas compared to rural surroundings. They discuss if UHI might be a contributing factor to more heat related mortality in Helsinki than in the other study area (Ruuhela et al., 2021). When it comes to cold effects, there is no difference in urban and rural areas (Macintyre et al., 2018).

The winters in Norway are getting shorter. Both in Tromsø and Oslo the winter is 22 days shorter than it was in the period 1961-1990. The winters in Norway are expected to be both warmer and precipitation will come as rain rather than snow. There are still periods with very low temperatures during the winter, but they are expected to be more rare in the future (Berger, 2021). In Norway there is no official definition on cold wave (Pedersen, 2013). In USA cold wave is defined as when the temperature has a rapid decrease within 24 hours followed by a long-lasting period of extreme low temperature. At which temperature the cold wave is valid is for the local National Weather Service (NWS) to decide (FEMA National Risk Index, N/A).

Cold wave is reported in World Meteorological Atlas of Mortality as a hazard causing disaster. Hazard is defined by them as "A process, phenomenon or human activity that may cause loss of life, injury or other health impacts, property damage, social and economic disruption or environmental degradation" (World Meteorological Organization, 2021, p. 12). They define disaster as a hazardous event causing serious disturbance in community or society at any scale. There is no clear definition on cold wave. They report the occurrence of cold wave in different pie charts from all parts of the world. In Europe cold wave is causing 9% of all disasters related to extreme weather events, in Asia it is 2% and in Africa it is 1%. In North America, Central America, and the Caribbean it is measured together and also the cold wave caused 1% of disasters due to extreme weather events. A definition of cold wave has not been mentioned (World Meteorological Organization, 2021).

Cold temperatures as well as warm temperatures, pose a risk of increased mortality in the population. In Northern Europe there are more people dying due to cold temperatures than warm temperatures (Masselot et al., 2023). In Norway there is 12% higher mortality during winter, there is a significant increase of mortality related to CVD and RD during winter, and the trend is obvious in ascending age. Cancer mortality did not have the same significant increase of mortality during winter (Brenn & Ytterstad, 2003).

IPCC (2022) predicts there will be minimal to moderate decrease in cold-related mortality in the Global North, while the Global South will experience increase in heat-related mortality by the end of the century. How winter UHI affect cold-related mortality is not much investigated (Cissè et al., 2022). A study from UK investigated cold-related mortality suggest UHI has a protective factor. But compared to the deaths of summer UHI there are not many cold-related deaths avoided with UHI (Macintyre et al., 2021).

2.5 Theories of nature and health

In all times we have been living in and with nature, as the urbanization extended it seriously changed how we live and distance ourselves from nature to a certain extend. Nature can be understood as an environment where humans have not interfered, a place with natural impressions from life of fauna and flowers, water, wind, and weather (Hartig et al., 2014). In research it is often not possible to exclude natural environments that have been influenced by humans. In urban areas parks that are regulated and maintained are defined as nature as in these areas you can find flower, fauna, and water (Hartig et al., 2014). Nature has gotten more attention and the importance of nature for the health has been continuously of current interest

among researchers. There are multiple theories on how nature affect us and why it is important for the human health. Stress Reduction Theory (SRT) and Attention Restoration Theory (ART) are the theories that are most used among researchers investigating environments for restorative purposes (van den Berg & Staats, 2018). According to the SRT being in nature reduces stress, almost immediately within minutes, depending on how much stress a person experience. When looking at natural environments acute stress can be reduced much more than looking at built environments. The reduction in stress can be beneficial to health with decreased heartrate, blood pressure, and muscle tension among several self-reported outcomes (Ulrich et al., 1991). Ulrich et al. (1991) emphasize the importance of natural environments instead of built nature like environments. Kaplan and Kaplan developed the ART during the 1980s, and they were particularly interested in how people used their cognitive senses in meeting with nature. They focused on four characteristics of environmental experience that will help persons refresh and reduce mental exhaustion (Kaplan & Kaplan, 1989 cited in van den Berg & Staats, 2018). It is *fascination* for the environment that will draw one 's attention towards the fascination of nature, *being away* - to have the moment where you could escape other things that might bother you or steal energy. They also illuminate *compatibility* as something that connect the person with the nature, that make the person feel like they are a part of nature. Last quality is sense of *extent* where the person sees the content of being in nature and how extended the connection is (Kaplan & Kaplan, 1989 cited in van den Berg & Staats, 2018).

In this thesis both theories have some importance and connection to the subject. Hartig et al, 1991 cited in van den Berg and Staats (2018) have argued that they in a sense fulfill each other rather than contradict one another. It depends on what your motivation and health struggle is to search nature as place for recovery. Stress is an important contributor to many diseases and also cardiovascular diseases (WHO, 2016) which have been investigated in this thesis.

Markevych et al. (2017) suggest in figure 1 how greenspace contribute to positive health outcomes. The three perspectives presented in the middle of the figure are widely used and known within the research and discussion on nature and health. The perspectives have originated from different theory grounding and can be seen separately, but also integrated. They suggest it can work as a plan for future work between disciplines. The perspectives build on pathways that are often mentioned in research studying the connection between greenspace and health (Markevych et al., 2017). These pathways are air quality, physical activity, social contacts, and stress, they are pathways among those most often mentioned when finding interrelationship between greenspace and health. They focus on different aspects of the

connection with nature, such as experience, physical environment, and as a setting for individual and social behavior where interaction with neighbors is straighten, and a sense of being part of the community is strengthened. These aspects are involved when connecting with nature and also how one can see the connection between greenspace and health and well-being (Hartig et al., 2014). Another mechanism that might influence the health of urban citizens is the reduced exposure of environmental microbiome. There are differences in exposure to microbiome depending on where you live, people living in rural environment tend to have higher gut microbiome diversity than people living in cities (Gilbert et al., 2018). This diversity of microbiome can be an explanation to geographical differential incidence of diseases like inflammatory bowel disease (Gilbert et al., 2018). Urban green space can contribute to more diversity in exposure to human microbiome and therefore strengthen the immune system (Pearson et al., 2020). The hypothesis is that being in contact with the surrounding environment affects our microbiomes (Mills et al., 2020).

If people have easy access to green areas, recreational areas, and live close to meeting places like school and shop they tend to be more active. Living close to green areas affect the health in a positive way with reduced stress, better mental health, and increased life expectancy across all social differences (Helsedirektoratet, 2021).

2.5.1 Defining greenspace

There is no universally accepted definition of urban green spaces in the connection with health and well-being. In many research studies urban green areas includes public parks, and gardens, sometimes also street trees, sport pitches, private, and semi-private gardens, roof gardens, and any places there is vegetation (WHO, 2016).

Taylor and Hochuli (2017) reviewed 125 journal articles to get a better understanding and overview of greenspace definitions. They found that many researchers fail to give a proper definition and that definitions provided are often quite different. Their opinion is that a definition should be both quantified and qualified to show how they understand and define greenspace. Pickard et al. (2015) defines urban green areas as areas covered with vegetation, such as trees, bushes, and grass. In the study to Venter et al. (2020), they use satellite data and NDVI measures to estimate how green the defined area is, using the technology to define surrounding greenness. Cox et al. (2018) made a survey asking the respondents how often, much, and long they were in contact with nature, giving them example of nature like private or public garden, playgrounds, parks, golf courses etc. Leaving it in a way to the participants to define what nature are for them. Many of the articles concerning greenspace and health read for

this thesis do not have a clear definition on greenspace. That is in coherence of what Taylor and Hochuli (2017) found in their review.

The fact that more people live in cities makes more distance for people and the nature, which reduces peoples contact with green environments (Markevych et al., 2017).

When planning for urban green spaces there are many considerations to take. It is possible that it is implemented with good intentions but may lead to opposite effects. A new park may increase the prices of surrounding residences which can lead to displacement of those who cannot afford living there anymore (Markevych et al., 2017), not using the right type of vegetation can worsen or cause allergy, excluding some people from using those facilities (Carinanos et al., 2019). . In this thesis NDVI is used to measure the amount of greenness, see section 2.6. Greenspace, greenness, and urban green area are the expressions used and it will mean the same thing; green vegetation in the cities measured by the NDVI. The recommendations on greenspace close to residents presented by WHO will be used in addition and discussed as Oslo municipality also use the same measurements of access to greenspace of at least 5000m^2 within 300 meters from home address (Oslo Kommune, 2020b; WHO, 2016).

The main focus in this thesis is that urban green spaces reduce temperature and can prevent urban heat islands. The vegetation of trees and bushes contribute to temperature decrease as they provide shadow (WHO, 2016). It also contributes to reducing air pollution buy storing CO_2, this is not the topic if the thesis, but the exposure of air pollution is investigated by the researchers in EXHAUSTION and part of their concern for CPD health (Exhaustion, 2020).

2.5.2 Urban green areas and temperature related health effects

Green areas, green buildings and roof in cities can provide local cooling, mostly because of evapotranspiration and shading (NIHHIS). Green roof also improve regulation of temperature in buildings, reduce CO_2 emissions and noise pollution, and improve storm water management (Venter et al., 2021). Vegetation contributes to differences in temperature in areas with or without trees in order to regulate temperature (Venter et al., 2020).

As many epidemiological studies show urban green space have several positive health effects like improved wellbeing and mental health, and reduction in cardiovascular disease (Markevych et al., 2017). An expert group at the World Health Organization (WHO) recommends that people living in cities should have access to green spaces of at least 5000 m^2 within 300 meters from their residential location (Barboza et al., 2021).

One of the important adaption strategies to combat the harmful effect of temperatures on cardiopulmonary diseases in cities is the concept of increasing green areas. Several studies show the importance of green areas for the health and health behavior. Urban green areas contribute to more physical activity as well as mitigate heat and air pollution (Plans et al., 2019). People living near urban green areas tend to have less cardio-vascular disease than those with little greenness in their neighborhood (Bereziartua et al., 2022). A study from Republic of Korea present similar results, that living near green areas in cities prevents cardiovascular disease, which is one of few broad studies in Asia on this theme (Seo et al., 2019). Trees and green vegetation in cities reduce temperature and capture CO_2 and is therefore an important contributor to mitigate urban heat islands (Chaston et al., 2022).

Depending on the size and amount of the trees and soil cover there are different degrees of cooling (Zardo et al., 2017). The increase of greenhouse gases has led to a dangerous increase especially of carbon dioxide (CO_2). As part of the photosynthesis the vegetation takes up carbon which again lower CO_2 in the atmosphere. During the spring and summer when there are green leaves on the trees there is less CO_2 in the atmosphere in the Northern Hemisphere, while during the cold season when there is less green vegetation, and more CO_2 is emitted in the atmosphere (Leichenko et al., 2019).

Intra city-planning of nature-based solutions has got more attention as ways to restore eco-systems and mitigate climate change. Nature-based solutions have different ways of working with nature to improve and restore the cities. It may involve to create green urban commons, green roofs as well as engage the citizens to take part in planting trees and other co-creation activities which gives a sense of place and belonging (Frantzeskaki, 2019). Green roofs and living walls in cities contribute to better air quality, and reduction in heat and noise. Several studies show that a reduction in heat also contributes to reduction in all-cause mortality, including CVD mortality and mental disorders (Sang et al., 2022).

A study on mortality of heatwaves and vegetation in Sydney estimated 117.3 (95% CI: 37.2-189.8) deaths per year in Sydney due to heat. The same study showed that areas with trees reduced the urban heat islands effect with 50%. With continuing temperature rise the number of UHI is estimated to increase. If one manages to reduce the urban heat islands there will be less people having their health affected. More trees and green vegetation is one way of reducing urban heat islands together with other measures to mitigate urban heat islands (Chaston et al., 2022).

There are also certain risks with nature-based solutions, particularly the risk of uneven access to urban green areas for the people with lower income cannot afford to live where the cities have invested in urban green areas. This is a global problem; low-income neighborhoods tend to have more public health issues and less green areas. Urban greening in some areas risk to make some parts of the city more heterogeneous and increase the property prices (Wolch et al., 2014).

The research on greenspace and health is not equally common in the world, there is not much research done in Africa, Asia, South America, and in poorer European countries. The climate, culture, and vegetation is different around the globe, one cannot assume greenspace is given better health everywhere (Markevych et al., 2017). When discussion climate adaption approaches Leichenko et al. (2019) emphasize the importance of locally adjusted measures. What seems to be best solution one place is not necessarily contributing to good climate adaption another place, leading to maladaptation. One example is use of air conditioning as a climate adaption strategy to heat exposure, but air conditioning is often using energy from fossil fuels and are thereby contributing to increase emissions of greenhouse gases (International Energy Agency, 2018).

2.5.3 NDVI as a measure of green areas

A well-used and acknowledged measure of greenness is NDVI i.e., Normalized Difference Vegetation Index. It is measured from satellites with infrared and near infrared, and ranges from -1 to +1. Green vegetation can only be on the plus side, the higher number the more chlorophyll there is in targeted vegetation. With NDVI one can measure increase and decrease of photosynthesis (Yengoh et al., 2015). A simple way to separate and understand the numbers is that 0 and below is often water, around zero represent bare soil and above zero is vegetation. The method has been used previously in several epidemiological studies to mark the greenness in the city-area of interest (Crouse et al., 2019). Measuring NDVI has its limitations, for example it does not give a vertical dimension of the green area, and the quality of the green areas cannot be measured by NDVI. There are several other measurements of urban green areas such as Urban Neighborhood Green Index Map which include the built environment in another way and it also measure the quality and quantity of the green areas (Gupta et al., 2012). The percentage of green areas (%GA) measures the green areas in places accessible to the public as parks, squares, and community gardens (Barboza et al., 2021). In the study to Iungman et al. (2023) they measured tree cover using data from Copernicus to estimate % tree coverage in area of interest. WHO (2016) argues that the use of NDVI as a measure of surrounding

greenness is beneficial since it is satellite data that is often updated. In this master thesis NDVI is used for measuring urban green areas.

2.6 Oslo; health, temperature, and mortality

Oslo municipality have ambitious goals on reducing greenhouse gas emissions up to 95% within 2030, with 2009 as a reference year. They are dependent on several factors, but a decisive initiative is to start carbon capture and storage at the waste disposal plant at Klemetsrud, Oslo. With a reduction in greenhouse gases, the air quality will be better and people suffering from air pollution are expected to have an improved health with less nuisance (Oslo Kommune, 2020a). In the strategy for public health, Oslo municipality emphasizes the importance of good climate adaptation for the health of the public. They emphasize the importance of involving vulnerable groups in the planning of urban development and climate adaption. When it comes to urban green spaces and public spaces, their strategy is to develop the existing network of green areas, avoid reduction of green spaces, and maintain and further expand the stand of city trees (Oslo Kommune, 2022). Around the city of Oslo, but still inside the border of Oslo municipality there are a wide area of forests, called Marka. For Oslo this is an advantage as this area will help to adjust temperature locally and protect against flood and erosion which are two events predicted to be an increasing problem for Oslo with the temperature rise (Oslo Kommune, 2020a).

In a health report from the municipality of Oslo there have been an increase in access to green areas as recommended, the latest numbers available from 2016 show that 95% of population in Oslo have access to at least 5000 m^2 within 300 meters from their residence. 98% of the population have access to green areas of at least 1000 m^2 within 300 meters (Oslo Kommune, 2020b).

The public health law in Norway emphasizes the importance of protecting the population to potential environmental threats. There are different jurisdictions between municipality, county and governmental (Folkehelseloven, 2012). Oslo is both a municipality and county, having their assignments performed a bit different than other Norwegian municipalities (Thorsnes, 2023). Both the county and municipality shall have an overview of the state of health and what influence the health in the county and municipality. It is both the negative and positive factors that affect the health of population that should be documented in the written overview (Folkehelseloven, 2012). A positive environmental factor is urban greenspace having several positive health outcomes (WHO, 2016). In Oslo there is good knowledge about the impact

greenspace have to the health and climate adaption. Due to increased temperature in the future, it is expected that Oslo will experience more drought, precipitation, and heat. Challenging environmental factors in Oslo due to climate change are temperature, air pollution, and water quality among several factors (Oslo Kommune, 2022). These are emphasized to be factors that could have health related consequences for the population in the future. Consequences is expected to affect those with low socioeconomic status, preexisting disease, and the elderly more. This is concern regarding public health for the population in Oslo now and in the future (Oslo Kommune, 2022).

As far as me and my supervisors and other researchers at NIPH in the section of Climate and Health are aware of, a quantitative analysis investigating exposure of temperature and mortality using surrounding greenness as an effect modifier have not been accomplished using Oslo data before. There are other studies that have used greenspace as exposure to measure prevalence of different health conditions and diseases in Oslo (Ihlebaek et al., 2018; Venter et al., 2020). It is important in Oslo to further investigate the impact of green areas on the temperature and mortality response. This has not been done until now and understanding these impacts could be very useful for future adaptation strategies.

In the next chapter, I describe the aims and research questions for this dissertation.

3 Aims and research questions.

The aim with the thesis is to highlight the understanding of the role of urban green areas and their impact on cardiovascular and pulmonary health in Oslo. Since there are many people suffering from cardiopulmonary diseases in Norway, it is of current interest to explore the significance of urban green areas as an adaptive measure in cities in the exposure of extreme temperatures. The hypothesis is living close to greenspace affect the all-cause mortality differently during high and cold temperatures in Oslo, the exposure of surrounding greenness will modify the thermal environments and give less exposure of extreme temperatures. I first have to find if there is increased mortality in Oslo during periods of extreme temperature. There is dearth of research investigating only Norwegian cities, and there is no priorly known quantitative research on Oslo. The target group in this investigation are adults residing in Oslo.

To get a better understanding, I have constructed my research questions in two parts, the first is more general question on CPD mortality due to temperature, the second is to the main focus, to find out if greenness have an impact on cardiovascular and respiratory mortality:

My main focus is to find out if surrounding greenness as an effect modifier for the exposure of temperature influence CPD mortality in Oslo. To get a better understanding I first have to investigate:

1. What impact do extreme temperatures in Oslo have on cardiovascular and respiratory mortality?

In the second part I have my main questions:

1. Do green spaces in Oslo have an impact on the association of temperature related cardiovascular and respiratory mortality?
2. What conclusions can we draw from the results for the development of green areas in Oslo?

4 Data and Methods

The thesis research is conducted at the Norwegian Institute of Public Health (NIPH) which is a key partner in the EXHAUSTION project. The EXHAUSTION project is a research collaboration in Europe aimed to investigate how climate change, air pollution, and temperature affect the cardiopulmonary health. With this research they wish to obtain knowledge on how we should adapt in the future and make Europe more resilient (Exhaustion, 2020). The project is funded by the European Union research and innovation program, Horizon, 2020. The main aim in the project is to identify adaption strategies that can help prevent and moderate cardiovascular and pulmonary diseases and premature death in vulnerable groups due to heatwaves and other extreme events. They have conducted research on city level, small-area, and individual cohort level, and in this thesis cohort data will be used. The cohort data used in EXHAUSTION is from total of five established cohort around Europe. With this data they wish to analyze vulnerable factors affecting individuals and sub-groups finding adaption measures to reduce the risk of disease and premature death among the general population and certain vulnerable sub-groups (Zhang et al., 2020). In this thesis people dying from CPD is the vulnerable sub-group.

4.1 Contribution to the thesis

Researchers at NIPH, had from another study merged epidemiological data from the participants in CONOR cohort with meteorological data, and cause of death register. The dataset with HUBRO participants, to be used in this analysis was extracted from the CONOR dataset and prepared by researchers at NIPH in EXHAUSTION. The R-scripts to be used, were also extracted from the scripts used for the CONOR cohort in EXHAUSTION and prepared for this analysis. I used RStudio to run the scripts, get figures and results for the tables (appendix 2-4). The statistical method used in this thesis was similar to other analysis performed in the EXHAUSTION project. The script used in RStudio was produced for the purpose of measuring temperature exposure and mortality. This method contained many steps I did not know from before and found complicated to grasp. Together with my supervisors we agreed on focus on some parts go get a better understanding in its entirety.

4.2 Data sources

In this section there is a presentation of the data sources used in this analysis. The flowchart (figure 2) shows an overview of the connection between the data sources.

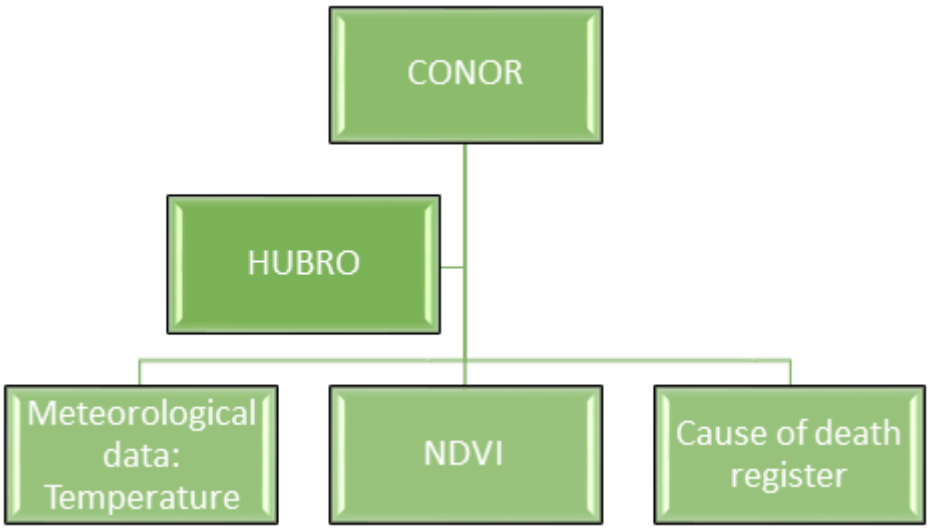

Figure 2 Flow chart to illustrate the connection between health registers and exposure data.

4.2.1 Cohort data

The data analyzed in this thesis has been collected from Cohort of Norway (CONOR) which consists of data from several Norwegian health surveys conducted from 1994 till 2003 (Folkehelseinstituttet, 2016). Data from the Oslo Health Study (HUBRO) is used to investigate the outcome in this thesis. It consists of health data from inhabitants from Oslo born in the years 1924, 1925, 1940, 1941, 1954, 1955, 1969, and 1970 (NIPH, 2019). Young people were also invited to the health survey starting in year 2000. Among the adults there were 46% of the invited who participated, in total 18 770 participants' (NIPH, 2019), only the data on adults is analyzed. Data from CONOR have already been linked in the EXHAUSTION project to the cause of death registry of Norway. The data between the cohort and the cause of death registry is merged using the national ID number. With use of Geographic Information System (GIS), the CONOR participants have been linked to historical residential addresses with exposure variables of interest for this thesis: temperature and NDVI, also mentioned as surrounding greenness.

4.2.2 Meteorological data and NDVI

The meteorological dataset available for this thesis is daily air temperature at a 1 km grid from whole Norway from the years 1995 to 2018. It provides mean, minimum, and maximum temperatures. In the analysis daily mean air temperature is used as done in the other European cities participating in EXHAUSTION. Other meteorological exposures as daily min/max air temperature, relative humidity, and wind were not equally available from all cohorts participating in EXHAUSTION.

The NDVI data used in this thesis is an average of 300- and 1000-meter radius from the participants residence, with data from different layers: the years 1995-1997 and 2008-2010. The layer with 1995-1997 was used to assign the exposure to 1994-2005 addresses, the layer 2008-2010 was used for 2006-2018 addresses. The mean NDVI index produced for June and July giving the average NDVI to work with. Image from the satellite Landsat 5 has been used to compile this data. To simplify the NDVI will be mentioned as 300 meters from residence.

4.2.3 Cause of death register data

Data from the cause of death register used here, contain information on the ICD code as the main cause of death. Every death in Norway is registered in the cause of death register (DÅR) with main cause of death, and if there were possible diagnosis happened close to death that might have been a contributing cause of the outcome (NIPH, 2020). The participants are only people from the HUBRO cohort who died from natural causes of death, meaning some kind of disease. People who died from accidents, intoxications, injuries, or other circumstances not caused by disease are not included. Every case has an ICD-10 code registered as cause of death. ICD is an International Classification of Diseases developed and controlled by the World Health Organization (WHO, 2022).

I divided the participants into different groups depending on cause of death from the ICD-10 code. The groups are all-cause mortality, cardiovascular disease (CVD) and respiratory disease (RD). All-cause mortality contains ICD-10 code A00-R99, from this CVD containing ICD-10 codes I00-I99, and respiratory diseases with ICD-10 codes J00-J99 were extracted. In the descriptive analysis, (table 2) there are an overview on how many participants there are in each group.

The research questions are answered using epidemiological data, both individual cohort-based data and registry data from the Norwegian Cause of Death register, have been used for previous research with CONOR data to link temperature and NDVI with the address to the participants. This applies also for the data from Oslo in HUBRO cohort used in this analysis. The merged

data contained of all participants from the HUBRO cohort who died from all-cause mortality in the years 2000-2018 together with data on temperature and NDVI for these years.

4.3 Study design

The period of study is from 1st January 2000 till 31st December 2018.

Surveys using cohort methodology usually focus on a specific topic of interest and follow the participants over time to see if and how they develop disease. Data is provided from health examination, biological indicators, lifestyle information including income, education, exercise, diet, smoking, and other qualitative data from questionnaires or interviews.

This is a case-crossover study, it examines short term exposure of environmental risk factors, the cases are their own controls. It is suitable especially when the exposure is momentary (Webb et al., 2020), as temperature is in this study. Each event (case) has been controlled for temperature by the same day of week within the same month. It is stratified by time, every case has 3 or 4 control days depending on which day they died, each day have their own temperatures. It is also controlled for seasonality, and day of week. Potential confounders from participants characteristics as age, sex, and health statues are controlled for when using within-participant comparison. Using control days before and after the event will eliminate for potential confounding of long-term trend analysis. Regarding temperature, humidity and wind can also play a role on how one is affected by ambient temperature (Tajet et al., 2022), which was not available in the dataset. Other meteorological data available was air pollution; NO_3, $PM_{2.5}$, PM_{10}, and ozone.

4.3.1 Effect modification using NDVI.

In the analysis I want to investigate whether greenness modify the effect between temperature and cardiopulmonary mortality. To understand the impact of NDVI on the exposure of temperature and CPD-related mortality I used the concept of effect modification, also called interaction. I used a conditional regression analysis with R script to understand the exposure of temperature on the outcome of interest, mortality. The same type of analysis was run for the effect modification to see if surrounding greenness affect the relationship between the temperature exposure and all-cause, CVD, and RD mortality. When analyzing the results, it is relevant to analyze cardiovascular diseases and pulmonary diseases separately to exposure of temperature. The lungs and heart are different organs and are affected different to extreme temperatures.

4.4 Statistical analyses

The analysis is performed in RStudio version 4.1.2 working in TSD, a security service used by researchers working with sensitive data, provided by the University of Oslo. The scripts to be analyzed consisted of several variables like date of death, cause of death registered with an ICD-10 code, age, ambient temperature for the day of death and up to 21 lag days with temperature. These scripts were made by and send to me from a researcher in epidemiologic in the EXHAUSTION project who have done this analysis from before on CONOR data. The results are presented in odds ratio (OR) as measure of association with 95% confidence intervals (CI). Odds ratio at 1 meaning there is no difference in outcome due to the exposure. An odds ratio at 1.4 mean there is 1.4 times increased risk of mortality due to exposure of warm or cold air temperatures (Webb et al., 2020).

4.4.1 Exposure assessment

In epidemiological studies investigating temperature affecting mortality is generally non-linear relationship, rather a U or J shaped curve. It is an increased risk of mortality related to temperature above or below the point where the red line touches the X axis (Zhang et al., 2020). That point is where odds ratio is 1, this is where the minimum mortality temperature occurs (MMT). Meaning the daily mean temperature where the mortality in a region or country is at a minimum (Folkerts et al., 2020). The MMT vary in different parts of the world depending on their climate. In Scandinavian countries the mean MMT is usually around 10-12ºC.

The purpose of lag days is to show how the exposure, in this case temperature, was before the event, death. The effect of exposure to temperature can have delayed outcome, therefore it is of interest to use lag days in the analysis. There were different amounts of lag days in different analysis. Cold effects were estimated by 21 lag days of temperature. For short term analysis, here the main analysis, the EXHAUSTION project has set limit to 10 lag days to look at both warm and cold effects of cardiopulmonary mortality. This is how the temperatures are 10 days prior to death. When using lag days, the temperatures are calculated in a complex way to get the effect to measure the outcome. If it is 10 lag days it starts measuring temperature at the 10^{th} day prior to the event, this temperature affects the 9^{th} day and so on until day zero, the day of death. I also used additional analysis with 0-3 lag days. Other studies measuring temperature and mortality, has shown that for measures of warm temperature it is more correct to use 0-3 lag days, while for cold temperatures it is necessary to have more lag days, preferably 0-21 (Gasparrini et al., 2015). In the additional analysis it is tested for seasonality, to see if there is any difference in the association due to seasonality, then it is used 0-3 lag days on warm season

and 0-21 lag days in cold season. In the main analysis for this study temperature with 10 lag days has been used, prior the event: death due to CPD. In the additional analysis 21 lag days have been used mainly to see at the cold effect, for warm effects 3 lag days have been used. For cold effect there is usually longer lag to measure effect off temperature, while for warm effect there is usually best to use 3 lag days.

4.4.2 Distributed Lag Non-linear Model

For the statistical analysis a modelling framework called Distributed Lag Non-Linear model (DLNM) was used in R. This is developed quite recently and is useful when investigating conditions that are non-linear and estimate effects that are potentially delayed after the specific exposure. For exposures like extreme temperature or air pollution the effect can occur a time after the exposure. If there is a non-linear exposure-response the DLNM can at the same time represent non-linear exposure-response and delayed effects (Gasparrini et al., 2017).

4.4.3 Conditional logistic regression

To estimate the effect of daily mean air temperature on cardiopulmonary mortality, conditional logistic regression was performed. When there is individually matched case-control data the conditional logistic regression is a suitable statistical model as it also controls for confounders (Webb et al., 2020). In linear regression the independent variable is continuous, while in logistic regression it is categorical variable that can only have 2 values, true or false, married or not married, dead or alive. The result of the logistic regression is measured as odds ratio (Ringdal, 2018).

Different functions in RStudio were set up through the script for the different analysis. For the effect estimation of temperature and mortality, a case crossover analysis was done where the distribution of temperature was calculated and a list with mean temperature was created. The values for temperature were showed in 25^{th} and 75^{th} centering. In the list it contained percentiles of temperature distributions for effect estimates compared to centering temperature. The percentiles were marked at 1, 2.5, 5, 10, 90, 95, 97.5, 99. When reading the tables with estimates in the results it shows odds ratio (OR) with 95% confidence intervals of mortality for cold or warm effects. Cold effects are presented by decrease from 25^{th} centering to 1^{st} percentile of temperature distribution. Warm effects are estimated for an increase in daily mean air temperatures from the 75^{th} centering to the 99^{th} percentile of temperature distribution. See table 2 and 3 in chapter 5 for results on warm and cold effects.

4.4.4 Interaction analysis

For the effect modifier each participant had a variable showing NDVI values within 300 meters from their residence. For the interaction analysis, the median for NDVI, 0.43 created two categories: category 1; NDVI lower than the median, category 2; the NDVI median and above. This division was determined in the script. It is done in the same way as the main analysis, with 10 lag days of temperature, participants with N/A in NDVI were excluded from the dataset in advance.

In interaction analysis it is necessary with a p-value, to see if there is a true difference in the exposure of surrounding greenness, measured in low and high NDVI. To get a p-value from the interaction analysis in RStudio a function Wald was performed.

4.4.5 Clarification on use of certain statistical terms

The main focus is to investigate if living close to urban green spaces is preventing premature cardiopulmonary death due to extreme temperature in Oslo. To get a better understanding, I first have to find out the relationship between temperature and mortality in Oslo. This have been investigated in other cohort participating in EXHAUSTION. There are prepared scripts for this kind of analysis which have been used here. These scripts are based on complex statistical methods. To understand the connection between temperature exposure and mortality there are terms which is important to understand the main objective and connection of the exposure and outcome. For example, lag days is part of the results in the analysis, also minimum mortality temperature (MMT) is part of some results. Therefore, these terms will be explained to a certain level. It appears challenging to do this analysis without including the meaning of rather complex statistical terms.

4.5 Research ethics

When doing medical research on humans it is essential to have an understanding on what the Helsinki declaration means. It was approved in 1964 by World Medical Association and have regularly gone through revisions. The declaration emphasizes the importance of informed consent from the participants in medical research. In medical research the researchers have a special responsibility for the participants, so they don't experience any unnecessary risks. They also have a certain responsibility for the research not being unethical. From the declaration come the idea of committees regulating and controlling researchers following implemented (Førde, 2014).

NIPH have already applied and got the approval at the regional ethics committee known as REK for the whole project researchers working on, and for my participation to access data in the project. This thesis is included in that approval (appendix 1).

All the data material and analysis were stored in Services for sensitive data (TSD). They satisfy the requirement for managing personal and sensitive data. I did the analysis in RStudio in the TSD-server (University of Oslo, 2017). Each participant had a unique serial number from the cohort, it was not traceable or possible to identify the person.

The responsibility on the data processing were validated through a contract between me as a student, NIPH, and NMBU.

5 Results

The results are presented in different sections. First is the descriptive statistics of the population, table 1. Then the results from the exposure response curves are presented in histogram showing MMT. The results from main and additional analysis from the conditional logistic regression investigating temperature and CPD mortality are presented in the 3rd section. At last, there is the results of the analysis of interaction with NDVI.

5.1 Descriptive statistics

These results are from the HUBRO cohort investigating a small sample of residence of Oslo. The study time is 2000-2018. The population in Oslo by the end of 2018 was 673 469 inhabitants (Statistics Norway, 2023). In total there were 15 590 observations in the HUBRO datasets, of these 3527 were real cases, the rest, 12 063 were within participation controls. Meaning it was 3527 cases in the group all-cause mortality, 1778 women and 1749 men. In the CVD group there were 1070 cases, 537 female and 533 males. Cases who died from RD were 302 in total, 158 females and 144 males, see table 1.

The mean age of death among the group of all-cause mortality was 79.8, in the CVD-group it was 81.7 and among those who died from respiratory disease it was 82.6. In the dataset minimum age of death in all-cause mortality was 32.3 years, in CVD it was 33.7 years, in RD 40.1 years but 1st quartile in all-cause was 74.9 years and in CVD it was 78 years. The mean 3rd quartile in all 3 groups were above 88 years, also maximum age of death was equal, above 94 years in all 3 groups.

In table 1 there are more people in the group with high NDVI close to their residence. The groups are divided by the median NDVI, 0.43. The mean NDVI is 0.417, the max is 0.7 and minimum is 0.03. There are more people who have high NDVI in their neighborhood than people having low NDVI within 300 meters from their residence. Between the groups of mortality cause the distribution of NDVI is very equal. Among those who have high NDVI around their residence there are 1.1% more people in all-cause mortality than CVD. In the category of low NDVI it is the other way around with 1.8% more people in CVD than all-cause mortality who have low NDVI around their residence (see table 1). As for those living close to greenspace in Oslo table 1 show there are around 55% of the participants in all-cause, CVD, and RD mortality that lived in areas with high NDVI. The percentage distribution between the groups within the category low and high NDVI were very equal. When it comes to the distribution of mortality cause and sex it is almost equally even for all-cause mortality and CVD. In RD there are more women who died from respiratory diseases than men.

Table 1 Descriptive statistic of participants.

Stratified by mortality cause. Age shows standard deviation in the brackets, for the other variables percentage is in the parenthesis.

	Mortality cause HUBRO cohort		
	All-cause	**CVD**	**Respiratory**
	N=3527	n=1070	n=302
Age at death			
Mean (SD)	79.8 (11.4)	81.7 (9.9)	82.6 (8.9)
Sex			
Female	1778 (50.4)	533 (49.8)	158 (52.3)
Male	1749 (49.6)	537 (50.2)	144 (47.7)
NDVI 300 meters			
Low NDVI <0.43	1554 (44)	479 (44.8)	134 (44.4)
High NDVI ≥0.43	1950 (55.3)	585 (54.7)	165 (54.7)
Missing	23 (0.7)	6 (0.5)	3 (0.9)

5.2 Exposure response curves

Figure 3-5 show the exposure response curves show the temperature distribution of mortality for the all-cause mortality, CVD, RD mortality. The X axis shows temperature, and the red line is odds ratio for mortality during different temperatures, the light grey shadow behind shows the confidence intervals. The point where the red line strikes the line of OR 1 is the MMT. The dashed black lines show the cut off for 2.5th percentile at the lowest temperatures and 97.5th percentile at the highest temperatures. Figure 3 shows the exposure response curve for natural mortality, at the coldest temperatures the OR is between 3 and 4, decreasing the warmer it gets, the OR stay just above 1 after the MMT. The MMT temperature is around 18-20ºC for all-cause mortality. For CVD mortality figure 4 shows OR start between 4 and 5 at the coldest temperature, the MMT is around 16ºC. After the MMT there is an increase of OR in warm temperatures. In figure 5 RD mortality exposure response curve is shown. The OR start at close to 5 at the coldest temperatures, the MMT is at 15ºC. The OR then increase to 6 at the warmest temperatures.

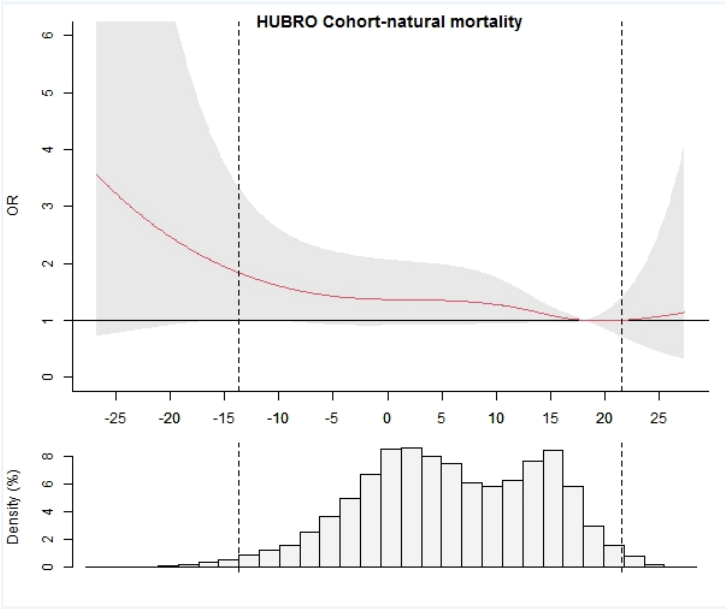

Figure 3 Exposure response curve all-cause mortality.

Relationship between daily mean air temperature and all-cause mortality in HUBRO cohort. The histogram shows the air temperature distribution in year 2000 to 2018. The red line represents OR values, the grey shadow is the confidence interval.

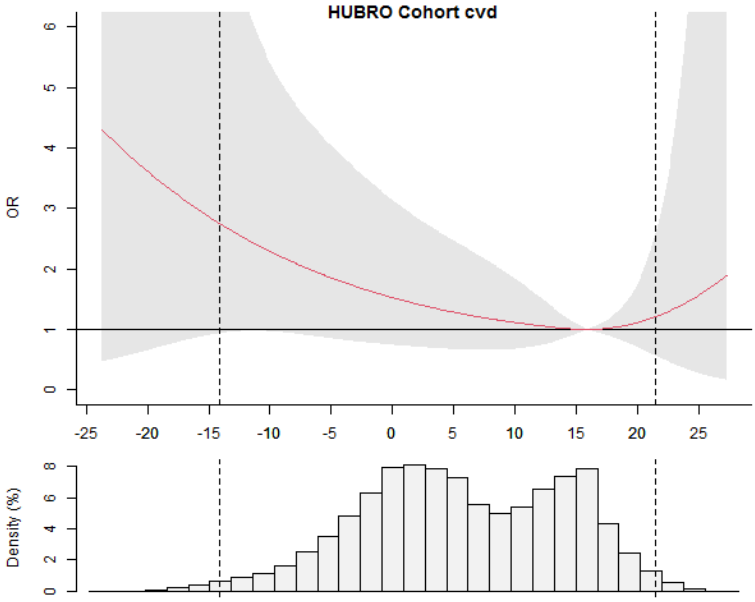

Figure 4 Exposure response curve CVD mortality.

Relationship between daily mean air temperature and CVD mortality in HUBRO cohort. The histogram shows the air temperature distribution in year 2000 to 2018. The red line represents OR values, the grey shadow is the confidence interval.

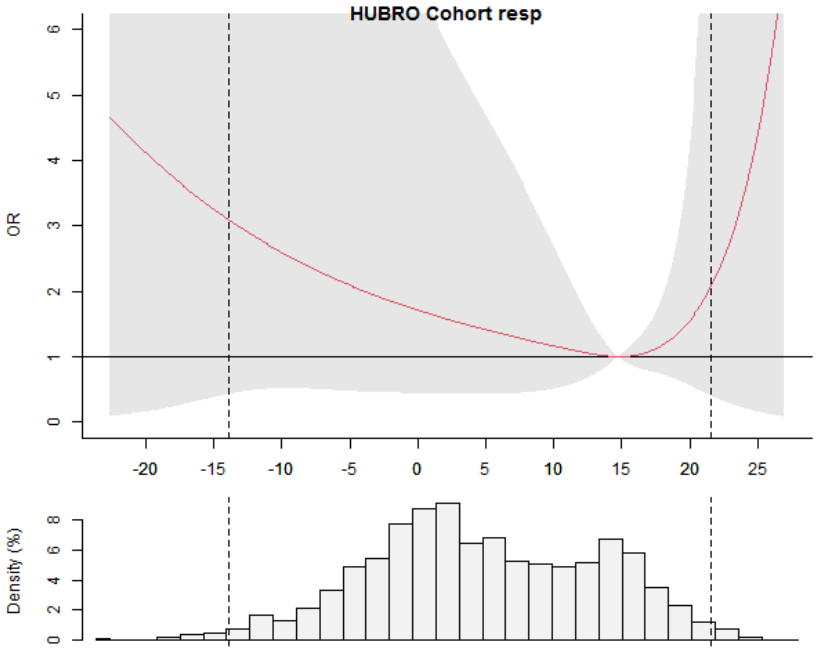

Figure 5 Exposure response curve RD mortality.

Relationship between daily mean air temperature and RD mortality in HUBRO cohort. The histogram shows the air temperature distribution 2000 to 2018. The red line represents OR values, the grey shadow is the confidence interval.

5.3 Results from the main analysis

Table 2 show the results from the main and additional analysis. In this section the result from the main analysis is presented first.

For the cold effect there is an increased odds ratio (OR) in all-cause mortality, cardiovascular and respiratory mortality, indicating that there can be an association between cold effect of temperature and mortality. On warm effect there is increased OR on CVD and RD, and on all-cause mortality the OR is under 1, with 0.85. Indicating there is increased mortality due to CVD and RD during warm temperatures. The confidence intervals in all tests contain 1, meaning there is no statistical significance to claim that those with CVD and RD have higher mortality during high temperatures. I cannot claim there is a correlation between decrease and increase in temperature and increased mortality. There is a narrow confidence interval, as all-cause mortality with warm effect show indicates good precision (table 3), that the real value is close to the true OR (Webb et al., 2020).

5.3.1 Results from the additional analysis

In table 2 the analysis from lag 0-3 and below is part of the additional analysis. In the analysis of lag 0-3 on warm effect measuring RD mortality the OR is 4.92 (1.48-16.4). for all-cause

mortality and CVD mortality the OR was above 1 but the confidence interval contained 1 and showed no statistical significance. On cold effect all-cause mortality and CVD mortality had OR below 1, both with confidence intervals containing 1, while RD mortality had OR above 1 with 2.05 (0.75-5.58)

For lag 0-21 on cold effect all-cause mortality and CVD mortality had OR just above 1, RD mortality had OR 11.46 (0.94-139.56). On warm effects all-cause mortality and CVD mortality had OR just above 1, while RD mortality had OR below 1 with 0.52 (0.05-4.84).

In the age group 65+ on cold effects all-cause mortality and CVD mortality have OR above 1, RD mortality below 1. For warm effect all-cause mortality and CVD mortality have OR below 1, RD mortality above 1. None of the confidence intervals show statistical significance since they contain OR 1.

In the age group 75+ all-cause mortality, CVD, RD mortality in both warm and cold effect have OR above 1. None of them gave statistically significant results since the confidence interval contain 1.

Among the male's all-cause mortality, CVD mortality and RD mortality all showed OR above 1 on cold effects. On warm effects all the three mortality causes were below OR 1. All the confidence intervals contained 1.

For female the OR was above 1 on warm effects, for all-cause mortality, CVD, and RD mortality. On cold effects only RD mortality was below 1. For females all confidence intervals contained OR 1 in both cold and warm effect.

The analyses for warm season May – September showed OR below 1 for all-cause mortality and CVD mortality on both cold and warm effects. For the respiratory mortality the OR was above 1 on both cold and warm effects. None of the confidence intervals for warm season shewed statistically significance since they all contained OR 1.

For cold season November – March all-cause mortality, CVD mortality and RD mortality showed OR above 1 in all the analyses. All the confidence intervals contained 1.

Table 2 Main and additional analysis.

ORs (95% CIs) of mortality for a decrease in daily mean air temperatures from the 25th to the 1st percentile of temperature distribution (cold effects) and an increase in daily mean air temperatures from the 75th to the 99th percentile of temperature distribution (warm effects) in the main and additional analyses. The main analysis, lag 0-3, and lag 0-21 have temperature within brackets.

	Cold effect	Warm effect
Main analysis		
All-cause mortality	1.34 (0.85-2.11) (-13.6ºC)	0.85 (0.56-1.3) (21.5ºC)
Cardiovascular mortality	1.79 (0.76-4.2) (-14.1ºC)	1.17 (0.54-2.5) (21.5ºC)
Respiratory mortality	1.74 (0.36-8.29) (-13.9ºC)	1.9 (0.38-9.51) (21.6ºC)
Lag 0-3		
All-cause mortality		1.04 (0.76-1.43) (21.6 ºC)
Cardiovascular mortality		1.15 (0.66-2.02) (21.5ºC)
Respiratory mortality		**4.92 (1.48-16.4) (21.8ºC)**
Lag 0-21		
All-cause mortality	1.6 (0.8-3.21) (-13.6ºC)	
Cardiovascular mortality	1.42 (0.37-5.55) (-14ºC)	
Respiratory mortality	11.46 (0.94-139.56) (-14.1ºC)	
Age 65+		
All-cause mortality	1.22 (0.75-2.0)	0.98 (0.63-1.53)
Cardiovascular mortality	1.84 (0.75-4.50)	0.99 (0.66-1.47)
Respiratory mortality	0.77 (0.15-3.94)	2.1 (0.38-10.69)
Age 75+		
All-cause mortality	1.52 (0.88-2.58)	1.06 (0.66-1.72)
Cardiovascular mortality	1.72 (0.68-4.4)	1.15 (0.51-2.6)
Respiratory mortality	1.02 (0.17-5.91)	2.06 (0.35-12.01)
Males		
All-cause mortality	1.55 (0.82-2.93)	0.55 (0.29-1.05)
Cardiovascular mortality	2.3 (0.74-7.17)	0.99 (0.31-3.14)
Respiratory mortality	3.12 (0.4-24.34)	0.36 (0.04-3.45)
Females		
All-cause mortality	1.16 (0.61-2.21)	1.19 (0.67-2.11)
Cardiovascular mortality	1.44 (0.42-4.93)	1.41 (0.51-3.88)
Respiratory mortality	0.65 (0.06-7.42)	3.16 (0.2-51.08)

5.4 Results from the interaction analysis

Table 4 shows the results from the interaction analysis with NDVI. The NDVI is divided into 2 categories with the median, 0.43 as a line of demarcation.

For warm effect those with low NDVI close to residence dying of CVD have OR of 1.49 (0.49-4.47) and those with RD have OR on 4.88 (0.52-46.0), while all-cause mortality has OR below 1 with 0.94 (0.52-1.72). The confidence intervals are broad and indicate the results are not significant, the p-value is above 0.05 confirms there is not statistical significance.

In the category with high NDVI on warm effect all results have OR under 1, suggesting it is less mortality for all-cause, CVD and RD with more greenspace close to the residence. All-cause mortality has OR 0.77 (0.42-1.41), RD have OR on 0.62 (0.04-8.85), and CVD highest OR at 0.96 (0.3-3.03). All confidence intervals contain 1 and have p-values above 0.05 and is therefore not statistically significant.

During cold effect CVD mortality was increased with significant result in areas with high NDVI, all-cause mortality also indicated increased mortality in areas with high NDVI but not significantly. In areas with low NDVI it was adverse effect in these categories. For RD mortality living in areas with low NDVI indicated increased mortality, while areas with high NDVI indicated decreased mortality. For cold effects it was only CVD mortality in high NDVI that showed statistical significance.

It was 23 participants in the script in the group of all-cause mortality without NDVI data for their addresses. In the interaction analysis it was 3504 participants. The p-values comes from a Wald test performed in RStudio.

Table 3 Interaction analysis.

Surrounding greenness measured in NDVI, the median is 0.43, the category of low is below 0.43 and high is 0.43 and above. **2** ORs (95% CIs) of mortality for a decrease in daily mean air temperatures from the 25th to the 1st percentile of temperature distribution (cold effects) and an increase in daily mean air temperatures from the 75th to the 99th percentile of temperature distribution (warm effects).

	All-cause mortality		**Cardiovascular mortality**		**Respiratory mortality**	
	Warm Effect	**Cold Effect**	**Warm Effect**	**Cold Effect**	**Warm Effect**	**Cold Effect**
NDVI low <0.43	0.94 (0.52-1.72)	0.92 (0.43-1.97)	1.49 (0.49-4.47)	0.22 (0.05-1.03)	4.88 (0.52-46.0)	4.53 (0.31-66.42)
P-value for interaction	0.627		0.162		0.874	
NDVI high ≥0.43	0.77 (0.42-1.41)	1.63 (0.93-2.87)	0.96 (0.3-3.03)	**4.82 (1.6-14.43)**	0.62 (0.04-8.85)	0.62 (0.07-5.2)

6 Discussion

In this part the results, methods, and sample size will be discussed using updated and relevant literature. In the first section results from the analysis is discussed, followed by discussion on the method. In the last section there will be a sum up of what is most important results from this study concerning Oslo. Throughout the text I present it from an Oslo point of view. First there is a summary of main findings.

6.1 Summary of main findings

In the main analysis, exposure of temperature and mortality in Oslo 2000-2018 were measured. The results are presented in three cause of death groups: all-cause mortality, CVD, and RD mortality. For cold effect the OR was above 1 for all three categories of death cause, indicating there is an association between cold temperatures and increased mortality. For warm temperatures the OR were above 1 for CVD and RD mortality, it was below 1 for all-cause mortality. None of the confidence intervals showed significant results. In the additional analyze it was one significant result, warm effect with 0-3 lag days on respiratory mortality, the OR was 4.92 (1.48-16.4). Indicating almost 5 times increased mortality for RD with high temperature increase. There is a clear difference between the sex on warm effect. For male the OR is below 1 in all three mortality categories, for women the OR is above 1 in all categories. All the confidence intervals contain 1 and the results are not statistically significant.

In the interaction analyze, the results showed that those living in areas with high NDVI had lower odds for mortality due to warm temperatures. For CVD and RD mortality among those living in areas with low NDVI showed increased results. Indicating high levels of NDVI close to residence could be a protective factor for heat. All of the confidence intervals contained 1 meaning the results are negligible. For cold effects it was one significant result, CVD mortality was had OR 4.82 (1.6-14.43) in areas with high NDVI.

6.2 The results of the analysis

In this section the results of the different analysis will be discussed, to make it easier to read it is divided by the different analysis. Limitations and strengths will be discussed as well throughout the text. Though in this section I first want to describe and discuss the sample size since that is the main reason for several broad confidence intervals giving poor precision.

6.2.1 Sample size

One of the most important limitations to interpreting the results is the number of participants in the three categories. It was a total of 3527 participants, in the all-cause mortality category, of

these 1070 died from CVD and 302 from RD. The confidence intervals in all tests are most narrow for all-cause mortality, wider for CVD and most wide for RD. I interpret this can be explained by the number of participants in the groups are most in all-cause, and then gradually smaller in CVD and RD. In the RD group it is too few to get a proper result. In many of the analysis done in all-cause mortality the CI was narrow indicating good precision.

To say if 3527 is a high or low number depend on the circumstances, Wilker et al. (2014) investigated green space and ischemic stroke mortality with 1645 participants with quite narrow confidence intervals. In my study it has been challenging to investigate the RD mortality with only 302 participants. For this study it should probably be more reliable results with more participants, since it investigates mortality in a capital with 700 000 inhabitants (Oslo Kommune, 2023). The aim is not to have statistically significant results, but to show if there is a connection or not, if the confidence intervals are narrow the result is more reliable (Webb et al., 2020).

Throughout the discussion, it is good to have in mind the sample size probably has contributed to results with poor precision, especially for RD.

6.2.2 Main and additional results

Other studies investigating the connection between exposure of extreme temperature and mortality have found statistically significant results. In a study from United States, Basu et al. (2005) found increased mortality among elderly exposed for high temperature in the warmest regions of the country during summer. Their result showed an OR on 1.15 (95% CI: 1.07-1.24) in CPD mortality with 10º Fahrenheit temperature increase. A similar study from England and Wales, Hajat et al. (2007) found increased mortality among elderly, especially in urban areas, during heat. During periods of high temperatures relative risk (RR) for mortality was 1.03 (95% CI: 1.02-1.04) for each degree the temperature increased, a very trustworthy and precise confidence interval. Masselot et al. (2023) investigated several countries in Europe, for northern Europe they found cold temperature attributed to more deaths than warm, but warm temperatures were also, in some extent, attributable to mortality. The countries in south Europe had higher numbers of deaths attributed to warm temperatures. As the results in the main analyses indicated it is increased mortality due to warm effects. It was especially clear on warm effects in the analysis with lag 0-3 where RD mortality had OR 4.92 (1.48-16.4). This is very high odds ratio indicating it is almost 5 times increased risk of dying due to respiratory diseases when it is warmer temperatures. The broad confidence intervals indicate the real value can be between 1.48- and 16.4-times increased odds, this is a very uncertain result. If the OR was the

same but the confidence intervals were 4.5-5.2 it would be more certain the OR was accurate (Webb et al., 2020). Results from Witt et al. (2015) show increased mortality for RD during heat, it was 1.8%-8.2% higher on days with heat than normal summer temperatures. In this analysis it is not included air pollution, during high temperatures there is increasing occurrence of air pollution which is unfavorable for CVD mortality (Chen et al., 2018). Results from a meta-analysis in EXHAUSTION also showed increased air pollution during heat, and significant increased mortality due to respiratory diseases (EXHAUSTION, 2022). It might be that air pollution is the cause of high RD mortality due to warm effects. At a global level there is an increase in temperature related mortality and indicates there will be increased mortality due higher to temperatures in the future. For respiratory diseases there is especially increased ozone that appears at high ambient temperatures that is increasing the risk of illness and mortality (Cissè et al., 2022). This is a subject for further studies using data from Oslo. Urban green areas can work as adaption strategy to both heat and air pollution (Burkart et al., 2016). In lag 0-3, all-cause and CVD mortality, indicated increased risk of mortality due to warmer temperatures, though not statistically significant. When analyzing warm effects Gasparrini et al. (2015) mean it is most reliable to use shorter lag days since the warm effect affect the health almost immediately. While for cold effect it is better to use more lag days to be sure to observe the effect of being exposed to cold temperature.

In lag 0-21, cold effects all-cause and CVD mortality indicated increased mortality, without statistical significance. While RD mortality had much higher OR at 11.46 (0.94-139.56). It is a remarkable result with very wide confidence interval, the lowest number is close to 1. I interpret it might influenza giving the high OR. During the winter there is an increase in mortality due to influenza, in Norway there is around 1000 deaths per year due to influenza, most among the elderly population (Pripp, 2021). Influenza has code J09 and is included in the group of RD mortality. In the R script there are only 2 persons that have influenza as their main cause of death. When the doctor register a cause of death there are several diagnosis that can be registered that the person had before or got during the time before death (NIPH, 2020). It might be another cause why the person first gets sick or injured and then die, it can be the person get a hip fracture, and then it dies from a pulmonary embolism. As for influenza the person might have had that first and then got a fatal pneumonia. Even though the result for RD on cold effect have a very high OR and very wide CI it might be that the influenza caused increased mortality result in the high OR. There is generally more people dying during cold seasons (Masselot et al., 2023) and influenza is a disease that typically appears during cold season (Pripp, 2021).

That result is much higher than all-cause and CVD mortality in lag 0-21. The results have not been so pronounced different in the other additional analysis. Therefore, it is given more attention in this section.

Ruuhela et al. (2021) investigated the connection between both warm and cold temperatures and mortality in Finland which have similar climate to Norway, they had most reliable results when using up to 25 lag days for cold effect. Their results indicated statistical significance for increased mortality with temperature -15ºC in all their categories, but for -20ºC the results were not significant in all categories they had. That is what Gasparrini et al. (2015) found in their study, there is more mortality due to moderate cold than extreme cold. They investigated 11 countries with various climate in all continents except Africa, their findings are that cold temperature was more attributable to mortality than heat. Masselot et al. (2023) did a similar study in Europe with the same findings. Cold temperatures are attributed to more mortality than heat. Both studies mentioned had exposure response curves like those produced in this study, where most of them had higher prevalence of mortality on the left side, cold temperatures. Indicating the results from this study correspond to previous studies on the theme. The result in my study indicates it is more death due to cold effects in Oslo, especially for all-cause mortality in both main analysis and when using lag 0-21, although it was not statistical significant. Brenn and Ytterstad (2003) also saw increased mortality during the winter when investigating mortality rate for the years 1991-1995, and especially during winters with large influenza epidemic.

But as Cissè et al. (2022) predicts in the IPCC report on health and well-being there is increasing mortality caused by heat due to more heatwaves and increased temperatures, especially for CVD and RD. In the main analysis with 10 lag days for both warm and cold effect the results indicate there is increased odds for mortality due to CVD and RD but decreased for all-cause mortality. These results indicate what was found in RoLS cohort investigating CPD mortality due to extreme temperatures in Rome, also part of the EXHAUSTION project. They had 1.26 million participants, for CVD mortality it was 32% (95%CI: 23%-40%) increased risk and for RD the numbers were higher at 40% (95%CI 18%-66%) (Staffagio et al., 2021), but also with wider confidence intervals indicating poor precision for the risk of RD mortality due to heat.. They had many participants in the whole cohort. I have not managed to find the number for mortality due to RD. Kovats and Hajat (2008) found, in Europe older women are more vulnerable to die during heat than men. That is similar to what Staffagio et al. (2021) found, increased mortality among those +75 years and women due to heat. In the additional analysis

in this thesis females had higher OR than male on warm effects in all three mortality causes. Among age 75+ on warm effect there were overall higher OR than age 65+, indicating the same results as mentioned. None of the confidence intervals showed statistical significance.

There is a decrease in people suffering from cardiovascular disease in Norway, there is better medication, and less people smoke. Deaths due to CVD have decreased in Norway since 1970, but since year 2000 it looks like the graph decrease even more (Holtermann Ariansen, 2021). This might be an explanation to why it was not significant results for CVD death due to extreme temperature.

6.2.3 Exposure response results and MMT.

Cissè et al. (2022) emphasize elderly are among those more vulnerable to increased temperature due to climate change, and also those with preexisting conditions like CVD and RD. We are not there yet but as a consequence of climate change can we expect a decrease in average life expectancy? Humans have trough history struggled but also managed to adapt to changes. It is known that the human body can adapt to increased temperature during short period of time, but if the human body manage to adapt to higher temperatures for a longer period of time there is little research (Folkerts et al., 2020). The MMT in Oslo for all-cause mortality, CVD and RD mortality, varies between 15-18ºC. The numbers correspond to what Astrom et al. (2016) found in their study done in Sweden, a country Norway can compare oneself with in climate and social structure. They did not look at the diagnosis separately as done in this study, may make it somewhat challenging to compare. In my results the all-cause mortality had a slightly higher MMT around 18ºC. I interpret this suggest the mortality from CVD and RD occur in lower temperature and they are more influenced by colder temperature. Though the change is not big. The dashed lines in figure 3-5 showed the 2.5^{th} and 97.5^{th} percentile. In most studies, investigating mortality due to extreme temperatures use of the method with MMT, 2.5^{th} and 97.5^{th} percentile is the cut off for extreme cold at the left end and extreme heat at the right end, relative for the normal climate in the relevant country (Gasparrini et al., 2015). In my figures the cut off for extreme heat is around 22º. It corresponds what Gasparrini et al. (2015) found in their study investigating Stockholm, among other cities, who had its cut off at 22ºC for extreme heat. For cold effects the cut off is around -14ºC, in Stockholm it is around -7ºC (Gasparrini et al., 2015). It is important to stress that neither of the tables in this study or the results of MMT for Stockholm had statistically significant confidence intervals as they all contain 1.

The acclimation to the ambient temperatures is of great importance, on how the population can cope with high temperatures. Adaption to higher temperatures in the future is important

(Sanchez-Martinez et al., 2022). MMT is a measure suitable for measuring long term adaption to heat as it shows at what temperatures there is higher mortality. It is suggested MMT should be used as an indicator to measure long term adaption to heat for humans (Astrom et al., 2016). It is discussed within literature how the MMT will develop with warmer temperatures. Follos et al. (2021) mean the increase of MMT development is a sign that the population is adapting to higher temperatures in Spain. If the MMT used to be for instance 22ºC and have increased to 25ºC it means that people are better adapted to higher temperatures, the temperature, 25ºC, that before was associated with an (small) increase in mortality is now a temperature people are more comfortable with.

6.2.4 Results of the interaction analysis

Urban green areas can be a climate adaption strategy and many places have already implemented measurements for urban green spaces, with the aim to provide shade, prevent urban heat islands and store CO_2 to reduce air pollution (Heaviside et al., 2017). The results in the interaction analysis indicates living in areas with high NDVI reduce the odds for premature death during warm effects, also due to CVD and RD, the OR were below 1 in all three cause of death categories, although not statistically significant. In areas with low NDVI the results indicate increased risk for premature mortality due to CVD and RD, for all-cause mortality OR was below 1. This indicates living in areas with more surrounding greenness is protective for heat exposure on CPD mortality, and having less greenspace near the residence do not protect against CVD and RD. It is important to emphasize the areas with low NDVI are not totally without surrounding greenness, if so the NDVI values would have been 0 or below. None of the analysis in the interaction analysis showed statistical significance, some of the CI were very broad meaning there is poor precision. All the confidence intervals comparing low and high NDVI exposure overlap, this is also indicating there is no statistical significant difference between the group compared in the interaction analysis (Tobias et al., 2017). Villeneuve et al. (2012) found that living in areas with high NDVI have a slightly lower mortality rate than areas with low NDVI. In the systemic review of Gascon et al. (2016) their findings indicate reduced CVD mortality rate when living close to greenness. They emphasize the different exposure assessments to be the main limitation for the study. A study from New Zealand did not find any relationship between CVD mortality and access to urban green space (Richardson et al., 2010). It can be understood that surrounding greenness is not the solitary reason why greenness in some studies reduce mortality. Socio-demographic characteristics can also increase mortality among vulnerable populations in urban areas (Gronlund et al., 2015). The amount of surrounding greenness and the distance can be of importance for how it us used (Gascon et al.,

2016). Oslo municipality measure both amount and distance to urban green areas, their measures show high amount and short distance to greenspace. (Oslo Kommune, 2020b). How are the green areas used and how does it affect the health in a positive way? As Markevych et al. (2017) suggest in their figure green areas are important stress reduction, as Ulrich et al. (1991) emphasize the importance of, and reducing harm and building capacities is important for reducing the risk of CVD and all-cause mortality. But as Carinanos and Casares-Porcel (2011) highlight in their article allergy affects many people and can exclude inhabitants to use urban green spaces. With right knowledge on how to manage, plan, and maintain urban green areas it should be more inclusive to everyone, also those with allergy (Carinanos & Casares-Porcel, 2011). For many the motivation to seek green areas can be to restoring capacities. Even though many Norwegians are drawn to nature (Fugelli & Ingstad, 2001) one cannot assume that is the case for everyone. Ulrich et al. (1991) stressed the importance of natural environments being the only valid measure of greenspace to improve health. It is necessarily not true, many of the studies referred to earlier are from urban environments where much of the greenspaces are built and restored in some way (Gascon et al., 2016), this would Ulrich et al. (1991) have perceived as unnatural environment. Physical activity is mentioned in several studies when it comes to urban green areas and health measures (Hartig et al., 2014; Markevych et al., 2017). It is an important factor to prevent cardiovascular and respiratory diseases. Where it is green areas, it invites to be more physical active. It was not tested for physical activity in this analysis since the thesis is investigating mortality. But it is a preventive factor for non-communicable diseases and related to the use of greenspace physical activity (Markevych et al., 2017). Whether you are physical active or not, being in areas with high NDVI during heat can be good for the health. Areas with high NDVI contribute to reducing temperature and effects of urban heat islands (Plans et al., 2019).

There are several studies investigating heat and mortality using greenspace as an effect modifier finding heat-related mortality to be lowest in green areas (Burkart et al., 2016; Gronlund et al., 2015; Son et al., 2016). In the study from Lisbon Burkart et al. (2016) found that those living in areas with higher NDVI had less heat-related mortality. Oslo and Lisbon have some similarities, they are both close to the water and have approximately 600 000-700 000 inhabitants' (Lundbo, 2023; Oslo Kommune, 2023). But the climate is quite distinct. Portugal have been struck by many heatwaves and wildfires this decade, as well as many countries in south Europe (United Nations Environment Programme, 2022). Results from EXHAUSTION and the Italian cohort, RoLS found increased mortality due to CPD (Staffagio et al., 2021). In

a way it is not fair to compare north and south Europe, but with the predictions on higher temperatures in the future we should see to southern Europe to better understand, prepare, and adapt to the challenges with increased temperatures and what implications this have for cardiopulmonary health.

6.3 Methods and data

Here the methods, measurements, and data sources will be discussed, the strengths and limitations will be discussed in each section.

6.3.1 Temperature and NDVI

The temperature data used with 1x1 km grid for the whole mainland Norway, for this study that is a strength with both min, mean and max temperature every day. The temperature can vary within the city, and with these measures the temperature is more accurate where the people actual live. It has not been possible to judge if the temperature is from urban heat islands effects in this study.

The temperature is data for residential address, it is not possible to know how exposed the person actually have been to the temperature registered on their residential address. Cannot assume the person is home all day, especially not those who work. This might lead to non-differential misclassification, this might give underestimation of heat effects (Ragettli et al., 2023). Those who died in this study had high average age, they were probably not working, therefore one can assume they spend much time at their residential address and were exposed for the temperature registered there. A strength with the study is that the addresses were updated regularly and merged with correct exposure values.

In the deliverable on epidemiological methods written for the EXHAUSTION project, it is explained that the use of 10 lag days was to exclude deaths that were displaced. Further they explain the use of 10 lag days for both warm and cold effects can underestimate the effects of heat and cold effects, heat have shorter lag days while old effects have longer lag days. In the additional analysis there are some clear changes, the OR for CVD increased on warm effect using lag 0-3, and RD increased in both warm and cold effect using the lag days appropriate for purpose (Staffagio et al., 2022).

Even though the interaction analysis only had one result being statistically significant, the result indicate living in green areas could have a preventive factor against premature death during

warm effects. Green areas are often mentioned and implemented as climate adaption strategy to reduce the exposure of temperatures (Oslo Kommune, 2020a). It can be challenging to investigate when, so few people have *little* access to greenspace.

In this study there is no information on factors that explain and capture how the participants interact with the surrounding greenness. In the study to Qiu et al. (2021) they had information on exercise which correlated with the amount of surrounding greenness to the residential address, the more surrounding greenness the more participants were physical active. But they could not determine how much time the participants spent in surrounding greenness. In my study I have not controlled for if the amount of physical activity corresponds to the value of NDVI, that is for future investigation to be made. But there is a similar challenge as with the data in this thesis, I cannot be sure how the participants are interacted with the surrounding greenness. As Markevych et al. (2017) refer to in their figure (fig. 1) there are several pathways to use greenspace and experience improved health as an outcome. The high average age for the participants in my study can give a hint on how they interacted with surrounding greenness. It could have been to avoid environmental stressors like heat, air pollution, and noise, to be social with family and friends, or restoring capacities and experience stress reduction. Since my study is on short term exposure, up to 21 days before death it is very uncertain how the interaction with surrounding greenness were. Qiu et al. (2021) suggest from their findings there is higher interaction between individuals and the nature environment where there are high levels of surrounding greenness.

Regarding missing data for NDVI, it was a total of 23 persons of 3527 without registered NDVI values, it is 0.7%. Having missing data can contribute to skewness in the dataset and produce inaccurate numbers (Thrane, 2020). In this study there is more than 99% complete with NDVI values, it is a strength.

6.3.2 Categorization of NDVI

Oslo is a green city where many have good access to greenspace, the city almost fulfill the recommendations presented in the report of WHO (WHO, 2016), in Oslo 95% of the population have 5000 m^2 greenspace within 300 meter from their residence (Oslo Kommune, 2020b). With so much greenspace it can explain why so many have high NDVI in their neighborhood, more than half of the sample, 55.3% where in the category of high NDVI. In the category with low NDVI it is not only concrete, and people still have some amounts of surrounding greenness. In the study to Wilker et al. (2014) they divided the sample population of 1645 into four categories of NDVI using the quartiles to decide the division. They investigated the connection between

mortality due to ischemic stroke and how much surrounding greenness the participants had. In their results it is statistically significant results for those having most surrounding greenness, they had lower risk of dying due to ischemic stroke. The category with lowest surrounding greenness did not get statistical significance. In a similar study by Villeneuve et al. (2012) they also divided the NDVI in four categories using the quartiles with significant results for higher NDVI. Son et al. (2016) used three categories of NDVI to investigate mortality and surrounding greenness. They investigated how increased temperature will affect people with different amount of surrounding greenness. Their results showed that living in areas with high NDVI indicate lower risk of mortality due to temperature rise. It seems when using NDVI as measurement on mortality due to temperature it is most common to divide into three or four categories. Most of the studies I found divided the NDVI using the quartiles creating four categories. Unfortunately, it is not found any study dividing NDVI categories using mean or median as done in this analysis. The two categories of NDVI in high and low were divided by using the median at 0.43, the mean NDVI in this dataset were 0.42. This division was determined in the script, and I have not found any reason why median, and not mean was used. If the categories were divided in four categories as from the examples above, it might have given other results, as well as results being statistically significant. The numbers of observations in all-cause mortality were 3527, it should be enough participants to divide into four categories. Wilker et al. (2014) had fewer participants and got significant results. The distribution of NDVI values in my dataset ranks from 0.03 till 0.7 at the highest, the 1st quartile is 0.37. The low minimum NDVI indicates there is an outlier. The median NDVI is higher than the mean NDVI, from that I interpret the distribution of NDVI is left skewed (Thrane, 2020). Those in the category with low NDVI near their residence might have enough surrounding greenness to have a protective effect. With only two categories it can be challenging to determine how much greenness can work as preventive for mortality. Those living in areas with NDVI 0.42 compared to those living in areas with NDVI 0.44 are in different categories but have more equal surrounding greenness than those having 0.1 versus 0.4 NDVI in their surroundings. Both being in the group of low NDVI, making it difficult to determine whether it is lack of surrounding greenness or something else causing increased risk of mortality.

A challenge with the use of interaction analysis is to determine at which level to do the classification of the variables to be sure to see if there is an effect of the interaction. Since Oslo is a rather green city it would probably be best to divide into 4 groups as done in the study to

Villeneuve et al. (2012). The scripts were already set, and it was not tried to divide into more categories. This is something for further studies in Oslo to explore.

Another aspect of areas with high NDVI is that in cities green areas tend to have more expensive dwellings (Markevych et al., 2017). Those with more income often have better health, Burkart et al. (2016) discuss this might be an explanation why there is less heat-related mortality in areas with high NDVI, many of the residents have improved health status. Average life expectancy is a measure of health and living conditions (Salazar et al., 2019). There are big differences in average life expectancy within Oslo, in 2008-2011, the middle of the period for this study, it differed 8.8 years between the urban districts with highest and lowest average life expectancy for men (Norgård Berntsen, 2013). For further investigation comparing NDVI in the urban districts would be of interest for Oslo to see if the amount of surrounding greenness has an impact on expected life expectancy. In the data used in RStudio I could see only 40 participants lived in areas with NDVI below 0.2. This indicates poor vegetation (Barboza et al., 2021), unfortunately it is not possible to see where in the city these low values are.

Why was NDVI chosen? In this project the CONOR data have been merged with exposure data by researchers at NIPH. As mentioned before, there are several measurements to use when observe the amount of vegetation. NDVI is common to use in epidemiological studies, the measurement is easy to compare between studies, gives valid results and is functional to use (Markevych et al., 2017). Some of the challenges with the use of NDVI is not knowing the quality of greenness being measured, the same value of NDVI can indicate very different type of greenness, and therefore the use of the greenspace can vary even if the values are equal (Barboza et al., 2021). When recommendations and aims are set to a specific measure as it is in Oslo, it ensure the greenspace is of a certain size and accessible to the public (Oslo Kommune, 2020b). 5000 m^2 which is the other measurement used to define size of the greenspace in Oslo, it is almost the size of a 60 x 90 meters football field (Konverteratum, 2022). 1000 m^2, as 98% of the population in Oslo have within 300 meters from their residence is not a very large area, 5^{th} of a football field. But 95% of the population in Oslo have 5000 m^2, size of a football field, within 300 meters from their home (Oslo Kommune, 2020b), that size of greenspace should be considered as very good.

6.3.3 Use of register data

The interest of this study is urban areas. HUBRO is the 4^{th} largest cohort of CONOR, the largest is HUNT, which is Trondheim and the surrounding county. There is no good Norwegian cohort to compare these results with as the other cohorts is not only urban areas, but they also consist

of rural area. In the Nordic countries Sweden and Finland was a part of the cohorts of EXHAUSTION, they have bigger capitals, and they might have more significant results. In Oslo there have been an increase in heatwaves and extreme temperatures the last 30 years (Tajet et al., 2022), but it is not so high as countries in Southern Europe. Single days with high temperatures can also lead to increased mortality, but high temperatures over many days might give other results (Ragettli et al., 2023).

A strength with this study is that is controlled for all the temperatures in the exposure-response curves, not just the extreme cold or warm temperatures. In that way the risk is quantified across the whole spectrum. Ragettli et al. (2023) emphasize using DLNM both the duration and effects of extreme temperatures are best suited to investigate the exposure of temperature and mortality.

Weakness with the study in the interaction analysis is that I did not analyze for NDVI during the summer months. It would probably be too few participants if only investigating the summer months, with a result difficult to interpret. There is little research on how surrounding greenness affect connection between temperature and mortality during the cold season. Qiu et al. (2021) did analysis on that in China, their result indicates that it is higher mortality during cold season in areas with high NDVI. As Masselot et al. (2023) found it is more mortality due to cold weather in Europe. The results found in my interaction analysis is difficult to interpret for the cold season. The study to Qiu et al. (2021) is the only article found, investigating cold effect and NDVI, they emphasized the need for more research on how surrounding greenness can be an effect modifier to temperature exposure and mortality also during cold season. During the cold season there is less greenness to capture and store CO^2 and the emissions increase (Leichenko et al., 2019), in Oslo the surrounding it is hilly, making the city vulnerable for air pollution during calm winter days (Ihlebaek et al., 2021). To analyze for air pollution as well in the interaction analysis, might probably give a more sufficient result of the exposure to heat and cold temperatures. with the result in this thesis, it is challenging to interpret what it really means. Oslo is a big city and as many other cities there is air pollution that can affect the outcome of cardiovascular mortality (Chen et al., 2018). I think it would give a more adequate overview of the effect urban green areas might have for the cardiopulmonary health.

The cause of death is collected from the Norwegian Cause of Death Register. In the analysis the main cause of death is used. A problem with using mortality data can be to determine what the actual cause of death is if the person have many pre-existing diseases. This can be a source for errors when the formular is completed, risk of mis-specification (Webb et al., 2020). As mentioned before there are several diagnoses that can filled and leading to actual cause of death.

If there is a doctor not knowing all the diseases the patient had from before there is a risk for misdiagnosis (Webb et al., 2020). For the data used in this study it is difficult to control for if the person has got the right diagnosis. The cause of death register have an informative guide to prevent errors (NIPH, 2021).

6.3.4 Internal validation

The internal validation is when the study sample reflect on the true situation. This can be measured by confounders, and selection bias (Webb et al., 2020). When using case-crossover study the within-participant comparisons control for both known and unknown confounders (Basu et al., 2005). The method is used in many other studies before (Qiu et al., 2021; Ragettli et al., 2023). Air pollution would be possible to test for as a confounder in this study. It is an important factor for CPD mortality in urban areas (EXHAUSTION, 2022), and might explain some of the results in the analysis, like the high OR on CVD mortality in the interaction analysis, and increased OR for RD mortality with 0-3 lag days.

Selection bias is also part of internal validation. To get participants for a health study like HUBRO it might appeal more to those concern for their health, leaving those who might be more at risk of develop disease out. People who smoke are often less willing to participate in health studies, for this study investigating CPD mortality, where smoking is an important contributing factor to develop CPD, it might have affected the result (Webb et al., 2020). For the HUBRO cohort 46% of the invited participated in the investigation.

The strength of using cohort data is that as an observational study it gives the best results regarding the cause of disease, and by which exposures might have given the disease. It reduces the risk of recall bias as the participant do not know about what the outcome will be (Webb et al., 2020). The HUBRO cohort have many different variables, some of which the participants made their own judgement, for example how much time they were physical active per week, it might be some overestimate since they know it is a positive health determinant. The variables used in this study are collected from register and measurements. Since all the different variables are collected from the same register, meaning the cause of death is collected from its own register, the temperatures are from their particular register and so on, the risk of non-differential misclassification can therefore be assumed to be low (Webb et al., 2020).

6.3.5 External validation

If the results for this study is valid for other similar studies, it shows generalizability (Webb et al., 2020). My study indicates increased CPD mortality during both warm and cold effects. That is somewhat in accordance with the study of Masselot et al. (2023). My study could be

generalizability to cities in northern Europe, where climate and social structure is somewhat comparable to Oslo. But it would not be generalizability to cities in south Europe where the climate is different, and people seems more adapted to live with warmer climate and have knowledge on how to behave during heat exposure.

The mean age of the study sample for CPD mortality is above 80 years, meaning the study population is older adults. Vulnerable people, like old, very young, and those with pre-existing disease are more exposed for extreme temperatures (Cissè et al., 2022). In the additional analysis, the age group 75+ had higher OR than 65+ indicating the oldest are more vulnerable to both cold and warm effects. The results are not statistically significant.

6.4 Oslo – green areas as an adaption measure

How should Oslo adapt to rising temperatures and the health issues that comes with rising temperatures? Oslo have a population of 709 037 (Oslo Kommune, 2023), it is not a big capital compared to other European capitals. Nature is not far away no matter where you are, it is easily accessible for most people. Norwegians have tradition with using the nature during the whole year. I think having much green areas in the cities are important for the population, and there are usually criticism and protests if parks and other green areas is built down or turned into buildings. Markevych et al. (2017) highlight that residents tend to protest to preserve nearby green areas for the importance of their health and recreation. In the strategy of climate for Oslo it is amplified that Oslo Municipality should avoid building down and redistribute green areas (Oslo Kommune, 2020a). WHO acknowledge the importance for nature for everyone's health as they recommend green areas near the residence (WHO, 2016). Fugelli and Ingstad (2001) compared the meaning of nature to good health with other countries but could not find the same results of nature being so important as in Norway. Around Oslo is Marka, where it is plenty of prepared hiking trails in the woods for all year usage. It is accessible by public transport; most people are able to come there. Marka is also important for carbon storage for Oslo, but it is of importance to improve knowledge on how Marka is affected by climate changes (Oslo Kommune, 2020a).

Living in the Nordic countries people manage to adapt to cold season, there is central heating system, and people have the knowledge on how to behave during cold to preserve good health. During the summer in Norway, people might not take precaution and are not so well adapted to heat. This can be a challenge when adapting to increased temperatures and climate change. This is one of the reasons why the heatwave definition is upgraded, to get people to understand the

severity of a heatwave (Tajet et al., 2022). Oslo municipality is well aware why and how greenspace is important for climate adaption in the future, both to regulate temperature, handle storm, and heavy precipitation, to mitigate climate change they arrange for different species to be able to settle in green spaces and green connecting passages (Oslo Kommune, 2020a). Even if the results of the interaction analysis are not statistically significant it indicates that those living in areas with high NDVI are more protected for heat related mortality. The study to Qiu et al. (2021) indicates there is increased mortality in cold season in areas with high NDVI, the adverse effect from high NDVI during heat. None of their results were statistically significant. They emphasize there is need for more research on how greenspace can affect the mortality during cold season. In this study the interaction analysis had one significant result, CVD mortality was increased during cold in areas with high NDVI. Since the result is uncertain with broad CI, and the reason why it is significant is difficult to determine there is need for further investigation on NDVI during cold season as well. In Oslo there is higher CVD mortality during the winter (Brenn & Ytterstad, 2003) as also the results in main and additional analysis indicates. In the distribution of NDVI there is more people living in areas with high NDVI. But this result was significant different from RD mortality during cold so that is probably not the only explanation. This should be a subject for more investigation in Oslo, and other cities with different seasons using greenspace as a climate adaption measure.

There are plenty of suggestions on how to adapt increasing temperatures due to climate change (Leichenko et al., 2019). Within the subject of health and climate adaption there are still needed to do more research. WHO ask for more countries to have heat-health plan to prevent increased mortality and morbidity during heat waves (Sanchez-Martinez et al., 2022). After the large heat wave stroked Europe in 2003 and many people died, it is more awareness on the dangers to heat. In countries that are used to high ambient temperatures the awareness of how to handle extreme temperatures are better. While in Scandinavia we are not used to being exposed to high temperatures, when it finally comes the public opinion is to enjoy the warm weather outside in sun. My impression of awareness and knowledge on danger of extreme ambient temperatures is not much spoken about in Norway. In Scandinavia only Sweden has a heat-health action plan, (Sanchez-Martinez et al., 2022). In Oslo there is more attention to climate change also being a public health issue. In the latest report on public health climate change is a topic in focus (Oslo Kommune, 2022). The climate strategy for Oslo does not contain any plans for extreme temperatures or other events, but they emphasize the importance of preparedness plans for extreme events (Oslo Kommune, 2020a). Heat-health plans are not mentioned in the strategy.

When it came to greenspace my study showed almost no significant association between access to green space and health during. I have reflected that one reason can be that most residents in Oslo have easy access to greenspace. This is also the conclusion to Ihlebaek et al. (2018), they investigated asthma, diabetes type 2, and musculoskeletal pain and access to green areas in Oslo and found no significant results between groups. As Fugelli and Ingstad (2001) call attention to, I also think there is a strong tradition in Norway to be attracted to the nature, we use it as a place for recreational purposes, physical activity, escaping noise and air polluted roads.

In the exposure response curves there are very broad confidence intervals, but if you compare the OR in all curves, there are much more increase in OR with warmer temperatures. In the all-cause mortality group, the OR stay just above 1 after the MMT 17ºC while for the other groups, CVD and RD the OR increase much more in warmer temperatures as well. They are not significant, but it can give a hint on what challenges could be in the future with more frequent heatwaves in Norway. The method used in this thesis do not reveal if the warm effect was due to urban heat islands (UHI). It might have been one explanation to why it was increased mortality in areas with low NDVI experienced as greenspace protect against. During the heatwave in 2003 it was increased mortality in cities, a further explanation can be UHI contributing to increased mortality (Heaviside et al., 2017).

Climate adaption and mitigation starts at a local level, Oslo municipality emphasize the importance of climate adaption strategies in collaboration with local research communities to get the best strategies for Oslo. They stress why climate adaption and mitigation is important for the public health citizens in Oslo, with lower emissions there is less air pollution and improved health for many people, with better access to walkways and bicycle lanes more people are physical active (Oslo Kommune, 2020a). A recent study by Iungman et al. (2023) investigated effect of trees to urban heat islands. Their results showed that increased tree coverage by 30% could have prevented 40% of premature deaths due to UHI in 2015. These numbers are merged for all the European cities who were investigated in this study, meaning warmer cities in south Europe experience more heatwaves than northern Europe influence the result. In Oslo Venter et al. (2020) investigated how much tree canopy can mitigate the effect of heat stress to vulnerable people, they found out that each tree in Oslo can mitigate the risk of heat exposure for one vulnerable person 75+ years per day. Regarding temperature Oslo Kommune (2020a) acknowledge the importance of green areas like Marka and other green areas in Oslo are to adjust the temperature. Overall, Oslo are well aware of why urban green areas are important for the public health as climate adaption strategies. But there is need for more

research on this topic for better understanding and to prevent premature mortality and health issues due to extreme temperatures.

7 Conclusion

This study has shown poor statistical significance for most of the analysis. Only being significant for RD mortality on warm effect with lag 0-21, and CVD mortality in interaction analysis on cold effect. But the CI for both the significant results were very broad, probably due to few participants. The results are consistent with other studies showing increased mortality during cold temperature.

This study used case crossover with conditional logistic regression investigating if extreme temperatures in Oslo affect the CPD mortality in the population. Surrounding greenness was used as effect modifier, using NDVI as a measurement. The results indicate that surrounding greenness can be a protective factor against warm effects, while those living in areas with less surrounding greenness might have increased mortality. These results were not statistically significant but show a tendency towards green areas being meaningful, not only for restoration and physical activity, but also as a measure for climate adaption.

Due to few participants the results are difficult to interpret. From other cities there is clear relationship between mortality due to cardiopulmonary diseases and warm and cold temperatures. Since the average temperature is rising and will continue to do so, we can expect more, and pro-longed heatwaves and we should be prepared for increased morbidity and mortality among the population. Living close to surrounding greenness during heat lower the surrounding temperature and might contribute to decreased health issues.

It was unfortunately to little time to also investigate for mortality affected by air pollution and temperature together, there is not much research on this for Oslo from before, so there is a requirement for further investigation. Oslo municipality have ambitious aims in reducing greenhouse emissions and be a climate resilient municipality. They have already implemented public health concerns in their climate strategy. To further investigate how surrounding greenness affect extreme temperatures and CPD mortality in Oslo is of great importance since we know there will be more of extreme temperatures, especially heat in the future. We know it affects the health to people in other cities and countries not far away. Therefore, it essential for Oslo and Norway to also implement science to know how to adapt to climate change and prevent health issues and mortality. Oslo municipality acknowledge this importance by emphasize public health concerns in their climate strategy.

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Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst C	Øyvind Grønlie Olsen	22857547	25.07.2022	10347

Shilpa Rao-Skirbekk

Prosjektsøknad: Kardiopulmonære effekter av eksponering for ekstreme temperaturer og luftforurensning i Europa
Søknadsnummer: 2019/297
Forskningsansvarlig institusjon: Folkehelseinstituttet

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Prosjektet vil bruke epidemiologiske data og modellering for å avdekke sårbarhetsfaktorer av betydning for å anslå framtidig forekomst av CPD og å identifisere kostnadseffektive tiltak i Europa. Mens det er påvist en statistisk sammenheng mellom klimaparametere og helseproblemer, er de underliggende årsaksmekanismer og faktorer som øker eller reduserer sårbarheten fortsatt dårlig forstått. I dette prosjektet undersøker vi hvordan et bredt spekter av sårbarhetsfaktorer endrer virkningen av ekstrem varme og luftforurensning på CPD-dødelighet og sykelighet og i hvilken grad og hvordan tilpasningsstrategier er i stand til å speile og redusere disse sårbarhetsfaktorene. Prosjektet vil bruke registerdata, data fra helseundersøkelser og andre relevante datakilder til å undersøke kardiopulmonære effekter av ekstern temperatur og luftforurensning i den norske voksen populasjonen.

Vi viser til søknad om prosjektendring mottatt 08.06.2022 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk (REK) på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Søknaden om godkjenning av prosjektendringer omfatter at Ashley Ahimbisibwe, Kicki Svensson og Camilla Nyland inngår som prosjektmedarbeidere i forskningsprosjektet.

REK har ingen innvendinger til innlemmelsen av nye prosjektmedarbeisdere.

Vedtak

Med hjemmel i helseforskningsloven § 11godkjenner REK prosjektendringen.

Sluttmelding

Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp

eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Jacob Hølen
Sekretariatsleder
REK sør-øst

Øyvind Grønlie Olsen
Seniorrådgiver
REK sør-øst

Kopi til:

Folkehelseinstituttet
Terese Bekkevold

APPENDIX 2

00_Function.R

5/14/2023

```
#----------------------------------------#
# Name:00_FUNCTION                       #
# Project: EXHAUSTION                    #
# Version: 27.04.2021                    #
#----------------------------------------#

##-------------------------------------------------------------------------------------####
## 1. FUNCTION TO ESTIMATE MINIMUM OF A EXPOSURE-RESPONSE FUNCTION FROM A FITTED MODEL ####
##-------------------------------------------------------------------------------------####
findmin <- function(basis,model=NULL,coef=NULL,vcov=NULL,at=NULL,from=NULL,
                    to=NULL,by=NULL,sim=FALSE,nsim=5000) {
  #
  ##############################################################################
  # R code from https://github.com/gasparrini/2017_tobias_Epidem_Rcodedata/blob/master/findmin.R
  #
  #   ARGUMENTS:
  #   - basis: A SPLINE OR OTHER BASIS FOR AN EXPOSURE x CREATED BY DLNM FUNCTION
  #            CROSSBASIS OR ONEBASIS
  #   - model: THE FITTED MODEL
  #   - coef AND vcov: COEF AND VCOV FOR basis IF model IS NOT PROVIDED
  #
  #   - at: A NUMERIC VECTOR OF x VALUES OVER WHICH THE MINIMUM IS SOUGHT
  #   OR
  #   - from, to: RANGE OF x VALUES OVER WHICH THE MINIMUM IS SOUGHT.
  #   - by: INCREMENT OF THE SEQUENCES x VALUES OVER WHICH THE MINIMUM IS SOUGHT
  #
  #   - sim: IF BOOTSTRAP SIMULATION SAMPLES SHOULD BE RETURNED
  #   - nsim: NUMBER OF SIMULATION SAMPLES
  ##############################################################################



  ##############################################################################
  # CREATE THE BASIS AND EXTRACT COEF-VCOV
  #
  # CHECK AND DEFINE BASIS
  if(!any(class(basis)%in%c("crossbasis","onebasis")))
    stop("the first argument must be an object of class 'crossbasis' or 'onebasis'")
  #
  # INFO
  one <- any(class(basis)%in%c("onebasis"))
  attr <- attributes(basis)
```

```
range <- attr(basis,"range")
if(is.null(by)) by <- 0.1
lag <- if(one) c(0,0) else cb=attr(basis,"lag")
if(is.null(model)&&(is.null(coef)||is.null(vcov)))
  stop("At least 'model' or 'coef'-'vcov' must be provided")
name <- deparse(substitute(basis))
cond <- if(one) paste(name,"[[:print:]]*b[0-9]{1,2}",sep="") else
  paste(name,"[[:print:]]*v[0-9]{1,2}\\.1[0-9]{1,2}",sep="")
#
# SET COEF, VCOV CLASS AND LINK
if(!is.null(model)) {
  model.class <- class(model)
  coef <- dlnm:::getcoef(model,model.class)
  ind <- grep(cond,names(coef))
  coef <- coef[ind]
  vcov <- dlnm:::getvcov(model,model.class)[ind,ind,drop=FALSE]
  model.link <- dlnm:::getlink(model,model.class)
} else model.class <- NA
#
# CHECK
if(length(coef)!=ncol(basis) || length(coef)!=dim(vcov)[1] ||
   any(is.na(coef)) || any(is.na(vcov)))
  stop("model or coef/vcov not consistent with basis")
#
# DEFINE at
at <- dlnm:::mkat(at,from,to,by,range,lag,bylag=1)
predvar <- if(is.matrix(at)) rownames(at) else at
predlag <- dlnm:::seqlag(lag,by=1)
#
# CREATE THE MATRIX OF TRANSFORMED CENTRED VARIABLES (DEPENDENT ON TYPE)
type <- if(one) "one" else "cb"
Xpred <- dlnm:::mkXpred(type,basis,at,predvar,predlag,cen=NULL)
Xpredall <- 0
for(i in seq(length(predlag))) {
  ind <- seq(length(predvar))+length(predvar)*(i-1)
  Xpredall <- Xpredall + Xpred[ind,,drop=FALSE]
}
#
################################################################################
# FIND THE MINIMUM
#
pred <- drop(Xpredall%*%coef)
ind <- which.min(pred)
min <- predvar[ind]
#
################################################################################
# SIMULATIONS
#
if(sim) {
  # SIMULATE COEFFICIENTS
  k <- length(coef)
  eigen <- eigen(vcov)
  X <- matrix(rnorm(length(coef)*nsim),nsim)
```

```
    coefsim <- coef + eigen$vectors %*% diag(sqrt(eigen$values),k) %*% t(X)
    # COMPUTE MINIMUM
    minsim <- apply(coefsim,2,function(coefi) {
      pred <- drop(Xpredall%*%coefi)
      ind <- which.min(pred)
      return(predvar[ind])
    })
  }
  #
  ################################################################################
  #
  res <- if(sim) minsim else min
  #
  return(res)
}


##----------------------------------------------------------------------------------------####
## 2. FUNCTION TO ESTIMATE MAXIMUM OF A EXPOSURE-RESPONSE FUNCTION FROM A FITTED MODEL ####
##----------------------------------------------------------------------------------------####

findmax <- function(basis,model=NULL,coef=NULL,vcov=NULL,at=NULL,from=NULL,
                    to=NULL,by=NULL,sim=FALSE,nsim=5000) {
  #
  ################################################################################
  #   Adapted from R code findmin()
  #   ARGUMENTS:
  #   - basis: A SPLINE OR OTHER BASIS FOR AN EXPOSURE x CREATED BY DLNM FUNCTION
  #            CROSSBASIS OR ONEBASIS
  #   - model: THE FITTED MODEL
  #   - coef AND vcov: COEF AND VCOV FOR basis IF model IS NOT PROVIDED
  #
  #   - at: A NUMERIC VECTOR OF x VALUES OVER WHICH THE MINIMUM IS SOUGHT
  #   OR

  #   - from, to: RANGE OF x VALUES OVER WHICH THE MINIMUM IS SOUGHT.
  #   - by: INCREMENT OF THE SEQUENCES x VALUES OVER WHICH THE MINIMUM IS SOUGHT
  #
  #   - sim: IF BOOTSTRAP SIMULATION SAMPLES SHOULD BE RETURNED
  #   - nsim: NUMBER OF SIMULATION SAMPLES
  ################################################################################


  ################################################################################
  # CREATE THE BASIS AND EXTRACT COEF-VCOV
  #
  # CHECK AND DEFINE BASIS
  if(!any(class(basis)%in%c("crossbasis","onebasis")))
    stop("the first argument must be an object of class 'crossbasis' or 'onebasis'")
  #
  # INFO
  one <- any(class(basis)%in%c("onebasis"))
  attr <- attributes(basis)
```

```
range <- attr(basis,"range")
if(is.null(by)) by <- 0.1
lag <- if(one) c(0,0) else cb=attr(basis,"lag")
if(is.null(model)&&(is.null(coef)||is.null(vcov)))
  stop("At least 'model' or 'coef'-'vcov' must be provided")
name <- deparse(substitute(basis))
cond <- if(one) paste(name,"[[:print:]]*b[0-9]{1,2}",sep="") else
  paste(name,"[[:print:]]*v[0-9]{1,2}\\.1[0-9]{1,2}",sep="")
#
# SET COEF, VCOV CLASS AND LINK
if(!is.null(model)) {
  model.class <- class(model)
  coef <- dlnm:::getcoef(model,model.class)
  ind <- grep(cond,names(coef))
  coef <- coef[ind]
  vcov <- dlnm:::getvcov(model,model.class)[ind,ind,drop=FALSE]
  model.link <- dlnm:::getlink(model,model.class)
} else model.class <- NA
#
# CHECK
if(length(coef)!=ncol(basis) || length(coef)!=dim(vcov)[1] ||
   any(is.na(coef)) || any(is.na(vcov)))
  stop("model or coef/vcov not consistent with basis")
#
# DEFINE at
at <- dlnm:::mkat(at,from,to,by,range,lag,bylag=1)
predvar <- if(is.matrix(at)) rownames(at) else at
predlag <- dlnm:::seqlag(lag,by=1)
#
# CREATE THE MATRIX OF TRANSFORMED CENTRED VARIABLES (DEPENDENT ON TYPE)
type <- if(one) "one" else "cb"
Xpred <- dlnm:::mkXpred(type,basis,at,predvar,predlag,cen=NULL)
Xpredall <- 0
for(i in seq(length(predlag))) {
  ind <- seq(length(predvar))+length(predvar)*(i-1)
  Xpredall <- Xpredall + Xpred[ind,,drop=FALSE]
}
#
################################################################################
# FIND THE MINIMUM
#
pred <- drop(Xpredall%*%coef)
ind <- which.max(pred)
min <- predvar[ind]
#
################################################################################
# SIMULATIONS
#
if(sim) {
  # SIMULATE COEFFICIENTS
  k <- length(coef)
  eigen <- eigen(vcov)
  X <- matrix(rnorm(length(coef)*nsim),nsim)
```

```
    coefsim <- coef + eigen$vectors %*% diag(sqrt(eigen$values),k) %*% t(X)
    # COMPUTE MINIMUM
    minsim <- apply(coefsim,2,function(coefi) {
      pred <- drop(Xpredall%*%coefi)
      ind <- which.max(pred)
      return(predvar[ind])
    })
  }
  #
  ################################################################################
  #
  res <- if(sim) minsim else min
  #
  return(res)
}


##-------------------------------------------------------------------------------------------####
## 3. FUNCTION OF CASE-CROSSOVER ANALYSIS                                                     ####
##-------------------------------------------------------------------------------------------####

casecrs <- function (status, id, confounder=NULL, lag, varper, lagnk, cen=list(min=NULL,max=NULL,degree=
                     estpct, data){

  ## Input: status, id, confounder: variables used to define the formula applied to clogit() in the for
  ##                                case.status~exposure+confounder+strata(matched.set)
  ##                                status: case status, 1=case, 0=control
  ##                                id: ID for participants
  ##                                confounder: optional, vector of covariates to be included in the mo
  ##        lag: the maximum lag in the cross basis
  ##        varper: numeric vector of percentiles of the distribution of temperature for internal knots
  ##        lagnk: the number of internal knots in the lag-response dimension
  ##        cen: a list to define the centering temperature
  ##            - "min" and "max": optional, "TRUE" if the minimum or maximum mortality temperature to
  ##            - "degree": optional, numeric vector of temperature (?C)
  ##        estpct: numeric vector of percentiles of temperature distributions for effect estimate comp


  ## Build cross-basis function of temperature and lags
  ## Note: (1) exposure-response: natural cubic spline with internal knots placed at percentile of the
  ##                              distribution as defined by "varper"
  ##       (2) lag-response: natural cubic spline with an intercept and n="lag" internal knots placed a
  ##                         equally spaced values on the log scale

  ## 1. delete observations with NA in temperature
  dat <- subset(mort,rowSums(is.na(mort[which(names(mort)%in%paste0("temp_s",0:lag))]))==0)
  ## 2. extract matrix of temperature at lag0 to lag="lag"
  mat_temp <- as.matrix(dplyr::select(dat,paste0("temp_s",0:lag)))
  ## 3. define basis for temperature
  argvar <- list(fun="ns",knots=quantile(mat_temp,varper/100,na.rm=T))
  ## 4. define basis for lag
  arglag <- list(fun="ns",knots=logknots(lag,lagnk))
  ## 5. build the cross-basis function
```

```r
cb_temp <- crossbasis(mat_temp,lag=c(0,lag),argvar=argvar,arglag = arglag)

## Different percentile of the temperature matrix
tper <- quantile(mat_temp,seq(0,100,1)/100)

## Temperature summary for case days
tsum_case <- summary(subset(dat,status==1)$temp_s0)
tsum_case["SD"] <- sd(subset(dat,status==1)$temp_s0)

## Temperature summary for control days
tsum_control <- summary(subset(dat,status==0)$temp_s0)
tsum_control["SD"] <- sd(subset(dat,status==0)$temp_s0)

## Conditional logistic regression ####
## Note: "clogit" function in the "survival" package (same output as "clogistic" in "Epi" package)

if (is.null(confounder)==F){
  fml <- as.formula(paste0(status,"~cb_temp+strata(",id,")+",paste0(confounder,collapse = "+")))
} else {
  fml <- as.formula(paste0(status,"~cb_temp+strata(",id,")"))
}
mod <- clogit(fml,data=dat)

# Reduction to overall cumulative (it is irrelevant the cen value)
red <- crossreduce(cb_temp, mod, cen = 20)
# Store reduced coefs
coef <- coef(red)
vcov <- vcov(red)

## centering temperature
cen_temp <- NULL;cen_name <- NULL

if (is.null(cen$min)==F){
  cen_temp <- c(cen_temp,findmin(cb_temp,mod))
  cen_name <- c(cen_name,"min")
}
if (is.null(cen$max)==F){
  cen_temp <- c(cen_temp,findmax(cb_temp,mod))
  cen_name <- c(cen_name,"max")
}
if (is.null(cen$degree)==F){
  cen_temp <- c(cen_temp,cen$degree)
  cen_name <- c(cen_name,paste0(cen$degree," degree"))
}
if (is.null(cen$pct)==F){
  cen_temp <- c(cen_temp,quantile(mat_temp,cen$pct/100))
  cen_name <- c(cen_name,paste0(cen$pct,"th"))
}

## Predict ORs from each cen_temp to each estpct
estimate <- list()
for (k in 1:length(cen_temp)){
  pred <- crosspred(cb_temp, mod, model.link="logit", cen=cen_temp[k], at=quantile(mat_temp,estpct/10
```

```
    estimate[[k]] <-  round(data.frame(OR=pred$allRRfit,CIlow=pred$allRRlow,CIhigh=pred$allRRhigh),3)
    estimate[[k]]$temp <- as.numeric(rownames(estimate[[k]]))
    estimate[[k]]$perc <- paste0(estpct,"th")
    estimate[[k]]$cen <- cen_name[k]
    estimate[[k]] <- dplyr::select(estimate[[k]],c(cen,perc,temp,everything()))
  }
  estimate_all <- do.call(rbind,estimate)
  rownames(estimate_all) <- NULL

  ## output:result, a list containing the following elements
  ##        - n_case: number of cases
  ##        - n_control: number of controls
  ##        - tper: temperature distribution (percentiles)
  ##        - tsum_case: summary of temperature on case days
  ##        - tsum_control: summary of temperature on case days
  ##        - coef: coefficients for the overall association
  ##        - vcov: variance-covariance of coefs for overall association
  ##        - estimate: OR and CI at the "estpct" percentile of temperature distribution compared to ea
  ##        output for plots
  ##        - mat_temp: matrix of temperature
  ##        - cb_temp: cross-basis of temperature
  ##        - model_coef: coefficients of conditional logistic regression model
  ##        - model_vcov: variance matrix of conditional logistic regression model

  result <- NULL
  result$n_case <- nrow(subset(dat,status==1))
  result$n_control <- nrow(subset(dat,status==0))
  result$tper <- tper
  result$tsum_case <- tsum_case
  result$tsum_control <- tsum_control
  result$coef <- coef
  result$vcov <- vcov
  result$estimate <- estimate_all
  result$mat_temp <- mat_temp
  result$cb_temp <- cb_temp
  result$model_coef <- mod$coefficients
  result$model_vcov <- mod$var
  return(result)
}




##-------------------------------------------------------------------------------------####
## 4. FUNCTION OF CASE-CROSSOVER ANALYSIS FOR SUMMER MONTHS (LAG01)                    ####
##-------------------------------------------------------------------------------------####

casecrs_lag01 <- function (status, id, confounder=NULL, lag, varper, cen=list(min=NULL,max=NULL,degree=
                           estpct, data){

  ## Input: status, id, confounder: variables used to define the formula applied to clogit() in the for
  ##                                case.status~exposure+confounder+strata(matched.set)
  ##                                status: case status, 1=case, 0=control
```

```
##                                id: ID for participants
##                                confounder: optional, vector of covariates to be included in the mo
##        lag: the maximum lag in the cross basis
##        varper: numeric vector of percentiles of the distribution of temperature for internal knots
##        cen: a list to define the centering temperature
##            - "min" and "max": optional, "TRUE" if the minimum or maximum mortality temperature to
##            - "degree": optional, numeric vector of temperature (?C)
##            - "pct": optional, numeric vector of the percentiles of temperature distribution
##        estpct: numeric vector of percentiles of temperature distributions for effect estimate comp


## Build cross-basis function of temperature and lags
## Note: (1) exposure-response: natural cubic spline with internal knots placed at percentile of the
##                              distribution as defined by "varper"
##       (2) lag-response: natural cubic spline

## 1. delete observations with NA in temperature
dat <- subset(data,rowSums(is.na(data[which(names(data)%in%paste0("temp_s",0:lag))]))==0)
## 2. extract matrix of temperature at lag0 to lag="lag"
mat_temp <- as.matrix(dplyr::select(dat,paste0("temp_s",0:lag)))
## 3. define basis for temperature
argvar <- list(fun="ns",knots=quantile(mat_temp,varper/100,na.rm=T))
## 4. define basis for lag
arglag <- list(fun="ns")
## 5. build the cross-basis function
cb_temp <- crossbasis(mat_temp,lag=c(0,lag),argvar=argvar,arglag = arglag)

## Different percentile of the temperature matrix
tper <- quantile(mat_temp,seq(0,100,1)/100)

## Temperature summary for case days
tsum_case <- summary(subset(dat,status==1)$temp_s0)
tsum_case["SD"] <- sd(subset(dat,status==1)$temp_s0)

## Temperature summary for control days
tsum_control <- summary(subset(dat,status==0)$temp_s0)
tsum_control["SD"] <- sd(subset(dat,status==0)$temp_s0)

## Conditional logistic regression ####
## Note: "clogit" function in the "survival" package (same output as "clogistic" in "Epi" package)

if (is.null(confounder)==F){
  fml <- as.formula(paste0(status,"~cb_temp+strata(",id,")+",paste0(confounder,collapse = "+")))
} else {
  fml <- as.formula(paste0(status,"~cb_temp+strata(",id,")"))
}
mod <- clogit(fml,data=dat)

# Reduction to overall cumulative (it is irrelevant the cen value)
red <- crossreduce(cb_temp, mod, cen = 20)
# Store reduced coefs
coef <- coef(red)
vcov <- vcov(red)
```

```r
## centering temperature
cen_temp <- NULL;cen_name <- NULL

if (is.null(cen$min)==F){
  cen_temp <- c(cen_temp,findmin(cb_temp,mod))
  cen_name <- c(cen_name,"min")
}
if (is.null(cen$max)==F){
  cen_temp <- c(cen_temp,findmax(cb_temp,mod))
  cen_name <- c(cen_name,"max")
}
if (is.null(cen$degree)==F){
  cen_temp <- c(cen_temp,cen$degree)
  cen_name <- c(cen_name,paste0(cen$degree," degree"))
}
if (is.null(cen$pct)==F){
  cen_temp <- c(cen_temp,quantile(mat_temp,cen$pct/100))
  cen_name <- c(cen_name,paste0(cen$pct,"th"))
}

## Predict ORs from each cen_temp to each estpct
estimate <- list()
for (k in 1:length(cen_temp)){
  pred <- crosspred(cb_temp, mod, model.link="logit", cen=cen_temp[k], at=quantile(mat_temp,estpct/100
  estimate[[k]] <-  round(data.frame(OR=pred$allRRfit,CIlow=pred$allRRlow,CIhigh=pred$allRRhigh),3)
  estimate[[k]]$temp <- as.numeric(rownames(estimate[[k]]))
  estimate[[k]]$perc <- paste0(estpct,"th")
  estimate[[k]]$cen <- cen_name[k]
  estimate[[k]] <- dplyr::select(estimate[[k]],c(cen,perc,temp,everything()))
}
estimate_all <- do.call(rbind,estimate)
rownames(estimate_all) <- NULL

## output:result, a list containing the following elements
##        - n_case: number of cases
##        - n_control: number of controls
##        - tper: temperature distribution (percentiles)
##        - tsum_case: summary of temperature on case days
##        - tsum_control: summary of temperature on case days
##        - coef: coefficients for the overall association
##        - vcov: variance-covariance of coefs for overall association
##        - estimate: OR and CI at the "estpct" percentile of temperature distribution compared to ea
##        output for plots
##        - mat_temp: matrix of temperature
##        - cb_temp: cross-basis of temperature
##        - model_coef: coefficients of conditional logistic regression model
##        - model_vcov: variance matrix of conditional logistic regression model

result <- NULL
result$n_case <- nrow(subset(dat,status==1))
result$n_control <- nrow(subset(dat,status==0))
result$tper <- tper
result$tsum_case <- tsum_case
```

```
  result$tsum_control <- tsum_control
  result$coef <- coef
  result$vcov <- vcov
  result$estimate <- estimate_all
  result$mat_temp <- mat_temp
  result$cb_temp <- cb_temp
  result$model_coef <- mod$coefficients
  result$model_vcov <- mod$var
  return(result)
}



##-------------------------------------------------------------------------------------------####
## 5. crossreduce_int FUNCTION FOR INTERACTION ANALYSIS: 2 CATEGORIES                        ####
## Adapted from crossreduce_int_2APcats by Kai
## https://github.com/CHENlab-Yale/Two-way_effect_modifications/blob/master/crossreduce_int_2APcats.R
##-------------------------------------------------------------------------------------------####
crossreduce_int_2cats <- function (basis, model = NULL, type = "overall", value = NULL,
                                   coef = NULL, vcov = NULL, model.link = NULL, at = NULL, from = NULL,
                                   to = NULL, by = NULL, lag, bylag = 1, cen = NULL, ci.level = 0.95)
{
  if (all(class(basis) != "crossbasis")) {
    stop("the first argument must be an object of class 'crossbasis'")
  }
  name <- deparse(substitute(basis))
  attr <- attributes(basis)
  if (ncol(basis) == 1)
    cond <- name
  if (is.null(model) && (is.null(coef) || is.null(vcov))) {
    stop("At least 'model' or 'coef'-'vcov' must be provided")
  }
  type <- match.arg(type, c("overall", "var", "lag"))
  if (type != "overall") {
    if (is.null(value))
      stop("'value' must be provided for type 'var' or 'lag'")
    else if (!is.numeric(value) || length(value) > 1) {
      stop("'value' must be a numeric scalar")
    }
    if (type == "lag" && (any(value < attr$lag[1]) || any(value >
                                                          attr$lag[2]))) {
      stop("'value' of lag-specific effects must be within the lag range")
    }
  } else value <- NULL
  lag <- attr$lag
  if (lag != attr$lag && attr$arglag$fun == "integer")
    stop("prediction for lag sub-period not allowed for type 'integer'")
  if (!is.numeric(ci.level) || ci.level >= 1 || ci.level <=
      0) {
    stop("'ci.level' must be numeric and between 0 and 1")
  }
  cond <- if (ncol(basis) == 1L) name else
    paste(name, "[[:print:]]*v[0-9]{1,2}\\.l[0-9]{1,2}", sep = "")
```

```
cond.modif_cat2 <-  paste(name, "[[:print:]]*v[0-9]{1,2}\\.l[0-9]{1,2}\\:modif_cat2",
                          sep = "")

if (!is.null(model)) {
  model.class <- class(model)
  coef <- dlnm:::getcoef(model, model.class)
  ind.all <- grep(cond, names(coef))
  ind.modif_cat2 <- grep(cond.modif_cat2, names(coef))
  ind.main <- ind.all[ind.all != ind.modif_cat2]

  ### Extract the coef and vcov from the interaction model for modif categories
  coef.main <- coef[ind.main]
  coef.int_cat2 <- coef[ind.modif_cat2]
  ##vcov for modif categories
  vcov.all <- dlnm:::getvcov(model, model.class)
  vcov.main <- dlnm:::getvcov(model, model.class)[ind.main, ind.main, drop = FALSE]
  vcov.int_cat2 <- dlnm:::getvcov(model, model.class)[ind.modif_cat2, ind.modif_cat2, drop = FALSE]

  #cat=1
  coef_modifcat1 <- coef.main
  vcov_modifcat1 <- vcov.main
  #cat=2
  coef_modifcat2 <- coef_modifcat1+coef.int_cat2
  ####Important!! note that for interaction analysis, vcov(b1*b2)=var(b1)+var(b2)+2cov(b1,b2)
  ####This is only correct for cov(b1, b2) == cov(b2, b1); otherwise(like here), must using cov(b1, b
  vcov_modifcat2 <- vcov_modifcat1+vcov.int_cat2+dlnm:::getvcov(model, model.class)[ind.main, ind.modi
    dlnm:::getvcov(model, model.class)[ind.modif_cat2, ind.main, drop=FALSE]

  #model.link
  model.link <- dlnm:::getlink(model, model.class)
}
else model.class <- NA
npar <- ncol(basis)
range <- attr$range
at <- dlnm:::mkat(at, from, to, by, range, lag, bylag)
cen <- dlnm:::mkcen(cen, type = "cb", basis, range)
attributes(basis)$argvar$cen <- attr$argvar$cen <- NULL
if (type == "overall") {
  lagbasis <- do.call("onebasis", c(list(x = dlnm:::seqlag(lag)),
                                    attr$arglag))
  M <- diag(ncol(basis)/ncol(lagbasis)) %x% (t(rep(1, diff(lag) +
                                                     1)) %*% lagbasis)
  newbasis <- do.call("onebasis", c(list(x = at), attr$argvar))
  if (!is.null(cen)) {
    basiscen <- do.call("onebasis", c(list(x = cen),
                                      attr$argvar))
    newbasis <- scale(newbasis, center = basiscen, scale = FALSE)
  }
}
else if (type == "lag") {
  lagbasis <- do.call("onebasis", c(list(x = value), attr$arglag))
  M <- diag(ncol(basis)/ncol(lagbasis)) %x% lagbasis
  newbasis <- do.call("onebasis", c(list(x = at), attr$argvar))
```

```
  if (!is.null(cen)) {
    basiscen <- do.call("onebasis", c(list(x = cen),
                                      attr$argvar))
    newbasis <- scale(newbasis, center = basiscen, scale = FALSE)
  }
}
else if (type == "var") {
  varbasis <- do.call("onebasis", c(list(x = value), attr$argvar))
  if (!is.null(cen)) {
    basiscen <- do.call("onebasis", c(list(x = cen),
                                      attr$argvar))
    varbasis <- scale(varbasis, center = basiscen, scale = FALSE)
  }
  M <- varbasis %x% diag(ncol(basis)/ncol(varbasis))
  newbasis <- do.call("onebasis", c(list(x = seqlag(lag,
                                                    bylag)), attr$arglag))
}
dimnames(newbasis) <- list(seq(nrow(newbasis)), paste0("b",
                                                       seq(ncol(newbasis))))
##cat=1
newcoef_modifcat1 <- as.vector(M %*% coef_modifcat1)
names(newcoef_modifcat1) <- colnames(newbasis)
newvcov_modifcat1 <- M %*% vcov_modifcat1 %*% t(M)
dimnames(newvcov_modifcat1) <- list(colnames(newbasis), colnames(newbasis))
fit_modifcat1 <- as.vector(newbasis %*% newcoef_modifcat1)
se_modifcat1 <- sqrt(pmax(0, rowSums((newbasis %*% newvcov_modifcat1) * newbasis)))

if (type == "var") {
  names(fit_modifcat1) <- names(se_modifcat1) <- outer("lag", seqlag(lag, bylag),
                                                       paste, sep = "")
}
else names(fit_modifcat1) <- names(se_modifcat1) <- at

##cat=2
newcoef_modifcat2 <- as.vector(M %*% coef_modifcat2)
names(newcoef_modifcat2) <- colnames(newbasis)
newvcov_modifcat2 <- M %*% vcov_modifcat2 %*% t(M)
dimnames(newvcov_modifcat2) <- list(colnames(newbasis), colnames(newbasis))
fit_modifcat2 <- as.vector(newbasis %*% newcoef_modifcat2)
se_modifcat2 <- sqrt(pmax(0, rowSums((newbasis %*% newvcov_modifcat2) * newbasis)))

if (type == "var") {
  names(fit_modifcat2) <- names(se_modifcat2) <- outer("lag", seqlag(lag, bylag),
                                                       paste, sep = "")
}
else names(fit_modifcat2) <- names(se_modifcat2) <- at


##result list
list <- list(coef_modifcat1 = newcoef_modifcat1, vcov_modifcat1 = newvcov_modifcat1,
             coef_modifcat2 = newcoef_modifcat2, vcov_modifcat2 = newvcov_modifcat2,
             basis = newbasis, type = type, value = value)
if (type != "var")
```

```
    list$predvar <- at
  if (!is.null(cen))
    list$cen <- cen
  list <- c(list, list(lag = lag, bylag = bylag, fit_modifcat1 = fit_modifcat1, se_modifcat1 = se_modif
                       fit_modifcat2 = fit_modifcat2, se_modifcat2 = se_modifcat2))

  z <- qnorm(1 - (1 - ci.level)/2)
  if (model.link %in% c("log", "logit")) {
    #cat=1
    list$RRfit_modifcat1 <- exp(fit_modifcat1)
    list$RRlow_modifcat1 <- exp(fit_modifcat1 - z * se_modifcat1)
    names(list$RRlow_modifcat1) <- names(fit_modifcat1)
    list$RRhigh_modifcat1 <- exp(fit_modifcat1 + z * se_modifcat1)
    names(list$RRhigh_modifcat1) <- names(fit_modifcat1)
    #cat=2
    list$RRfit_modifcat2 <- exp(fit_modifcat2)
    list$RRlow_modifcat2 <- exp(fit_modifcat2 - z * se_modifcat2)
    names(list$RRlow_modifcat2) <- names(fit_modifcat2)
    list$RRhigh_modifcat2 <- exp(fit_modifcat2 + z * se_modifcat2)
    names(list$RRhigh_modifcat2) <- names(fit_modifcat2)
  }
  else {
    #cat1
    list$low_modifcat1 <- fit_modifcat1 - z * se_modifcat1
    names(list$low_modifcat1) <- names(fit_modifcat1)
    list$high_modifcat1 <- fit_modifcat1 + z * se_modifcat1
    names(list$high_modifcat1) <- names(fit_modifcat1)
    #cat2
    list$low_modifcat2 <- fit_modifcat2 - z * se_modifcat2
    names(list$low_modifcat2) <- names(fit_modifcat2)
    list$high_modifcat2 <- fit_modifcat2 + z * se_modifcat2
    names(list$high_modifcat2) <- names(fit_modifcat2)
  }
  list$ci.level <- ci.level
  list$model.class <- model.class
  list$model.link <- model.link
  class(list) <- "crossreduce"
  return(list)
}




##-------------------------------------------------------------------------------------------####
## 6. FUNCTION OF CASE-CROSSOVER EFFECT MODIFICATION: 2 CATEGORIES                           ####
##-------------------------------------------------------------------------------------------####

casecrs_int_2cats <- function (status, id, modif, confounder=NULL, lag, varper, lagnk, cen=list(degree=
                               estpct, data){

  ## Input: status, id, modif_cat, confounder: variables used to define the formula applied to clogit()
  ##                                case.status~exposure*modif+confounder+strata(matched.set)
  ##                                status: case status, 1=case, 0=control
```

```
##                                id: ID for participants
##                                modif: effect modifier with two categories
##                                confounder: optional, vector of covariates to be included in the mo
##        lag: the maximum lag in the cross basis
##        varper: numeric vector of percentiles of the distribution of temperature for internal knots
##        lagnk: the number of internal knots in the lag-response dimension
##        cen: a list to define the centering temperature
##            - "degree": optional, numeric vector of temperature (?C)
##            - "pct": optional, numeric vector of the percentiles of temperature distribution
##        estpct: numeric vector of percentiles of temperature distributions for effect estimate comp


## Build cross-basis function of temperature and lags
## Note: (1) exposure-response: natural cubic spline with internal knots placed at percentile of the
##                              distribution as defined by "varper"
##       (2) lag-response: natural cubic spline with an intercept and n="lag" internal knots placed a
##                         equally spaced values on the log scale

## 1. delete observations with NA in temperature and effect modifier
dat <- subset(data,rowSums(is.na(data[which(names(data)%in%c(paste0("temp_s",0:lag),modif))]))==0)
## 2. define the effect modifier
dat$modif_cat <- dat[,modif]
dat$modif_cat <- as.factor(dat$modif_cat)
dat$modif_cat <- ifelse(dat$modif_cat==levels(dat$modif_cat)[1],1,2)
dat$modif_cat <- as.factor(dat$modif_cat)
## 3. extract matrix of temperature at lag0 to lag="lag"
mat_temp <- as.matrix(dplyr::select(dat,paste0("temp_s",0:lag)))
## 4. define basis for temperature
argvar <- list(fun="ns",knots=quantile(mat_temp,varper/100,na.rm=T))
## 5. define basis for lag
arglag <- list(fun="ns",knots=logknots(lag,lagnk))
## 6. build the cross-basis function
cb_temp <- crossbasis(mat_temp,lag=c(0,lag),argvar=argvar,arglag = arglag)
## 7. build the one-basis function for temperature
b1temp <- onebasis(mat_temp, fun="ns", knots=quantile(mat_temp,varper/100,na.rm=T))

## Different percentile of the temperature matrix
tper <- quantile(mat_temp,seq(0,100,1)/100)

## Temperature summary for case days in the first subgroup
tsum_cat1 <- summary(subset(dat,status==1&modif_cat==1)$temp_s0)
tsum_cat1["SD"] <- sd(subset(dat,status==1&modif_cat==1)$temp_s0)

## Temperature summary for case days in the second subgroup
tsum_cat2 <- summary(subset(dat,status==1&modif_cat==2)$temp_s0)
tsum_cat2["SD"] <- sd(subset(dat,status==1&modif_cat==2)$temp_s0)

## Conditional logistic regression ####
## Note: "clogit" function in the "survival" package (same output as "clogistic" in "Epi" package)

if (is.null(confounder)==F){
  fml <- as.formula(paste0(status,"~cb_temp*modif_cat+strata(",id,")+",paste0(confounder,collapse = "+
} else {
```

```
  fml <- as.formula(paste0(status,"~cb_temp*modif_cat+strata(",id,")"))
}

mod <- try(clogit(fml,data=dat), silent=TRUE)

if (class(mod)[1]!="try-error"){
  # Reduction to overall cumulative (it is irrelevant the cen value)
  red <- crossreduce_int_2cats(cb_temp, mod, cen = 20)
  # Store reduced coefs
  #cat1
  coef.cat1 <- red$coef_modifcat1
  vcov.cat1 <- red$vcov_modifcat1
  #cat2
  coef.cat2 <- red$coef_modifcat2
  vcov.cat2 <- red$vcov_modifcat2

  ## centering temperature
  cen_temp <- NULL;cen_name <- NULL

  if (is.null(cen$degree)==F){
    cen_temp <- c(cen_temp,cen$degree)
    cen_name <- c(cen_name,paste0(cen$degree," degree"))
  }
  if (is.null(cen$pct)==F){
    cen_temp <- c(cen_temp,quantile(mat_temp,cen$pct/100))
    cen_name <- c(cen_name,paste0(cen$pct,"th"))
  }

  ## Predict ORs from each cen_temp to each estpct for each subgroup
  estimate_cat1 <- list()
  for (k in 1:length(cen_temp)){
    pred_cat1 <- crosspred(b1temp, coef=coef.cat1, vcov=vcov.cat1, model.link="logit",cen=cen_temp[k]
    estimate_cat1[[k]] <-  round(data.frame(OR=pred_cat1$allRRfit,CIlow=pred_cat1$allRRlow,CIhigh=pre
    estimate_cat1[[k]]$temp <- as.numeric(rownames(estimate_cat1[[k]]))
    estimate_cat1[[k]]$perc <- paste0(estpct,"th")
    estimate_cat1[[k]]$cen <- cen_name[k]
    estimate_cat1[[k]] <- dplyr::select(estimate_cat1[[k]],c(cen,perc,temp,everything()))
  }
  estimate_cat1_all <- do.call(rbind,estimate_cat1)
  rownames(estimate_cat1_all) <- NULL

  estimate_cat2 <- list()
  for (k in 1:length(cen_temp)){
    pred_cat2 <- crosspred(b1temp, coef=coef.cat2, vcov=vcov.cat2, model.link="logit", cen=cen_temp[k]
    estimate_cat2[[k]] <-  round(data.frame(OR=pred_cat2$allRRfit,CIlow=pred_cat2$allRRlow,CIhigh=pre
    estimate_cat2[[k]]$temp <- as.numeric(rownames(estimate_cat2[[k]]))
    estimate_cat2[[k]]$perc <- paste0(estpct,"th")
    estimate_cat2[[k]]$cen <- cen_name[k]
    estimate_cat2[[k]] <- dplyr::select(estimate_cat2[[k]],c(cen,perc,temp,everything()))
  }
  estimate_cat2_all <- do.call(rbind,estimate_cat2)
  rownames(estimate_cat2_all) <- NULL
```

```
    ## output:result, a list containing the following elements
    ##        - n_cat1: number of participants in the 1st subgroup
    ##        - n_cat2: number of participants in the 2nd subgroup
    ##        - tper: temperature distribution (percentiles)
    ##        - tsum_cat1: summary of temperature on case days for the 1st subgroup
    ##        - tsum_cat2: summary of temperature on case days for the 2nd subgroup
    ##        - coef_cat1: coefficients for the overall association for the 1st subgroup
    ##        - coef_cat2: coefficients for the overall association for the 2nd subgroup
    ##        - vcov_cat1: variance-covariance of coefs for overall association for the 1st subgroup
    ##        - vcov_cat2: variance-covariance of coefs for overall association for the 2nd subgroup
    ##        - estimate_cat1: OR and CI at the "estpct" percentile of temperature distribution compare
    ##        - estimate_cat2: OR and CI at the "estpct" percentile of temperature distribution compare
    ##        output for plots
    ##        - mat_temp: matrix of temperature
    ##        - b1temp: one-basis of temperature

    result <- NULL
    result$n_cat1 <- nrow(subset(dat,modif_cat==1))
    result$n_cat2 <- nrow(subset(dat,modif_cat==2))
    result$tper <- tper
    result$tsum_cat1 <- tsum_cat1
    result$tsum_cat2 <- tsum_cat2
    result$coef_cat1 <- coef.cat1
    result$vcov_cat1 <- vcov.cat1
    result$coef_cat2 <- coef.cat2
    result$vcov_cat2 <- vcov.cat2
    result$estimate_cat1 <- estimate_cat1_all
    result$estimate_cat2 <- estimate_cat2_all
    result$mat_temp <- mat_temp
    result$b1temp <- b1temp
    return(result)
  } else {
    result <- NULL
    result$n_cat1 <- nrow(subset(dat,modif_cat==1))
    result$n_cat2 <- nrow(subset(dat,modif_cat==2))
    result$tper <- tper
    result$tsum_cat1 <- tsum_cat1
    result$tsum_cat2 <- tsum_cat2
    result$coef_cat1 <- NA
    result$vcov_cat1 <- NA
    result$coef_cat2 <- NA
    result$vcov_cat2 <- NA
    result$estimate_cat1 <- NA
    result$estimate_cat2 <- NA
    result$mat_temp <- NA
    result$b1temp <- NA
    return(result)
  }
}



##-------------------------------------------------------------------------------####
```

```r
## 7. crossreduce_int FUNCTION FOR INTERACTION ANALYSIS: 3 CATEGORIES                    ####
## Adapted from crossreduce_int_2APcats by Kai
## https://github.com/CHENlab-Yale/Two-way_effect_modifications/blob/master/crossreduce_int_2APcats.R
##-------------------------------------------------------------------------------------------####
crossreduce_int_3cats <- function (basis, model = NULL, type = "overall", value = NULL,
                                   coef = NULL, vcov = NULL, model.link = NULL, at = NULL, from = NULL,
                                   to = NULL, by = NULL, lag, bylag = 1, cen = NULL, ci.level = 0.95)
{
  if (all(class(basis) != "crossbasis")) {
    stop("the first argument must be an object of class 'crossbasis'")
  }
  name <- deparse(substitute(basis))
  attr <- attributes(basis)
  if (ncol(basis) == 1)
    cond <- name
  if (is.null(model) && (is.null(coef) || is.null(vcov))) {
    stop("At least 'model' or 'coef'-'vcov' must be provided")
  }
  type <- match.arg(type, c("overall", "var", "lag"))
  if (type != "overall") {
    if (is.null(value))
      stop("'value' must be provided for type 'var' or 'lag'")
    else if (!is.numeric(value) || length(value) > 1) {
      stop("'value' must be a numeric scalar")
    }
    if (type == "lag" && (any(value < attr$lag[1]) || any(value >
                                                          attr$lag[2]))) {
      stop("'value' of lag-specific effects must be within the lag range")
    }
  } else value <- NULL
  lag <- attr$lag
  if (lag != attr$lag && attr$arglag$fun == "integer")
    stop("prediction for lag sub-period not allowed for type 'integer'")
  if (!is.numeric(ci.level) || ci.level >= 1 || ci.level <=
      0) {
    stop("'ci.level' must be numeric and between 0 and 1")
  }
  cond <- if (ncol(basis) == 1L) name else
    paste(name, "[[:print:]]*v[0-9]{1,2}\\.l[0-9]{1,2}", sep = "")

  cond.modif_cat2 <-  paste(name, "[[:print:]]*v[0-9]{1,2}\\.l[0-9]{1,2}\\:modif_cat2",
                            sep = "")

  cond.modif_cat3 <-  paste(name, "[[:print:]]*v[0-9]{1,2}\\.l[0-9]{1,2}\\:modif_cat3",
                            sep = "")

  if (!is.null(model)) {
    model.class <- class(model)
    coef <- dlnm:::getcoef(model, model.class)
    ind.all <- grep(cond, names(coef))
    ind.modif_cat2 <- grep(cond.modif_cat2, names(coef))
    ind.modif_cat3 <- grep(cond.modif_cat3, names(coef))
    ind.main <- ind.all[ind.all != ind.modif_cat2&ind.all != ind.modif_cat3]
```

```
  ### Extract the coef and vcov from the interaction model for modif categories
  coef.main <- coef[ind.main]
  coef.int_cat2 <- coef[ind.modif_cat2]
  coef.int_cat3 <- coef[ind.modif_cat3]

  ##vcov for modif categories
  vcov.all <- dlnm:::getvcov(model, model.class)
  vcov.main <- dlnm:::getvcov(model, model.class)[ind.main, ind.main, drop = FALSE]
  vcov.int_cat2 <- dlnm:::getvcov(model, model.class)[ind.modif_cat2, ind.modif_cat2, drop = FALSE]
  vcov.int_cat3 <- dlnm:::getvcov(model, model.class)[ind.modif_cat3, ind.modif_cat3, drop = FALSE]

  #cat=1
  coef_modifcat1 <- coef.main
  vcov_modifcat1 <- vcov.main
  #cat=2
  coef_modifcat2 <- coef_modifcat1+coef.int_cat2
  ####Important!! note that for interaction analysis, vcov(b1*b2)=var(b1)+var(b2)+2cov(b1,b2)
  ####This is only correct for cov(b1, b2) == cov(b2, b1); otherwise(like here), must using cov(b1, b
  vcov_modifcat2 <- vcov_modifcat1+vcov.int_cat2+dlnm:::getvcov(model, model.class)[ind.main, ind.modi
    dlnm:::getvcov(model, model.class)[ind.modif_cat2, ind.main, drop=FALSE]
  #cat=3
  coef_modifcat3 <- coef_modifcat1+coef.int_cat3
  ####Important!! note that for interaction analysis, vcov(b1*b2)=var(b1)+var(b2)+2cov(b1,b2)
  ####This is only correct for cov(b1, b2) == cov(b2, b1); otherwise(like here), must using cov(b1, b
  vcov_modifcat3 <- vcov_modifcat1+vcov.int_cat3+dlnm:::getvcov(model, model.class)[ind.main, ind.modi
    dlnm:::getvcov(model, model.class)[ind.modif_cat3, ind.main, drop=FALSE]
  #model.link
  model.link <- dlnm:::getlink(model, model.class)
}
else model.class <- NA
npar <- ncol(basis)
range <- attr$range
at <- dlnm:::mkat(at, from, to, by, range, lag, bylag)
cen <- dlnm:::mkcen(cen, type = "cb", basis, range)
attributes(basis)$argvar$cen <- attr$argvar$cen <- NULL
if (type == "overall") {
  lagbasis <- do.call("onebasis", c(list(x = dlnm:::seqlag(lag)),
                                    attr$arglag))
  M <- diag(ncol(basis)/ncol(lagbasis)) %x% (t(rep(1, diff(lag) +
                                                     1)) %*% lagbasis)
  newbasis <- do.call("onebasis", c(list(x = at), attr$argvar))
  if (!is.null(cen)) {
    basiscen <- do.call("onebasis", c(list(x = cen),
                                      attr$argvar))
    newbasis <- scale(newbasis, center = basiscen, scale = FALSE)
  }
}
else if (type == "lag") {
  lagbasis <- do.call("onebasis", c(list(x = value), attr$arglag))
  M <- diag(ncol(basis)/ncol(lagbasis)) %x% lagbasis
  newbasis <- do.call("onebasis", c(list(x = at), attr$argvar))
  if (!is.null(cen)) {
    basiscen <- do.call("onebasis", c(list(x = cen),
```

```
                                        attr$argvar))
    newbasis <- scale(newbasis, center = basiscen, scale = FALSE)
  }
}
else if (type == "var") {
  varbasis <- do.call("onebasis", c(list(x = value), attr$argvar))
  if (!is.null(cen)) {
    basiscen <- do.call("onebasis", c(list(x = cen),
                                        attr$argvar))
    varbasis <- scale(varbasis, center = basiscen, scale = FALSE)
  }
  M <- varbasis %x% diag(ncol(basis)/ncol(varbasis))
  newbasis <- do.call("onebasis", c(list(x = seqlag(lag,
                                                    bylag)), attr$arglag))
}
dimnames(newbasis) <- list(seq(nrow(newbasis)), paste0("b",
                                                       seq(ncol(newbasis))))
##cat=1
newcoef_modifcat1 <- as.vector(M %*% coef_modifcat1)
names(newcoef_modifcat1) <- colnames(newbasis)
newvcov_modifcat1 <- M %*% vcov_modifcat1 %*% t(M)
dimnames(newvcov_modifcat1) <- list(colnames(newbasis), colnames(newbasis))
fit_modifcat1 <- as.vector(newbasis %*% newcoef_modifcat1)
se_modifcat1 <- sqrt(pmax(0, rowSums((newbasis %*% newvcov_modifcat1) * newbasis)))

if (type == "var") {
  names(fit_modifcat1) <- names(se_modifcat1) <- outer("lag", seqlag(lag, bylag),
                                                       paste, sep = "")
}
else names(fit_modifcat1) <- names(se_modifcat1) <- at

##cat=2
newcoef_modifcat2 <- as.vector(M %*% coef_modifcat2)
names(newcoef_modifcat2) <- colnames(newbasis)
newvcov_modifcat2 <- M %*% vcov_modifcat2 %*% t(M)
dimnames(newvcov_modifcat2) <- list(colnames(newbasis), colnames(newbasis))
fit_modifcat2 <- as.vector(newbasis %*% newcoef_modifcat2)
se_modifcat2 <- sqrt(pmax(0, rowSums((newbasis %*% newvcov_modifcat2) * newbasis)))

if (type == "var") {
  names(fit_modifcat2) <- names(se_modifcat2) <- outer("lag", seqlag(lag, bylag),
                                                       paste, sep = "")
}
else names(fit_modifcat2) <- names(se_modifcat2) <- at

##cat=3
newcoef_modifcat3 <- as.vector(M %*% coef_modifcat3)
names(newcoef_modifcat3) <- colnames(newbasis)
newvcov_modifcat3 <- M %*% vcov_modifcat3 %*% t(M)
dimnames(newvcov_modifcat3) <- list(colnames(newbasis), colnames(newbasis))
fit_modifcat3 <- as.vector(newbasis %*% newcoef_modifcat3)
se_modifcat3 <- sqrt(pmax(0, rowSums((newbasis %*% newvcov_modifcat3) * newbasis)))
```

```
if (type == "var") {
  names(fit_modifcat3) <- names(se_modifcat3) <- outer("lag", seqlag(lag, bylag),
                                                       paste, sep = "")
}
else names(fit_modifcat3) <- names(se_modifcat3) <- at

##result list
list <- list(coef_modifcat1 = newcoef_modifcat1, vcov_modifcat1 = newvcov_modifcat1,
             coef_modifcat2 = newcoef_modifcat2, vcov_modifcat2 = newvcov_modifcat2,
             coef_modifcat3 = newcoef_modifcat3, vcov_modifcat3 = newvcov_modifcat3,
             basis = newbasis, type = type, value = value)
if (type != "var")
  list$predvar <- at
if (!is.null(cen))
  list$cen <- cen
list <- c(list, list(lag = lag, bylag = bylag, fit_modifcat1 = fit_modifcat1, se_modifcat1 = se_modif
                     fit_modifcat2 = fit_modifcat2, se_modifcat2 = se_modifcat2,
                     fit_modifcat3 = fit_modifcat3, se_modifcat3 = se_modifcat3))

z <- qnorm(1 - (1 - ci.level)/2)
if (model.link %in% c("log", "logit")) {
  #cat=1
  list$RRfit_modifcat1 <- exp(fit_modifcat1)
  list$RRlow_modifcat1 <- exp(fit_modifcat1 - z * se_modifcat1)
  names(list$RRlow_modifcat1) <- names(fit_modifcat1)
  list$RRhigh_modifcat1 <- exp(fit_modifcat1 + z * se_modifcat1)
  names(list$RRhigh_modifcat1) <- names(fit_modifcat1)
  #cat=2
  list$RRfit_modifcat2 <- exp(fit_modifcat2)
  list$RRlow_modifcat2 <- exp(fit_modifcat2 - z * se_modifcat2)
  names(list$RRlow_modifcat2) <- names(fit_modifcat2)
  list$RRhigh_modifcat2 <- exp(fit_modifcat2 + z * se_modifcat2)
  names(list$RRhigh_modifcat2) <- names(fit_modifcat2)
  #cat=3
  list$RRfit_modifcat3 <- exp(fit_modifcat3)
  list$RRlow_modifcat3 <- exp(fit_modifcat3 - z * se_modifcat3)
  names(list$RRlow_modifcat3) <- names(fit_modifcat3)
  list$RRhigh_modifcat3 <- exp(fit_modifcat3 + z * se_modifcat3)
  names(list$RRhigh_modifcat3) <- names(fit_modifcat3)
}
else {
  #cat1
  list$low_modifcat1 <- fit_modifcat1 - z * se_modifcat1
  names(list$low_modifcat1) <- names(fit_modifcat1)
  list$high_modifcat1 <- fit_modifcat1 + z * se_modifcat1
  names(list$high_modifcat1) <- names(fit_modifcat1)
  #cat2
  list$low_modifcat2 <- fit_modifcat2 - z * se_modifcat2
  names(list$low_modifcat2) <- names(fit_modifcat2)
  list$high_modifcat2 <- fit_modifcat2 + z * se_modifcat2
  names(list$high_modifcat2) <- names(fit_modifcat2)
  #cat3
  list$low_modifcat3 <- fit_modifcat3 - z * se_modifcat3
```

```
    names(list$low_modifcat3) <- names(fit_modifcat3)
    list$high_modifcat3 <- fit_modifcat3 + z * se_modifcat3
    names(list$high_modifcat3) <- names(fit_modifcat3)
  }
  list$ci.level <- ci.level
  list$model.class <- model.class
  list$model.link <- model.link
  class(list) <- "crossreduce"
  return(list)
}


##-------------------------------------------------------------------------------------####
## 8. FUNCTION OF CASE-CROSSOVER EFFECT MODIFICATION: 3 CATEGORIES                      ####
##-------------------------------------------------------------------------------------####

casecrs_int_3cats <- function (status, id, modif, confounder=NULL, lag, varper, lagnk, cen=list(degree=
                               estpct, data){

  ## Input: status, id, modif_cat, confounder: variables used to define the formula applied to clogit()
  ##                                case.status~exposure*modif+confounder+strata(matched.set)
  ##                                status: case status, 1=case, 0=control
  ##                                id: ID for participants
  ##                                modif: effect modifier with three categories
  ##                                confounder: optional, vector of covariates to be included in the mo
  ##        lag: the maximum lag in the cross basis
  ##        varper: numeric vector of percentiles of the distribution of temperature for internal knots
  ##        lagnk: the number of internal knots in the lag-response dimension
  ##        cen: a list to define the centering temperature
  ##            - "degree": optional, numeric vector of temperature (?C)
  ##            - "pct": optional, numeric vector of the percentiles of temperature distribution
  ##        estpct: numeric vector of percentiles of temperature distributions for effect estimate comp


  ## Build cross-basis function of temperature and lags
  ## Note: (1) exposure-response: natural cubic spline with internal knots placed at percentile of the
  ##                              distribution as defined by "varper"
  ##       (2) lag-response: natural cubic spline with an intercept and n="lag" internal knots placed a
  ##                         equally spaced values on the log scale

  ## 1. delete observations with NA in temperature and effect modifier
  dat <- subset(data,rowSums(is.na(data[which(names(data)%in%c(paste0("temp_s",0:lag),modif))]))==0)
  ## 2. define the effect modifier
  dat$modif_cat <- dat[,modif]
  dat$modif_cat <- as.factor(dat$modif_cat)
  dat$modif_cat <- ifelse(dat$modif_cat==levels(dat$modif_cat)[1],1,ifelse(dat$modif_cat==levels(dat$mo
  dat$modif_cat <- as.factor(dat$modif_cat)
  ## 3. extract matrix of temperature at lag0 to lag="lag"
  mat_temp <- as.matrix(dplyr::select(dat,paste0("temp_s",0:lag)))
  ## 4. define basis for temperature
  argvar <- list(fun="ns",knots=quantile(mat_temp,varper/100,na.rm=T))
  ## 5. define basis for lag
  arglag <- list(fun="ns",knots=logknots(lag,lagnk))
```

```r
## 6. build the cross-basis function
cb_temp <- crossbasis(mat_temp,lag=c(0,lag),argvar=argvar,arglag = arglag)
## 7. build the one-basis function for temperature
b1temp <- onebasis(mat_temp, fun="ns", knots=quantile(mat_temp,varper/100,na.rm=T))

## Different percentile of the temperature matrix
tper <- quantile(mat_temp,seq(0,100,1)/100)

## Temperature summary for case days in the first subgroup
tsum_cat1 <- summary(subset(dat,status==1&modif_cat==1)$temp_s0)
tsum_cat1["SD"] <- sd(subset(dat,status==1&modif_cat==1)$temp_s0)

## Temperature summary for case days in the second subgroup
tsum_cat2 <- summary(subset(dat,status==1&modif_cat==2)$temp_s0)
tsum_cat2["SD"] <- sd(subset(dat,status==1&modif_cat==2)$temp_s0)

## Temperature summary for case days in the third subgroup
tsum_cat3 <- summary(subset(dat,status==1&modif_cat==3)$temp_s0)
tsum_cat3["SD"] <- sd(subset(dat,status==1&modif_cat==3)$temp_s0)

## Conditional logistic regression ####
## Note: "clogit" function in the "survival" package (same output as "clogistic" in "Epi" package)

if (is.null(confounder)==F){
  fml <- as.formula(paste0(status,"~cb_temp*modif_cat+strata(",id,")+",paste0(confounder,collapse = "+
} else {
  fml <- as.formula(paste0(status,"~cb_temp*modif_cat+strata(",id,")"))
}

mod <- try(clogit(fml,data=dat), silent=TRUE)

if (class(mod)[1]!="try-error"){
  # Reduction to overall cumulative (it is irrelevant the cen value)
  red <- crossreduce_int_3cats(cb_temp, mod, cen = 20)
  # Store reduced coefs
  #cat1
  coef.cat1 <- red$coef_modifcat1
  vcov.cat1 <- red$vcov_modifcat1
  #cat2
  coef.cat2 <- red$coef_modifcat2
  vcov.cat2 <- red$vcov_modifcat2
  #cat3
  coef.cat3 <- red$coef_modifcat3
  vcov.cat3 <- red$vcov_modifcat3

  ## centering temperature
  cen_temp <- NULL;cen_name <- NULL

  if (is.null(cen$degree)==F){
    cen_temp <- c(cen_temp,cen$degree)
    cen_name <- c(cen_name,paste0(cen$degree," degree"))
  }
  if (is.null(cen$pct)==F){
```

```
  cen_temp <- c(cen_temp,quantile(mat_temp,cen$pct/100))
  cen_name <- c(cen_name,paste0(cen$pct,"th"))
}

## Predict ORs from each cen_temp to each estpct for each subgroup
estimate_cat1 <- list()
for (k in 1:length(cen_temp)){
  pred_cat1 <- crosspred(b1temp, coef=coef.cat1, vcov=vcov.cat1, model.link="logit",cen=cen_temp[k]
  estimate_cat1[[k]] <-  round(data.frame(OR=pred_cat1$allRRfit,CIlow=pred_cat1$allRRlow,CIhigh=pred
  estimate_cat1[[k]]$temp <- as.numeric(rownames(estimate_cat1[[k]]))
  estimate_cat1[[k]]$perc <- paste0(estpct,"th")
  estimate_cat1[[k]]$cen <- cen_name[k]
  estimate_cat1[[k]] <- dplyr::select(estimate_cat1[[k]],c(cen,perc,temp,everything()))
}
estimate_cat1_all <- do.call(rbind,estimate_cat1)
rownames(estimate_cat1_all) <- NULL

estimate_cat2 <- list()
for (k in 1:length(cen_temp)){
  pred_cat2 <- crosspred(b1temp, coef=coef.cat2, vcov=vcov.cat2, model.link="logit", cen=cen_temp[k
  estimate_cat2[[k]] <-  round(data.frame(OR=pred_cat2$allRRfit,CIlow=pred_cat2$allRRlow,CIhigh=pred
  estimate_cat2[[k]]$temp <- as.numeric(rownames(estimate_cat2[[k]]))
  estimate_cat2[[k]]$perc <- paste0(estpct,"th")
  estimate_cat2[[k]]$cen <- cen_name[k]
  estimate_cat2[[k]] <- dplyr::select(estimate_cat2[[k]],c(cen,perc,temp,everything()))
}
estimate_cat2_all <- do.call(rbind,estimate_cat2)
rownames(estimate_cat2_all) <- NULL

estimate_cat3 <- list()
for (k in 1:length(cen_temp)){
  pred_cat3 <- crosspred(b1temp, coef=coef.cat3, vcov=vcov.cat3, model.link="logit", cen=cen_temp[k
  estimate_cat3[[k]] <-  round(data.frame(OR=pred_cat3$allRRfit,CIlow=pred_cat3$allRRlow,CIhigh=pred
  estimate_cat3[[k]]$temp <- as.numeric(rownames(estimate_cat3[[k]]))
  estimate_cat3[[k]]$perc <- paste0(estpct,"th")
  estimate_cat3[[k]]$cen <- cen_name[k]
  estimate_cat3[[k]] <- dplyr::select(estimate_cat3[[k]],c(cen,perc,temp,everything()))
}
estimate_cat3_all <- do.call(rbind,estimate_cat3)
rownames(estimate_cat3_all) <- NULL

## output:result, a list containing the following elements
##        - n_cat1: number of participants in the 1st subgroup
##        - n_cat2: number of participants in the 2nd subgroup
##        - tper: temperature distribution (percentiles)
##        - tsum_cat1: summary of temperature on case days for the 1st subgroup
##        - tsum_cat2: summary of temperature on case days for the 2nd subgroup
##        - coef_cat1: coefficients for the overall association for the 1st subgroup
##        - coef_cat2: coefficients for the overall association for the 2nd subgroup
##        - vcov_cat1: variance-covariance of coefs for overall association for the 1st subgroup
##        - vcov_cat2: variance-covariance of coefs for overall association for the 2nd subgroup
##        - estimate_cat1: OR and CI at the "estpct" percentile of temperature distribution compare
##        - estimate_cat2: OR and CI at the "estpct" percentile of temperature distribution compare
```

```
    ##        output for plots
    ##        - mat_temp: matrix of temperature
    ##        - b1temp: one-basis of temperature

    result <- NULL
    result$n_cat1 <- nrow(subset(dat,modif_cat==1))
    result$n_cat2 <- nrow(subset(dat,modif_cat==2))
    result$n_cat3 <- nrow(subset(dat,modif_cat==3))
    result$tper <- tper
    result$tsum_cat1 <- tsum_cat1
    result$tsum_cat2 <- tsum_cat2
    result$tsum_cat3 <- tsum_cat3
    result$coef_cat1 <- coef.cat1
    result$vcov_cat1 <- vcov.cat1
    result$coef_cat2 <- coef.cat2
    result$vcov_cat2 <- vcov.cat2
    result$coef_cat3 <- coef.cat3
    result$vcov_cat3 <- vcov.cat3
    result$estimate_cat1 <- estimate_cat1_all
    result$estimate_cat2 <- estimate_cat2_all
    result$estimate_cat3 <- estimate_cat3_all
    result$mat_temp <- mat_temp
    result$b1temp <- b1temp
    return(result)
  } else {
    result <- NULL
    result$n_cat1 <- nrow(subset(dat,modif_cat==1))
    result$n_cat2 <- nrow(subset(dat,modif_cat==2))
    result$n_cat3 <- nrow(subset(dat,modif_cat==3))
    result$tper <- tper
    result$tsum_cat1 <- tsum_cat1
    result$tsum_cat2 <- tsum_cat2
    result$tsum_cat3 <- tsum_cat3
    result$coef_cat1 <- NA
    result$vcov_cat1 <- NA
    result$coef_cat2 <- NA
    result$vcov_cat2 <- NA
    result$coef_cat3 <- NA
    result$vcov_cat3 <- NA
    result$estimate_cat1 <- NA
    result$estimate_cat2 <- NA
    result$estimate_cat3 <- NA
    result$mat_temp <- NA
    result$b1temp <- NA
    return(result)
  }
}


## 9. Description of continuous variables ####
desc_con <- function(x0,digit){
  x <- x0[!is.na(x0)]
  nmin <- length(x)
```

```
  nall<-length(as.vector(x0))
  percent<-round((nall-nmin)/nall*100,digits=1)
  mean<-round(mean(x),digits=digit)
  sd <- round(sd(x),digits=digit)
  p25 <- round(quantile(x,probs=0.25),digits=digit)
  p50 <- round(quantile(x,probs=0.50),digits=digit)
  p75 <- round(quantile(x,probs=0.75),digits=digit)
  iqr <- round(p75-p25,digits=digit)
  min <- round(min(x),digits=digit)
  max <- round(max(x),digits=digit)
  out <- data.frame(N=nmin,Missing=percent,mean=mean,SD= sd,min=min,p25=p25,median=p50,p75=p75,max=max,
  out
}

## 10. Description of categorical variables ####
desc_cat <- function(x0) {
  x <- x0[!is.na(x0)]
  nmin <- length(x)
  nall<-length(as.vector(x0))
  nmiss <- nall - nmin
  percentmiss<-round(nmiss/nall*100,digits=1)

  n <- c(table(x),"NA"=nmiss)
  percent <- round(prop.table(table(x))*100,1) # ATTENTION: Percentages are calculated for reduced N!
  perc<-c(percent,percentmiss)
  out <- cbind(n,perc)
  out
}
```

APPENDIX 3

R script main interaction

5/14/2023

```
#-------------------------------------------------#
# Name: R code_short-term temperature and mortality #
# Adapted from EXHAUSTION script                   #
# Version: 02.03.2023                              #
#-------------------------------------------------#

rm(list=ls())

## Load packages to be used; Author's R version 4.1.0
library(dlnm)
library(dplyr)
library(survival)
library(splines)
library(miceadds)

## Set the working directory
path <- "N:/durable/LEVEL3_MORTALITY/"
setwd(path)

## load the functions
source("Kicki/R code_adapted/00_FUNCTION.R")


## 1. Import data sets ####

## Note: The data set should include the following variables
##       (1) status: indicator of the case (=1) or control (=0)
##       (2) temp_s0 - temp_s10: single-day lags of air temperature
##       (3) id (ID for participants): only participants who experienced events during the follow up (ca
load.RDS(filename="Kicki/R code_adapted/DATA_EXHAUSTION_HUBRO_mort.RDS","mort") #for the first dataset

mort<-DATA_EXHAUSTION_HUBRO_mort

## create data sets for each mortality outcome
mort_natural <- mort ## natural cause mortality
mort_cpd <- subset(mort,cause_death%in%c(sprintf("I%02d", 0:99),sprintf("J%02d", 0:99),as.character(390
mort_cvd <- subset(mort,cause_death%in%c(sprintf("I%02d", 0:99),as.character(390:459))) ## cardiovascul
mort_ihd <- subset(mort,cause_death%in%c(sprintf("I%02d", 20:25),as.character(410:414))) ## ischemic he
mort_cerebr <- subset(mort,cause_death%in%c(sprintf("I%02d", 60:69),as.character(430:438))) ## cerebrova
mort_resp <- subset(mort,cause_death%in%c(sprintf("J%02d", 0:99),as.character(460:519))) ## respiratory
mort_copd <- subset(mort,cause_death%in%c(sprintf("J%02d", 40:44),"J47",as.character(c(490:492,494:496))
```

```r
## create a list containing all datasets
dlist <- list(mort_natural,mort_cpd,mort_cvd,mort_ihd,mort_cerebr,mort_resp,mort_copd)
## names of the outcomes in the order of that in the dlist
name_outcome <- c("mort_natural","mort_cpd","mort_cvd","mort_ihd","mort_cerebr","mort_resp","mort_copd"


## 2. Effect estimation (refer to the function "casecrs" in "00_FUNCTION.R") ####

## output with elements for creating exposure-response curves ####
result1 <- list()

## output to be saved, not including "mat_temp" and "cb_temp" to reduce the size
out1 <- list()

for (i in 1:length(dlist)){
  mort_hubro <- dlist[[i]]
  result1[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(min=TRU
                          estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  out1[[i]] <- within(result1[[i]],rm(mat_temp,cb_temp))
}
names(result1) <- names(out1) <- name_outcome
saveRDS(out1,file = "Kicki/short-term_temp_mort_HUBRO.RDS")



## 3. Exposure-response curves ####

## e.g. natural-cause mortality
tiff("Kicki/short-term_temp_mort_natural_HUBRO.tiff",width=600,height=500) #change dataset here, exampl
layout(mat = matrix(c(1,2),2,1, byrow=TRUE),  height = c(7,3))
par(mar=c(2, 4, 1, 1))

# get the output for figures
mat_temp <- result1$mort_natural$mat_temp; cb_temp <- result1$mort_natural$cb_temp
coef <- result1$mort_natural$model_coef; vcov <- result1$mort_natural$model_vcov

# centering temperature MMT, if MMT < 5%, use 5%, if MMT > 95%, use 95%
mmt <- findmin(cb_temp,coef=coef,vcov=vcov);temp5 <- quantile(mat_temp,0.05);temp95 <- quantile(mat_temp
cen_plot <- ifelse(mmt<temp5,temp5,ifelse(mmt>temp95,temp95,mmt))

# exposure-response function
cp <- crosspred(cb_temp, coef=coef, vcov=vcov, model.link="logit", cen=cen_plot, by=0.1, cumul=T)
plot(cp, "overall", ylab="OR", xlab="Temperature", lwd=1.5, xlim=range(mat_temp),ylim=c(0,6),col=2) ## a
mtext("HUBRO Cohort",cex=1.2,line=-0.5,font=2) ## add cohort name

abline(v=quantile(mat_temp,c(1,99)/100),lty=2,lwd=1)
axis(1,at=-8:8*5)

# histogram
breaks <- c(min(mat_temp,na.rm=T)-1,seq(cp$predvar[1],cp$predvar[length(cp$predvar)],length=30),max(mat_
hist <- hist(mat_temp,breaks=breaks,plot=FALSE)
hist$density = hist$counts/sum(hist$counts)*100
plot(hist,freq=FALSE,col=grey(0.95),main=NULL,xaxt="n",xlim=range(mat_temp),ylab="Density (%)")
```

```
abline(v=quantile(mat_temp,c(1,99)/100),lty=2,lwd=1)
layout(mat = matrix(c(1,2),2,1, byrow=TRUE),  height = c(5,5))
dev.off()


## 4. Effect modification ####

## 4.1 Greenness ####
result1 <- list()
## output to be saved, not including "mat_temp" and "b1temp" to reduce the size
out1 <- list()

for (i in 1:length(dlist)){
  data <- dlist[[i]]
  data$ndvi_cat <- ifelse(data$NDVI>=median(data$NDVI,na.rm=T),1,0)
  result1[[i]] <- casecrs_int_2cats(status="status",id="LOPENR",modif="ndvi_cat",lag=10,varper=c(10,75,9
                                    estpct=c(1,2.5,5,10,90,95,97.5,99),data=data)
  out1[[i]] <- within(result1[[i]],rm(mat_temp,b1temp))
}
names(result1) <- names(out1) <- name_outcome
saveRDS(out1,file = "Kicki/short-term_temp_mort_greennes_HUBRO.RDS")


## 4.2 Socio-economic: income ####
result2 <- list()
## output to be saved, not including "mat_temp" and "b1temp" to reduce the size
out2 <- list()

for (i in 1:length(dlist)){
  data <- dlist[[i]]
  data$income_cat <- ifelse(data$income_h>=median(data$income_h,na.rm=T),1,0)
  result2[[i]] <- casecrs_int_2cats(status="status",id="LOPENR",modif="income_cat",lag=10,varper=c(10,75
                                    estpct=c(1,2.5,5,10,90,95,97.5,99),data=data)
  out2[[i]] <- within(result2[[i]],rm(mat_temp,b1temp))
}
names(result2) <- names(out2) <- name_outcome
saveRDS(out2,file = "Kicki/short-term_temp_mort_income_HUBRO.RDS")


## 4.3. Education  ####
result3 <- list()
## output to be saved, not including "mat_temp" and "b1temp" to reduce the size
out3 <- list()

for (i in 1:length(dlist)){
  data <- dlist[[i]]
  result3[[i]] <- casecrs_int_3cats(status="status",id="LOPENR",modif="edulev",lag=10,varper=c(10,75,90)
                                    estpct=c(1,2.5,5,10,90,95,97.5,99),data=data)
  out3[[i]] <- within(result3[[i]],rm(mat_temp,b1temp))
}
names(result3) <- names(out3) <- name_outcome
saveRDS(out3,file = "Kicki/short-term_temp_mort_education_HUBRO.RDS")
```

APPENDIX 4

Sensitivity analysis

5/14/2023

```
#---------------------------------------#
# Name:5.1_sensitivity_case-crossover   #
# Project: EXHAUSTION                   #
# Version: 01.12.2021                   #
#---------------------------------------#
rm(list=ls())

##_____________________________________________________________________________________####
##                          Sensitivity analysis: case-crossover                        ####
##-------------------------------------------------------------------------------------###

## Load packages to be used; Author's R version 3.6.3
library(dlnm)
library(dplyr)
library(survival)
library(splines)
library(miceadds)
library(lubridate)

## Set the working directory
path <- "N:/durable/LEVEL3_MORTALITY/"
setwd(path)

## load the functions
source("Kicki/R code_adapted/00_FUNCTION.R")

## Import data sets ####

## Note: The data set should include the following variables
##       (1) status: indicator of the case (=1) or control (=0)
##       (2) temp_s0 - temp_s10: single-day lags of air temperature
##       (3) id (ID for participants): only participants who experienced events during the follow up (c
mort <- readRDS("N:/durable/LEVEL3_MORTALITY/Kicki/R code_adapted/DATA_EXHAUSTION_HUBRO_mort.RDS") ## w

## create data sets for each mortality outcome
mort_natural <- mort ## natural cause mortality
mort_cpd <- subset(mort_natural,cause_death%in%c(sprintf("I%02d", 0:99),sprintf("J%02d", 0:99),as.chara
mort_cvd <- subset(mort_natural,cause_death%in%c(sprintf("I%02d", 0:99),as.character(390:459))) ## cardi
mort_ihd <- subset(mort_natural,cause_death%in%c(sprintf("I%02d", 20:25),as.character(410:414))) ## isc
mort_cerebr <- subset(mort_natural,cause_death%in%c(sprintf("I%02d", 60:69),as.character(430:438))) ##
mort_resp <- subset(mort_natural,cause_death%in%c(sprintf("J%02d", 0:99),as.character(460:519))) ## resp
mort_copd <- subset(mort_natural,cause_death%in%c(sprintf("J%02d", 40:44),"J47",as.character(c(490:492,4
```

```r
## create a list containing all data sets
dlist <- list(mort_natural,mort_cpd,mort_cvd,mort_ihd,mort_cerebr,mort_resp,mort_copd)
## names of the outcomes in the order of that in the dlist
name_outcome <- c("mort_natural","mort_cpd","mort_cvd","mort_ihd","mort_cerebr","mort_resp","mort_copd"


## 1. Lag 0-3 of temperature ####
sens1 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  sens1[[i]] <- casecrs(status="status",id="LOPENR",lag=3,varper=c(10,75,90),lagnk=1,cen=list(pct=c(25,
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens1[[i]] <- within(sens1[[i]],rm(mat_temp,cb_temp))
}
names(sens1) <- name_outcome
saveRDS(sens1,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_lag_03.RDS")


## 2. Lag 0-21 of temperature
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens2 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  sens2[[i]] <- casecrs(status="status",id="LOPENR",lag=21,varper=c(10,75,90),lagnk=3,cen=list(pct=c(25
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens2[[i]] <- within(sens2[[i]],rm(mat_temp,cb_temp))
}
names(sens2) <- name_outcome
saveRDS(sens2,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_lag_21.RDS")



## 3. age 65+ ####
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens3 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort <- subset(mort,age_death>=65)
  sens3[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(pct=c(25
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens3[[i]] <- within(sens3[[i]],rm(mat_temp,cb_temp))
}
names(sens3) <- name_outcome
saveRDS(sens3,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_age65plus.RDS")


## 4. age 75+ ####
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens4 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort <- subset(mort,age_death>=75)
  sens4[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(pct=c(25
```

```
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens4[[i]] <- within(sens4[[i]],rm(mat_temp,cb_temp))
}
names(sens4) <- name_outcome
saveRDS(sens4,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_age75plus.RDS")


## 5. male ####
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens5 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort <- subset(mort,sex==1)
  sens5[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(pct=c(25
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens5[[i]] <- within(sens5[[i]],rm(mat_temp,cb_temp))
}
names(sens5) <- name_outcome
saveRDS(sens5,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_male.RDS")


## 6. female ####
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens6 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort <- subset(mort,sex==0)
  sens6[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(pct=c(25
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens6[[i]] <- within(sens6[[i]],rm(mat_temp,cb_temp))
}
names(sens6) <- name_outcome
saveRDS(sens6,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_female.RDS")


## 7. cold season (Nov-March) ####
##lag10
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens7 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort$month <- month(mort$d_death)
  sens7[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(pct=c(25
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens7[[i]] <- within(sens7[[i]],rm(mat_temp,cb_temp))
}
names(sens7) <- name_outcome
saveRDS(sens7,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_coldseason_lag10.RDS")


## 8. warm season (May-Sep) ####
## lag 10
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
```

```r
sens8 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort$month <- month(mort$d_death)
  mort <- subset(mort,month%in%5:9)
  sens8[[i]] <- casecrs(status="status",id="LOPENR",lag=10,varper=c(10,75,90),lagnk=2,cen=list(pct=c(25
                        estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens8[[i]] <- within(sens8[[i]],rm(mat_temp,cb_temp))
}
names(sens8) <- name_outcome
saveRDS(sens8,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_warmseason_lag10.RDS")


## lag 1
mort<- mort_natural #to get a big dataset again, it was only 619 obs from the last loop
sens8.2 <- list()
for (i in 1:length(dlist)){
  mort <- dlist[[i]]
  mort$month <- month(mort$d_death)
  mort <- subset(mort,month%in%5:9)
  sens8.2[[i]] <- casecrs_lag01(status="status",id="LOPENR",lag=1,varper=c(10,75,90),cen=list(pct=c(25,
                                estpct=c(1,2.5,5,10,90,95,97.5,99),data=dat)
  sens8.2[[i]] <- within(sens8.2[[i]],rm(mat_temp,cb_temp))
}
names(sens8.2) <- name_outcome
saveRDS(sens8.2,file = "Camilla/Results-HUBRO/sensitivity analysis/sensitivity_warmseason_lag1.RDS")
```

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