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Economic impact of cardiopulmonary morbidity due to ambient air temperature exposure in Norway

Økonomiske konsekvenser av kardiopulmonale sykdommer som følge av temperatureksponering i Norge

Christian Rikter-Ydse
Master in Public Health Science

Preface

This thesis is the final product which concludes my master's program in Public Health Science at NMBU, where I have been a student for 2 years. I have been involved in the research and writing of this thesis in the months of January to May 2022, and it culminated in this. The format of the article has been chosen to fit so-called level 2 journals, and we aim to submit it to one of the Nature-related journals.

I have treasured these few months, where I have been allowed to study and work with this engaging and relevant topic. The issue of climate change has always been an interest of mine, and the opportunity to combine it with my interest in health, has been a privilege.

This period that now lies behind has been fun, challenging, frustrating and incredibly meaningful. I want to thank my supervisors for all your insightful support and guidance. Thank you Marte Kjøllesdal, for your amazing support and good advice. Thank you Torbjørn Wisløff and Shilpa Rao for bringing me along on this adventure, letting me explore and learn within this topic, in an immensely including and warm environment at the Norwegian Institute of Public Health. I am truly grateful for your support along the way.

Thank you, Anne van der Heijden, for your helpfulness and excellent R guidance. As I started from scratch in January with no programming experience, your advice along the way have meant the world to me – they are worth more than countless hours of Googling.

Finally, thank you, my wife Cecilie, for supporting and cheering for me at home throughout this period, regardless of my motivation or energy levels. For reminding me to eat, sleep and enjoy this process.

I hope you enjoy this read.

Christian Rikter-Ydse

Oslo, May 2022

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1. Abstract

Background: The economic impact of Cardiopulmonary diseases (CPDs) in Europe have been proven to be substantial. This study aimed to estimate the economic burden of CPDs in Norway, and to assess the relationship between ambient air temperature and the direct health care costs from the Norway Control and Payment of Health Reimbursements (KUHR). Additionally, associations between sex, age, and socioeconomic factors and these costs were assessed.

Problem statement: Economic impact of cardiopulmonary morbidity due to ambient air temperature exposure in Norway

Method: This retrospective cost-of-illness study was based on the Cohort of Norway (CONOR) cohort in the years 2008-2018 and linked to healthcare costs retrieved from KUHR, and data on education and income variables from Statistics Norway. Data on daily mean ambient air temperature exposure was retrieved from the SeNorge2 dataset, with a grid spacing of 1km. Direct healthcare costs in 2018 Norwegian Kroner (NOK) were calculated by using reimbursement rates from KUHR, and a generalized linear model was applied to assess the costs related to ambient air temperature exposure, as well as sociodemographic factors.

Results: A total of 139 567 participants with a mean age of 68.2, was included. The total cost of CPD in the period 2008-2018 was NOK 1 512 651 719, of which 66.3% related to cardiovascular disease (CVD) visits, 31.2% to respiratory disease (RD) visits, and 2.4% for visits relating to both. A 1℃ increase in mean temperature the preceding week to a visit was associated with a 0.33% increase in cost ($p<0.001$). RD related costs increased with 0.55% ($p<0.001$). No association was found between temperature exposure and cost impact for CVD visits or visits with both. Sex, age, and education levels were significantly associated with changes in health care costs. Females had 7.36% ($p<0.001$) lower costs than males in total. RD costs increased with 0.72% ($p<0.001$) per year of age, but CVD costs decreased by 0.21% per year ($p<0.001$). Each level of higher education was associated with a 2.42% ($p<0.001$) decrease in RD costs, but a 2.76% ($p<0.001$) increase in CVD costs.

Conclusion: Direct costs of CPDs in primary health care amounted to a substantial economic impact and increased ambient air temperature exposures seemed to increase direct health care costs related to CPDs. The total cost of CPD is likely much higher, when factoring in prescription costs, hospital visits and indirect costs.

1.1. Abstrakt - Norsk

Bakgrunn: Den økonomiske byrden som følge av kardiopulmonale sykdommer (CPD) i Europa er bevist å være betydelige. Denne studien siktet på å estimere de direkte økonomiske kostnadene av kardiopulmonale sykdommer (CPD) i Norge, og undersøke sammenhengen mellom økte temperaturer og direkte helsekostnader, samt sammenhengen mellom kjønn, alder og sosioøkonomisk status for direkte helsekostnader.

Problemstilling: Økonomiske konsekvenser av kardiopulmonale sykdommer som følge av temperatureksponering i Norge.

Metode: Denne retrospektive cost-of-illness studien var basert på deltakere fra Cohort of Norway (CONOR) i årene 2008-2018, som ble koblet til Kontroll og utbetaling av helserefusjoner (KUHR), med data på utdanning og inntekt fra Statistisk Sentralbyrå, og informasjon om daglige gjennomsnittstemperaturer fra SeNorge2. Direkte kostnader, oppgitt i 2018 NOK, ble beregnet ut ifra refusjonstakster, og en generalisert lineær modell ble brukt for å undersøke temperatureksponeringens påvirkning på helsekostnader, og hvordan helsekostnadene hang sammen med kjønn, alder og de sosioøkonomiske variablene.

Resultater: Totalt 139 567 deltakere ble inkludert i studien. De totale direkte kostnadene utgjorde NOK 1 512 651 719 i perioden 2008-2018, hvorav 66.3% var relatert til legebesøk for kardiovaskulære sykdommer, 31.2% for respiratoriske sykdommer, og 2.4% til legebesøk for begge samtidig. En økning på 1°C i gjennomsnittstemperatur foregående uke for et legebesøk var assosiert med en økning i totale direkte helsekostnader på 0.33% ($p<0.001$), imens det for respiratoriske legebesøk ble funnet en økning på 0.55% ($p<0.001$). Ingen assosiasjon ble funnet mellom økte temperaturer og kardiovaskulære legebesøk eller legebesøk for kardiovaskulære og respiratoriske sykdommer i ett. Kjønn, alder og utdanningsnivå ble assosiert med endringer i helsekostnader, hvor kvinner ble assosiert med en nedgang i totale helsekostnader med 7.36% ($p<0.001$). Respiratoriske kostnader økte med stigende alder med 0.72% ($p<0.001$) per år, mens det for kardiovaskulære kostnader sank med 0.21% ($p<0.001$). For hvert økte utdanningsnivå sank respiratoriske kostnader med 2.42%($p<0.001$), mens det for kardiovaskulære kostnader økte med 2.76% ($p<0.001$).

Konklusjon: Direkte kardiopulmonale helsekostnader utgjorde en betydelig størrelse, og eksponering for økt temperatur så ut til å øke disse helsekostnadene. Den totale økonomiske byrden er sannsynligvis mye større, dersom man inkluderer kostnader for sykehusinnleggelser og legemiddelbruk.

2. Introduction

Cardiopulmonary diseases (CPDs) are a group of diseases consisting of cardiovascular (CVDs) and respiratory diseases (RDs) – two disease categories that make up a significant economic burden on the health care system. CVDs alone are the global leading cause of death, responsible for 32% of all deaths, killing an estimated 17,9 million annually, of which 85% are due to heart attacks and strokes. RDs also make up a significant burden - an estimated 235 million people worldwide suffer from asthma, and over 3 million people die annually from chronic obstructive pulmonary disease (COPD) alone (WHO, 2021a, n.d.-a). In Europe, CPDs have an estimated annual cost of around €590 billion (Gibson et al., 2013; Timmis et al., 2020). Since prevalence of these diseases are closely linked to climate change, we can also expect the costs to increase over the coming years, as the global temperatures rise, and people become more exposed to periods of elevated heat (WHO, 2018). How we meet the climate changes, and how we work towards mitigating and adapting to them, will greatly impact the scale of health care costs related to CPDs (EXHAUSTION, n.d.).

There is a political willingness concerning the issue of climate change and human health in Norway. The Norwegian Directorate of Health states that it is important that we continuously work towards gaining knowledge about the climate change’s effect on the human health, as we work to mitigating the effects (Helsedirektoratet, 2021). Through Norway’s commitment to the Paris Agreement, of limiting the global warming to 1.5℃ compared to preindustrial times, the Norwegian government is working towards cutting emissions by 50-55% by 2030 compared to 1990-levels and by 90-95% by 2050 (Meld. St. 13 (2020-2021)), which is. This commitment is also enshrined in the Norwegian Climate Change Act (Klimaloven, 2017).

It is important that we systematically approach the public health challenges we face (Folkehelseloven, 2012, §1,5), to best promote health throughout society. This includes exploring how climate change affect our health and the economic impact it brings. Since we must prioritize public spending in how we meet the challenge of climate change, quantifying the economic burden of diseases or conditions is an important prerequisite to do so (Direktoratet for forvaltning og økonomistyring, 2021). According to CICERO, existing quantitative projections of the cost associated with temperatures suffer from too simple modelling of the complex relationship between “climatic and non-climatic factor, human health, and the socio-economic consequences” (CICERO, n.d.).

This study aims to estimate the direct economic burden of CPDs in Norway and assess how ambient air temperature exposure impact these costs. The impact of sex, age, education, and income on costs will also be assessed. By providing research on this topic, we hope to provide further incentive to work on mitigating climate change and its impact on economics and health. To my knowledge, this is the first study of its kind to be conducted in Norway.

2.1. EXHAUSTION

This thesis a part of the EU project EXHAUSTION, which the Norwegian Institute of Public Health (NIPH) is a part of. The study has a broader aim to explore the link between temperature and air pollution exposure and health outcomes, as well as socioeconomic impacts. This thesis contributes to the work package working on estimating the economic costs (EXHAUSTION, n.d.).

2.2. The structure of the thesis

Together with this extended summary, I have also written an article, where the main findings of this study are presented. This extended summary provides further depth into the relevance of the thesis, background as well as the methodological choices, and more in-depth discussion of results.

First, I will present the problem statement, with underlying research questions. Second, I will give the relevant background for this thesis, placing it in a context that is relevant for the public health challenges we face today. Third, step-by-step I will walk through my methodological approach, explaining my choices considering the research questions before results will be presented. Fourth and finally, I will discuss the findings in light of previous relevant research, as well as my methodological approach, before I reach a conclusion and present recommendations for further actions and research.

3. Problem statement

The chosen problem statement for this thesis was:

"Economic impacts of cardiopulmonary morbidity due to ambient air temperature exposure due to climate change in Norway"

The objectives are:

1. To estimate the direct cost of CPD from the KUHR registry
2. To explore the association between ambient air temperature exposure and CPD costs
3. To explore the impact of age, sex, and socioeconomic status and direct CPD costs

4. Background

The Earth's atmosphere, and its composition, has changed since preindustrial times, especially concerning the levels of carbon dioxide (CO_2), methane (CH_4), and nitrous oxide (N_2O) (Patz & Frumkin, 2016). Scientists approximate that about half of all anthropogenic (human made) greenhouse gases emitted between 1750 and 2010 were emitted after 1970. Emission levels in 2011 exceeded 2005 levels with 43%. Economic growth and population growth are two driving factors, and the global emissions have exceeded the improvements in energy efficiency. This contributes to warming the planet, and the climate change can be a threat to the human health.

In august of 2021, United Nation's Intergovernmental Panel on Climate Change (IPCC) published a report stating that we have already passed an increase in global average temperatures compared to pre-industrial times by 1.1℃, with a 1.6℃ increase over land, and 0.9℃ increase over sea. Temperatures are increasing at a faster rate than ever before, and extreme weather events such as wildfires, heatwaves and drought are expected to occur more often and affect more people (IPCC, 2021). Heatwaves are defined as five or more consecutive days of at least 5℃ higher that the average maximum temperature in the 1961-1990 baseline period (Patz & Frumkin, 2016).

The human body is limited in its capacity to adapt to heat stress (Patz & Frumkin, 2016), and especially elderly people have a lower ability to regulate their body temperature, and are thus more vulnerable to adverse effects of high ambient temperatures (Miljødirektoratet, 2019). The amount of people exposed to heat increases with climate change, and events of extreme temperature are increasing in both magnitude, duration, and frequency. Recent studies suggest that anthropogenic global warming was responsible for up to 37% of all heat-related deaths worldwide, in the period 1991-2018 (Vicedo-Cabrera et al., 2021). In 2017 alone, an additional 175 million people globally were affected by heatwaves (WHO, 2018). During the summer of 2003, 16 European countries registered more than 70 000 excess deaths due to heatwaves (Robine et al., 2008). More recent reports state that Northern Europe is experiencing increasingly more days with "strong" and "very strong" heat stress, and the summer of 2021 was reported to be the summer with the second most days of "very strong" and "extreme" heat stress ever recorded (Copernicus Climate Change Service, 2022). The Norwegian Directorate of Health acknowledges the adverse effects climate change has on the human health, and states that it is important that we gain knowledge about the consequences of climate change on human health, as we work towards mitigating them (Helsedirektoratet, 2021). Without adapting to the heat, it is estimated that we can expect annual mortality rates in Europe of between 60 000 and 165 000 by the year 2080 due to heatwaves (Miljødirektoratet, 2019).

4.1. Cardiopulmonary diseases (CPDs)

First, it is expedient to understand a bit about CPDs, the occurrence of CPDs in Norway and factors that contribute to the development of these diseases. Cardiovascular diseases (CVDs) are diseases that affect the heart and blood vessels, such as ischemic heart disease (reduced oxygen to the heart) or cerebrovascular disease (reduced blood supply to the brain), while respiratory diseases (RDs) are diseases that affect the airways and lung structure, such as COPD, a chronic condition including narrowing airways, inflammation and swelling, and possibly destruction of parts of the lung (WHO, 2021a, 2021b, n.d.-a). Combined, we talk about these two diseases as CPDs. In Norway, CPDs make up five of the top ten most common causes of death, with ischemic heart disease, stroke and COPD all being in the top four (Øverland et al., 2018).

One in five Norwegians live with either a confirmed CVD, or with the risk of developing one, and in 2020, approximately 483 000 persons in the age group 0-74 in Norway was in contact with either their general practitioner (GP) or the emergency room related to cardiovascular incidents (Ariansen et al., 2021). Respiratory diseases also impose a substantial impact, with approximately 150 000 people in Norway living with COPD, equal to 6% of the Norwegian population (Folkehelseinstituttet, 2018). In general, males have higher incidence rates, health service utilization and mortality rates than females due to CVDs and RDs (Ariansen et al., 2021; Folkehelseinstituttet, 2018).

4.2. Socioeconomic status and health

As the overall goal for public health work in Norway is to even out social health inequalities (Folkehelseloven, 2012, §1), it is important that we know about how CPDs and its cost are distributed. Dahlgren and Whitehead's model of health determinants show different factors that can affect the human health, all the way from the core factors sex and age, and outwards through individual lifestyle choices, social network, education and work, and cultural and environmental factors (Dahlgren & Whitehead, 1991). Social determinants of health are non-medical factors, either internal or external, such as education and income levels that affect health outcomes (Braveman & Gottlieb, 2014). It is suggested that these determinants might be even more important in terms of health outcomes than the lifestyle or health care choices we make. The distribution of health quality in society is strongly associated with socioeconomic status, and follows a gradual increase from the lowest status groups to the highest status groups (Sosial- og helsedirektoratet, 2005). People of low socioeconomic status are more likely to experience adverse CVD and RD outcomes, due to a complex series of biological, behavioral, and psychological factors, such as hypertension, smoking, poor diet choices or access to healthy foods, physical activity levels, poor self-care, social support, or chronic stress. Lower education levels also limit job opportunities to low-income jobs with a stressful workday, which in turn can limit opportunities even further (Gershon et al., 2012; Havranek et al., 2015; Schultz et al., 2018). However, inversely, existing health issues can also affect the access to education or the ability to work, again affecting income levels (Strand & Madsen, 2018). Alcohol and tobacco use make up a substantial risk factor for death in Norway, and 20% of all deaths in 2016 for ages under 70 was attributed smoking (Øverland et al., 2018), which impacts differently depending on socioeconomic status. For instance, statistics from 2021 shows that in Norway, the share of daily smokers in primary school, high school and university educated people was 16%, 11% and 3% respectively (Helsedirektoratet, 2022). However, this trend is not seen in alcohol consumption, which inversely seems to increase with higher education levels (Schultz et al., 2018).

With some background information on how socioeconomic factors can impact health, I will now explain how the human health can be impacted by ambient air temperature exposure.

4.3. Temperature exposure and CPD effects

There are several complex mechanisms in the human body through which ambient air temperature exposure affects health outcomes. As heat stress increases, the heart rate increases, leading to more time under load, and thus puts more strain on the heart. Decreased cerebral perfusion is also linked to heat exposure, which can predispose to diseases like stroke (Crandall & Wilson, 2015). The heat dilates blood vessels near the skin and can impose a risk especially for people with preexisting heart conditions. Sudden increases in temperature can exacerbate congestive heart failure, and increase incidences of myocardial infarction after just 1-6 hours after exposure (Rice et al., 2014). On the other hand, cold stress cause blood vessels to contract, and makes the blood more viscous. These mechanisms decrease the blood flow, among others to the brain, and increase the workload of the heart (Seltenrich, 2015). Heat can affect the respiratory function through increased airway resistance, and is especially associated with exacerbation in people with already existing respiratory diseases, such as asthma or COPD, and sudden increases in temperature is linked with increased emergency department (ED) visits and hospitalizations due to RDs (Rice et al., 2014). Cold temperatures can also affect the respiratory system; by inhaling cold air, the airways are susceptible to cooling down and drying out, increasingly so with higher respiratory rates. This causes inflammation in the respiratory system and can exacerbate symptoms of respiratory diseases (D'Amato et al., 2018).

Whether cold or hot temperatures impose the greatest risk to the human health, differs with geographical location. A recent European-wide study show that heat had more adverse health effects in the southern part of Europe, such as Portugal, rather than in the Nordic countries. In Portugal, an increase in daily temperature from the 75th percentile to the 99th percentile, compared to annual average, was associated with a 46% increase in adverse cardiovascular outcomes. In Sweden, the same percentile-wise increase seemed to have a protective effect, with a decrease in risk of adverse cardiovascular event of 12%. What on the other hand seemed to have adverse effects on CPD health outcomes in Sweden, was extreme cold temperatures, where a decrease of daily mean temperature from the 25th percentile to the 1st percentile, where they registered an increase of mortality by 6% (Stafoggia et al., 2021).

A study from Helsinki, Finland utilizing data from the summers 2001-2017 to look at hospitalization rates, found that heatwaves could impose a threat on cardiopulmonary health, even in the Nordic climate. While increased daily temperature was associated with a decrease in all respiratory hospitalization, long lasting (over 10 days) or intense heatwaves were associated with increased risk of respiratory hospitalizations in the age group ≥75. However, no clear association was found for cardiovascular diseases, for either daily mean temperature or heatwaves, but rather suggestive associations between heatwaves and myocardial and cerebrovascular hospital admissions. The authors discussed that the absence of heat related CVD morbidity was due to the mild summers in Finland, and that when the heatwaves first occurred, the already at-risk and vulnerable people die before reaching the hospital, and thus joining the mortality statistics rather than the morbidity statistics (Sohail et al., 2020).

4.4. Economic cost of CPDs

With the adverse effect of heat on cardiopulmonary morbidity in mind, it is expedient to look at the relationship between cardiopulmonary morbidity and economic burden.

The economic cost of cardiopulmonary morbidity in Europe has been extensively researched. Cardiovascular diseases were estimated to a cost of €210 billion in Europe in 2015. 53% of the cost related to direct health care, in which 51% for inpatient hospital care and 25% for medication. 26% of the costs were related to productivity loss, and 21% related to informal care of CVD patients (Timmis et al., 2020). According to the European Respiratory Journal, the estimated annual cost of respiratory diseases in Europe in 2013 was €380 billion, including direct primary and hospital care costs estimated at €55 billion, indirect loss of production costs at €42 billion and DALYs at €280 billion (Gibson et al., 2013). DALY (disability-adjusted life years) is a measure of disease burden, and is defined as the loss of healthy life years (WHO, n.d.-b).

In a study by Kinge et al. (2017), based on the Global Burden of Disease from 2013, the Norwegian costs of cardiovascular and respiratory diseases where estimated. With data extracted from the Norway Control and Payment of Health Reimbursement (KUHR) the Norwegian Patient Register (NPR) and the prescription drug registry, they aggregated the total health care expenses. From the International Classification of Disease 10 (ICD-10) chapters IX (circulatory diseases) and X (respiratory diseases), they estimated an economic health care cost of NOK 17.8 billion and NOK 11.1 billion respectively (Kinge et al., 2017).

A Swedish article by Hallberg et al. (2016) looked at the direct costs of different cardiovascular events in patients with high cholesterol levels. Costs were based on prescriptions, primary care and in- and outpatient care, stated in € 2012 values. Patients were divided in 3 groups, depending on their CVD risk, and if they had either 1: A history of major CVD, 2: CVD related disease, or 3: low/unknown risk. The patients in group 1 were in general older and more comorbid than participants in the other groups. They found that for groups 1 and 2, the costs associated with cardiovascular events were significantly higher than for group 3, with stroke and myocardial infarction being the costliest diseases at €10,194 and €9823 for stroke in groups 1 and 2 respectively, and €8801 and €9807 for myocardial infarction in groups 1 and 2 respectively (Hallberg et al., 2016). In this study, it seemed that the older, more comorbid people had higher costs related to them.

In a study from Germany, health care costs related to heart failure was estimated. Results showed that each heart failure patient on average had 6.1 visits to their general practitioner (GP) per year, as well as 1.7 visits to cardiologists, and 0.8 hospital stays annually. Total disease-related health care costs were estimated to €3150 per patient annually, of which 74% was due to hospitalization costs, 9% related to rehabilitation, 9% to medication and 8% to outpatient contacts (GPs and cardiologists). These costs also seemed to increase with disease severity (Biermann et al., 2012).

Regarding RD related costs, Lisspers et al. (2018) calculated the direct and indirect costs of COPD in patients of 40 years and older in Sweden, during the year 2013. They found in their study that COPD patients had more comorbidities and medication use compared to the reference population, and thus higher direct health care costs; €13,179 compared to the reference population at €2,716. For direct COPD costs, the burden was lowest in the age group 45-50 years, and highest in the 85+ year group. Though the highest cost was related to hospital nights not related to COPD, indicating that costs increased not only with age, but also with comorbidities. For indirect costs, the costs were highest in the working age group 50–55-year group, where indirect costs were much higher than direct costs, at €28,000 versus €8,000. Disease severity also had an impact on cost, with "mild" COPD costing €7319 versus €11 808 for "very severe" (Lisspers et al., 2018). Another Swedish study also indicated that the total cost of COPD treatment in the general population increased by disease severity, with mean annual costs for "very severe COPD" amounting to €17 355 compared to €596 for "mild COPD". "Moderate COPD" costed €3245 and "severe COPD" costed €5686. The main direct cost drivers were hospitalization for "very severe COPD" and medication costs for the other categories. Males were overrepresented in the "severe" and "moderate" category, while there was a 50/50 division in the "very severe" group. The main indirect cost drivers were sick leave for "mild COPD" and early retirement for the other categories. When scaling the costs from the study and applied it to the Swedish population, the researchers estimated a total annual cost of €1.5 billion (Jansson et al., 2013).

This existing research provides insight into the costs related to different CPDs, both direct and indirect, and how the direct costs can be further broken down. This is important, as it will help to see the results from this thesis as a part of a bigger context.

4.4.1. Studies calculating cost of CPD due to temperature exposure

To my knowledge, this is the first study of its kind in Norway, and similar existing research is very scarce. However, one study from New York State studied the economic cost of excess hospital admissions related to respiratory diseases attributable to extreme heat and tried predicting future outcomes. With a mean summer temperature of 22.3℃ in the baseline period of 1991-2004, they estimated 100 excess hospital admissions with a direct cost of US$644 069 per year, distributed 616 hospitalization days. Projections for the years 2080-2099 with a scenario of temperatures in the range of 24.2℃ - 28.2℃, estimated 206-607 excess admissions with US$26-76 million in annual costs, distributed on 1299-3744 hospitalization days (Lin et al., 2012).

CPDs clearly impose a substantial economic burden both on an individual level as well as at a societal level. Further, I will go into the chosen methods for this thesis, that allowed me to calculate the economic burden for my sample population.

4.5. Cost-of-illness

Cost-of-illness (COI) is a type of analysis which goal is to evaluate the total burden an illness imposes on society. It can be used on a wide variety of outcomes, such as a disease's effect on morbidity, quality of life, or direct and indirect financial costs (Jo, 2014). A COI analysis is therefore a suitable tool for providing quality information about health care costs to health policymakers. Health care costs can be divided into direct and indirect costs. Examples of direct costs are medical prescriptions, inpatient care, or physicians' costs, such as general practitioners (GPs) or specialists. Indirect costs are typically costs not related to the disease itself, but costs as a consequence, such as productivity loss (Jo, 2014). COI analyses can be either prevalence-based or incidence-based, to either calculate the economic burden over a given period, or over a lifetime. This study is a retrospective prevalence-based study, as it studies costs that occurred in a specific time frame, and the sampling has been done in the past. A strength of COI analysis is just this; as the collection has already been done, they are both time- and cost-effective. Though, a prerequisite for good quality in the analysis is that the datasets on which the analyses are carried out provide sufficient information on the topic one wants to explore. There are different approaches to calculating the costs of a disease. Top-down approaches uses aggregated data to calculate the attributable risk of a disease using an attributable fraction in the population. Bottom-up approaches uses data on individual level to aggregate the total burden. Since this study utilizes the cost registered in KUHR on an individual basis, to then calculate the total cost, this is a bottom-up approach. (Jo, 2014).

In summary, in my thesis I utilize a retrospective COI analysis to provide information about the direct costs related to CPD diagnoses registered in KUHR for the period 2008-2018.

4.6. Generalized Linear Model

To explore the effect temperature had on CPD costs, I used a general linear model with a gamma distribution and log-link. A common way of dealing with cost data is to either simply overlook the fact that the data is non-normally distributed, or by transforming the data to make it fit the assumptions of linear regression (Lee & Conway, 2022). By using linear regression, one would encounter a problem when it comes to heteroskedasticity, and by simply log transforming the costs, there would probably be issues for most people to interpret the results in terms of log-currency – further the transformation of log-currency back to actual cost is complicated (Lee & Conway, 2022). General linear models (GLMs) are especially fitting for cost-of-illness analyses, as they can be used in cases of modelling complex outcomes, where the data is not normally distributed, such as data on health care expenditure. The distribution of the health care expenditure in my study was severely positively skewed. By implementing a Gamma distribution and log link to my general linear model, I could avoid the aforementioned issues associated with linear regression and log transformed currency. The fundamental difference in GLMs with log links compared to regular "identity" links, is that the exponentiated coefficients from the analyses are interpreted as a relative difference with the value 1.0 as a baseline. So the changes are interpreted as percentage change and not changes in NOK (Lee & Conway, 2022).

Further, I will step-by-step go through the methodological approach in this thesis, which will provide transparency and reliability to the thesis.

5. Method

5.1. Ethics

The Helsinki Declaration of 1964 was developed by the World Medical Association, and it works as a set of ethical principles which all medical researchers should submit to (World Medical Assiciation, 2018). We can clearly see the Norwegian laws on research are in line with these principles. Research ethics is a fundamental prerequisite to ensure all research is being conducted in a manner which safeguards the people on whom the research is based. Thus, all research conducted in Norway is strictly regulated by the same legislation, to ensure the same requirements are applied (Forskningsetikkloven, 2017, §1). As my thesis is based on health register data, a REK approval was needed (Helseforskningsloven, 2008, §10). Since I joined an already running project at NIPH, they had already applied to REK for access to the data, and only needed to apply for me to join as a project member. This application was accepted in the summer of 2021.

Due to the sensitivity of the data, all data processing was done in Service for Sensitive Data (TSD), a secure platform developed and provided by the University of Oslo, to meet the requirements of the Norwegian privacy regulation (University of Oslo, n.d.).

5.2. Sample

Participants in this study were included from the Cohort of Norway study (CONOR), a large multipurpose study, and collection of health care data from several large Norwegian health surveys. The study population in CONOR is somewhat heterogenous, and represents a variety from different geographical locations (Næss et al., 2007), and by using this large cohort, one can link the participants to a number of health registries through their personal 11-digit personal ID. Data on health care costs were retrieved from Norway Control and Payment of Health Reimbursement (KUHR), and daily mean temperature exposure data was retrieved from the SeNorge2 dataset. Data on education levels and household income were retrieved from Statistics Norway (SSB). Access to all data was given for the years 2008-2018. All data was linked to the participants of CONOR by their unique ID.

Total N for the sample population was 139 567, while participants with available information on temperature (n=139 394), education (n=139 187) and household income (n=137 383) were included in their respective analyses.

5.3. Health care cost

Norway Control and Payment of Health Reimbursement (KUHR) is a database containing information on reimbursement claims from health institutions, such as general practitioners, emergency rooms, and specialist doctors (Helsedirektoratet, 2019). Diagnoses were given in both ICPC-2 and ICD-10 codes, which is used by the primary health services and the specialist health services, respectively (Direktoratet for e-helse, n.d.-a, n.d.-b). Only diagnosis codes starting with either “I” (cardiovascular), “K” (cardiovascular), “R” (respiratory) or “J” (respiratory) were kept, based on conditions “K” and “R” for ICPC-2 and “J” and “I” for ICD-

10, as these are the disease codes that contain all the CPD relevant diagnoses. To facilitate for later calculations, participants with more visits per day were collapsed into one, and each visit was categorized as either “1=cardiovascular”, “2=respiratory disease” or “3=both/cardiopulmonary disease”.

5.4. Temperature data

Temperatures were retrieved from the SeNorge2 dataset, which provides daily mean temperature on a 1km grid spacing across mainland Norway (Lussana et al., 2018). These temperatures were linked to the project participants individual addresses and gave information on their temperature exposure for every day in the period 2008-2018.

Since I did not know which day prior to the visit the temperature had the greatest effect on the cost, I needed information on not only the temperature of the day itself, but the 7 days prior as well. To incorporate temperature lag, I created multiple date columns for the individual visit, one for the specific day, and one for each of the 7 days prior to the day of the visit. One visit would have a total of 8 days (temperature of date + 7 lag days) connected to it. I also created a column containing the value of the mean temperature the preceding week of a visit. This enabled me to look at more temperatures, to see if there were any trends in the days prior to the date of the visit.

5.5. Socioeconomic factors

Variables on socioeconomic factors were retrieved from SSB. The household income variable was registered as household income divided by the number of consumer units by EU-standard (microdata.no, n.d.). The first registered adult is weighted as 1, the next adult as 0.5, while any children are weighted as 0.3. So, e.g., a household with two adults and one child equals to 1.8 consumer units. Household income was used as a continuous variable, and values were weighted against the reference value of NOK in 2018 (SSB, n.d.). Education levels were registered as the highest level achieved by 1st October the same year as the visit (SSB, 2020). This categorical variable was divided into six groups, with assigned values 0-5. Group 1= Primary school, group 2= High school, group 3= Vocational school, group 4= University and college degree < 4 years, group 5= University and college degree for ≥4 years and over, group 0= No or undisclosed education.

5.6. Analyses

For the first part of my analysis, I aggregated the total direct costs of CPDs. Then I fitted a generalized linear model to explore how the costs were associated with temperature, sex, age, education, and income. I did all the data processing, such as cleaning and combining data sets, as well as the calculation of cost and regressions, in the free statistical program R Studio 4.12, inside TSD. Confidence intervals are stated in 95%, and statistically significant results defined by a p-value below 0.05.

5.6.1. Objective 1 - Cost estimation and aggregation of costs

According to the Norwegian Medicines Agency, a good method of estimating the actual cost of a doctor's visit, is by multiplying the reimbursement rate by 2 (Statens Legemiddelverk, 2018). To adjust for inflation, I weighted the cost of each visit in each year to the annual average value for 2018, as this was the most recent year from which I had data (SSB, n.d.). By adding up all the multiplied, weighted reimbursement rates, I would get a good overview of the direct cost. I calculated both the total costs for all the 11 years, the costs for each year, as well as the mean and median for each year. How the costs were distributed by disease categories was also calculated.

5.6.2. Objective 2 and 3 – Generalized linear model

For objective 2 and 3, I fitted a generalized linear model to explore the association between temperature exposure and direct costs, as well as age, sex, and socioeconomic factors and direct costs. In R, the syntax for a generalized linear model is written as the following: *glm(dependent_variable~independent_variable+covariate, dataset, distribution_family(link)).*

For objective 2, I wanted to look at the association between temperature exposure and direct health care costs. I started by running a crude regression for each day; from lag7 to the date of the visit, as well as the mean temperature for the preceding week, to see if there were any particular days that would stand out from the others in terms of impact on costs.

The variables sex, age, education, and income were added as moderators in the regression analysis, as this is the standard way of controlling for possible interactions (Mehmetoglu & Mittner, 2020). The moderator variables do not affect the temperature exposure but can impact the exposure's effect on the outcome. E.g., increased temperatures will likely have a greater impact on elderly people's health, and thus health care spending than on younger, generally healthier people. The regression analysis looked as follows: *glm(cost ~ temp + age + sex + education + income + age*temp + sex*temp + education*temp + income*temp, data = df, family = Gamma(link"log")).*

For objective 3, the analyses conducted on associations between costs and sex, age and socioeconomic factors, the following code was written: *glm(cost~exposure, data = df, family = Gamma(link="log").*

6. Results

Here, I will present the main results from the analyses in the article. Tables from the article will not be presented here.

6.1. Sample population

The included sample population of 139 567 consisted of a slightly higher proportion females (52.9%) than males (Table 1). The median age was 69, and median household income per consumer unit was NOK 353 041. Distribution of education indicated most participants with high school education (44,5%), followed by primary school (24,4%) and then university/college ≤4 years (21%). Mean all year temperature 2008-2018 was 4.99°C.

6.2. Objective 1 – cost estimation

In this objective I calculated the total direct cost of CPD in the period 2008-2018 in accordance with the aforementioned guidelines - by adding up the multiplied reimbursements adjusted for 2018-values. For this period, reimbursements totaled NOK 1 512 651 719 (Table 2), of which 66,29% was due to CVDs, 31,26% due to RDs, and 2,45% for both in one visit. The annual costs increased from NOK 125 million in 2008 to NOK 132 million in 2018 (Table 2). The mean cost per visit was NOK 487 for all years and increased from NOK 471 in 2008 to NOK 502 in 2018. The median cost per visit for all years was NOK 264 and decreased from NOK 293 in 2008 to NOK 238 in 2018.

6.3. Objective 2 – temperature exposure and CPD costs

In this objective I explored the association between ambient air temperature exposure and direct CPD costs, by applying a generalized linear model (GLM) with a gamma distribution and log link. The mean temperature over the last 8 days were associated with the highest cost impact in all disease category (visits) except for visits with both CVDs and RDs. For this category, the temperature on the 7th day before the visit (lag7) was the day associated with the highest increase in cost.

After adding the moderator variables sex, age, education, and income, the regression analyses were run once again. An increase of 1℃ in mean temperature over 8 days was associated with an increase of total costs in all disease categories of 0.33% (95%CI [+0.18%, +0.48%, p <0.001) (Table 3). Age seemed to significantly impact the effect of temperature on cost (+0.01%, p <0.001). Also, a significant association was found between increased temperatures and RD costs, with an increase of 0.55% (95%CI [+0.26%, +0.84%], p <0.001). Also here, age seemed to have a significant, yet marginal impact on the effect of temperature on costs (+0.008%, p <0.018). No significant association was found between increase in temperature exposure and CVD costs (+0.08%, 95%CI [-0.10, +0.26%], p 0.35) or visits with both CVDs and RDs in one (-0.22% 95%CI [-1.30%, +0.86%], p 0.68).

6.4. Objective 3 – age, sex, and socioeconomic factors and CPD costs

In objective 2 I wanted to explore the association between sex, age, education levels and income levels and direct CPD costs. The GLM was fitted to these variables, one by one.

Sex was associated with significant differences in costs (Table 4). Lower costs were associated to females across all diseases categories, with a total decrease in 7.36% (95%CI [-7.63, -7.1%], p<0.001). Highest cost difference in sex was for RDs, where females were associated with a decrease in 9.42% (95%CI [-9.9%, -8.91%], p<0.001).

Age was associated with higher total CPD costs (Table 4), with the highest association for RDs, with an increase of 0.7% (95%CI [+0.70, +0.75%], p<0.001) in costs for each increase in year of age. However, for CVDs, higher age was associated with lower costs, with a decrease of 0.21% (95%CI [-0.22%, -0.19%], p<0.001) for each year.

Higher education levels were associated with increased total CPD costs (Table 4), with the main driver being CVD costs, where each level of education was associated with an increase in costs of 2.7% (95%CI [+2.6%, +2.9%], p<0.001). However, education levels seemed to have a protective effect of costs related to RDs, with a decrease of 2.42% (95%CI [-2.64%, -2.20%], p<0.001) for each education level.

Income levels were not associated with any effect on CPD costs, in any disease category.

7. Discussion

Total direct costs for CPDs in Norway in the period 2008-2018 was NOK 1 512 651 719, with mean costs per visit increasing and median costs decreasing over the years. Overall costs increased with higher temperatures, as did RD related costs. No significant association was found for CVD related costs or costs from visits with both CVDs and RDs in one. Costs seemed to vary significantly between sex, age, and education levels, but not for income.

7.1. Objective 1 – cost estimation

The total cost of CPD in Norway for 2008-2018 imposed a substantial economic burden, with a total cost for all years at NOK 1 512 million in the sample of this study. This cost seemed to increase over the years, from NOK 125 million in 2008 to NOK 132 million in 2018. As the mean cost per visit increased from NOK 471 to NOK 502, and the median cost decreased from NOK 293 to NOK 238, showing a positive skew in the cost distribution, it might indicate that the total costs gradually were due to a fewer number of participants with high single costs per visit.

As this study was only based on cost data retrieved from KUHR, and thus only direct costs related to visits were implemented, the real cost is likely to be much higher. This is indicated by what we can see in Kinge et al. (2017), where the total costs of cardiovascular and respiratory diseases in Norway were calculated at NOK 17.8 billion for cardiovascular diseases and NOK 11.1 billion for respiratory diseases, which is a considerable higher amount than the results in this study. Importantly, my sample included 139 567 participants, whereas Kinge et al estimated CPD related costs in the total Norwegian population. In Timmis et al. (2020), most of the direct health care costs related to CVDs are made up of inpatient care and medication, 51% and 25% of the costs respectively, neither of which are included in this study. And as we can read from Lisspers et al. (2018), the indirect cost represented a x3.5 higher cost than the direct cost for COPD patients in Denmark. Yet, with the results from my study, we get a good insight in what the costs consists of and how they develop over time.

7.2. Objective 2 – temperature exposure and CPD costs

In this objective I explored the association between increase of ambient air temperature and direct health care costs, to assess the economic impact increased temperatures could have on direct health care costs. The analyses showed no significant association between temperature, CVD visits and visits for CVDs and RDs in one. However, the mean temperature of the preceding week to a visit showed significant impact on costs related to all disease categories with an increase of 0.33%, as did it for costs related to RD visits, with an increase of 0.55%. To put numbers into perspective: A 1℃ increase in mean temperature the preceding week of a visit would amount to an increase of total cost for the sample population in the period 2008-2018 of NOK 5 001 650, while for RD visits it would mean an increase of NOK 2 600 433. To put it in a wider perspective, if one would apply these numbers to the direct costs reported in Kinge et al. (2017), we could see an increase in cost for the Norwegian population of NOK 95 700 000 for all CPD costs and NOK 61 050 000 for RD costs in one year, which is a substantial amount.

I found these results intriguing, particularly since there are no directly comparable studies available. Existing related research also seem to differ in their estimations on temperature exposure and morbidity outcomes. The study from New York State found that in their scenario of increased mean summer temperature of 1.9-5.9℃, increased costs due to excess hospitalization amounted to US$26-$76 million (Lin et al., 2012). It is hard to directly compare my findings to this study, considering not only the geographical and climatic differences with temperature differences, but also population and outcome measurement differences. As previous studies show that hospitalization costs make up a far larger amount of the total direct costs than GP and outpatient visits (Biermann et al., 2012; Gibson et al., 2013; Timmis et al., 2020), the estimates in my study would probably look quite different if I were to include these. However, the direction for the trend in RD related costs shown in the New York study is somewhat comparable to the findings in my study.

When comparing my study to other studies conducted in climatic environments more like Norway, there are still some clear differences, which makes it hard to compare directly. While costs in my study increased with higher temperatures in the total visits and RD visits, Stafoggia et al. (2021) found in their study that adverse outcomes in Sweden seemed to increase with lower temperatures, and that higher temperatures were rather associated with a protective effect on adverse CPD outcomes. This in stark contrast to southern-European countries, where the opposite effect was observed. As the regression analysis in this study only showed either a positive or negative impact on costs due to temperature exposure, it is difficult to assess how the costs would have been distributed across different temperatures. Maybe cold and heat would affect CVDs and RDs differently. Looking at the mechanisms of temperature's impact on CVDs and RDs (Crandall & Wilson, 2015; D'Amato et al., 2018; Rice et al., 2014; Seltenrich, 2015) together with the findings in Stafoggia et al. (2021), it is quite clear that both extremes of temperature impact the human health, and could thus impact the costs. This interaction could have looked different if one were to adjust for seasonal variability.

The Norwegian and Finnish climates are also quite similar, which makes the conditions around temperature exposure comparable. Where I found no association between increased CVD costs for increased temperatures, the authors of the Helsinki study also found no evidence of increased hospitalization related to CVDs due to heat, only a suggestive impact on some CVD outcomes (Sohail et al., 2020). As the authors discusses in their study, the absence of heat related morbidity might be due to the mild summers in the Nordic environment, and when strong heatwaves first appear, the most at-risk people die before reaching hospitalization. As no such data was available for my study, this is difficult to comment, but it would make sense that the mild climate in Norway could help explain this absence of CVD costs in my study. Further, the authors of the Finnish study found a protective effect of increased temperatures for all RD related hospitalization, though an increase in RD hospitalization for patients ≥75 years for long or intense heatwaves, lasting more than 10 days (Sohail et al., 2020). As it was the prolonged increases in temperature in my study that was the most impactful for RD costs, it might be relevant to compare this trend to the Helsinki study. If temperatures for a longer lag period was available, it would be interesting to see the development with extended periods of elevated temperatures.

In summary, even though I found associations between increased temperature exposure and especially RD costs, the mild Norwegian climate could help explain the absence of CVD related costs. The picture of whether cold or hot temperatures would have the biggest impact on costs, could be further explored by including seasonal variability.

7.3. Objective 3 - age, sex, and socioeconomic factors and CPD costs

Direct CPD related health care costs varied significantly between sex, age, and education levels. Females were associated with lower health care costs across all disease categories of 7.36%, and a decrease in RD related costs of 9.42%. This is consistent with the existing research stating that males have higher incidence rates of both CVDs and RDs than females (Ariansen et al., 2021; Folkehelseinstituttet, 2018).

For age, the highest cost impact was found for RDs, with an increase of 0.7% in costs for each increase in year of age. However, for CVDs, higher age was associated with lower costs, with a significant decrease of 0.2% for each year. The decrease in CVD related health care costs with age, seems contradictory to the increased incidence of CVD related to aging (Rodgers et al., 2019). Why this is, is not fully clear as previous studies have shown that CVD related cost tend to increase with comorbidities and age (Hallberg et al., 2016). However, it seems that for registered GP costs in Norway, the proportion of total costs for which the older age group is responsible decrease as the proportion of costs for hospitalization and nursing homes increase (Kalseth & Halvorsen, 2020). It might be possible that the costs remaining for the GPs are related to low complex visits, with the more complex ones being handled in hospitals and nursing homes, and thus resulting in lower costs for GP visits. It might also be that younger participants with complex diseases demanding resource intensive treatment drive up the costs for the younger participants, indicated by the statistics in Kalseth and Halvorsen (2020), showing that 36.3% of all registered GP costs was in the age group 40-64. But as I did not have information on this, it is difficult to say. This would be interesting to further look into, especially taking into account that 74% of CVD related costs in Germany were due to hospitalization, while only 8% of costs were registered at general practitioners (Biermann et al., 2012), and that the picture of costs could change if hospitalization data was included.

Income levels were not found to impact health care costs, although one cannot rule out that this picture of no association would change if one were to include medication and hospitalization data. In Norway, income seem to have a more prominent health impact within lower socioeconomic groups, but the effect seems to decrease with higher income levels (Sosial- og helsedirektoratet, 2005). Further, income levels can vary every year, and is not necessarily stable, and some argue that education levels, which apply to every adult, is a more stable and robust measure of socioeconomic status (Bjerkaas et al., 2015).

Education levels were found to impact direct health care costs; higher education seemed to be associated with lower RD related costs, but higher CVD related costs. Primary health care use differ between education levels among people of poor health, especially elderly people; use of general practitioners is higher among lower educated individuals, while the use of specialists is higher among high-educated people (Strand & Madsen, 2018). In general, poor health, including prevalence of RDs and CVDs is more common in groups of lower socioeconomic status (Gershon et al., 2012; Schultz et al., 2018), impacted by among others smoking, which is much more common among people with lower education (SSB, 2021), and if implemented could help explain the trend. However, information on alcohol consumption was not available – a known major risk factor for adverse CVD outcomes, that seem to increase with education levels, and could be a confounder in this analysis (Schultz et al., 2018).

In summary, costs varied significantly by sex, age, and education, while no significant changes were found for income. These results provide further information on how the direct CPD costs are distributed and can be nuanced even more by implementing other measures of direct health care costs.

7.4. Method discussion

In this part of the thesis, I will discuss the methodological approach, its strengths, and weaknesses. Firstly, to assess the full direct health care costs, it would make sense to include data on hospitalization and medication use, as we have seen that the majority of morbidity costs related to CPDs are associated with hospitalization and medication use, and outpatient and GP visits only account for a smaller amount of the costs (Biermann et al., 2012; Gibson et al., 2013; Timmis et al., 2020). However, knowing more about the development of direct total, mean and median costs in this sample population, provides a valuable insight to the overall development, which could be representative for the development in the Norwegian population.

It is important that the methodological approach is adapted to best answer the research question. As some participants would have more than one diagnosis registered on their doctor's visit, it was difficult to isolate and assess the impact each diagnosis had on the costs. This is due to the reimbursements codes not being diagnose-specific, but instead linked to treatment rates. So even though I had detailed insight of the relevant diagnose codes for each visit on an individual level, the aggregated sum of costs would much likely also contain costs related to other diagnoses treated in the same visit. This is a clear disadvantage of my bottom-up COI approach, but is not something unique for my study, as it is the case for all bottom-up COI studies (Jo, 2014). I handled this issue as best I could, by creating 3 separate disease categories, as otherwise, the visits with both CVDs and RDs would affect the costs in the other categories one way or another, for instance by risking double registration. But outside of this, it is very difficult to differentiate the costs to a more detailed extent.

As explained, the generalized linear model with the gamma distribution and log link was specifically chosen to tackle the challenges imposed by the complexity of health care costs. As there would have been challenges in dealing with "log currency" through simple linear regression, the exponentiated coefficients are rather interpreted as percentage change, and is therefore the recommended tool for this kind of scenario. Thus it provided the best approach in helping to accurately estimate the outcome (Lee & Conway, 2022).

7.5. Ensuring quality throughout the study

It is imperative for the results that the quality of the study is ensured throughout the process. I have done this by ensuring both internal and external validity. Firstly, as this study is based on register data, the issue of recall bias is mitigated, as the information that is used is based on objective and concrete measures like GP visits and the following costs. CONOR, with its population size and representativity, as well as its flexibility to link participants to numerous health registries, makes it a good cohort to study. However, the participation rate in the CONOR cohort is around 58%, with the lowest representation from the urban areas. Participation rates also seem to decline during the study period, and are the lowest among participants under 30 years (Næss et al., 2007). Furthermore, generally, participants in baseline examinations of cohort studies tend to be females of high socioeconomic status, who live healthier lifestyles compared to non-participants (Enzenbach et al., 2019), so even though one try to make the study as objective as possible, it is difficult to completely eliminate the selection bias, which is important to remember when assessing the generalizability of the results. With that said, the sex distribution in this study was 52.9% female, only slightly higher than male participation, income levels were somewhat comparable to that of the Norwegian population (SSB, 2022), and the distribution of education levels was quite consistent with the general Norwegian distribution, although there was actually lower representation from the higher education levels than the distribution in the general population (SSB, 2021).

Transparency and reliability are ensured by providing a step-by-step description throughout the entirety of the process, from selection of participants, choice of methodological approach, analyses, and results, as well as strengths and weaknesses of the study. The step-by-step description also enables this study to be verified, as it can be replicated from start to finish exactly what has been done.

Even though this study and its results cannot be directly compared to existing research, it is interesting to observe that the trend, especially for RD related costs, have similar trajectory as other studies exploring heat related morbidity (Lin et al., 2012; Sohail et al., 2020). Taking this into account, while looking at the measures taken to ensure the internal validity in this thesis, I would argue that the external validity is also ensured, and that the results are somewhat generalizable to the Norwegian population.

7.6. Strengths and limitations of the study

7.6.1. Strengths of this study

One strength of this study is its uniqueness, and that there are no other similar studies have been conducted in Norway. Further, the sample size and heterogeneity speak to the study's generalizability to the Norwegian population.

7.6.2. Limitations of this study

However, its uniqueness also means that, naturally there are no direct comparisons from the Nordic climate, in terms of results, so it is difficult to assess whether the results make sense on their own, although one can compare trends of morbidity, which affect costs. As previously seen and discussed, the issue of seasonal variability needs to be addressed, as it constitutes a clear limitation of this study. Both high and low temperatures could impact CPDs and therefore also health related costs. In this study, it is difficult to assess the impact of either the cold or heat, as through the regression analysis, only a positive or a negative impact on cost was a possible outcome. The present work can further be extended by analyzing explicitly whether there is a U-shaped relationship between temperature exposure and costs, by creating variables based on extreme high or low temperatures, or by modelling the shape of the temperature impact on cost, such as through regression splines (Steyerberg, 2019), and would probably be an even better approach.

Further, this study was not able to differentiate the variation in costs due to seasonal variability from costs due to increased temperatures alone. It would be a major task to include this type of analysis in the study, and one would probably need more than 11 years of follow-up to assess this. This is something that future research could benefit from including.

Some confounders were not included in this study, such as severity of disease, or whether the patients had a history of CVDs or RDs, which has been indicated to have a significant effect on the health care costs (Hallberg et al., 2016; Jansson et al., 2013; Lisspers et al., 2018). By including this, I would have been able to differentiate the costs between more risk factors, and with the development of mean versus median costs over time, it would be interesting to see whether these costs were associated with more comorbid people. Information on alcohol consumption, a major CVD risk factor which also tends to increase with higher education levels, was not included (Schultz et al., 2018), neither was information on smoking, which is known to be a risk factor for both cardiovascular and respiratory health (WHO, 2021a, 2021b).

8. Interpretation and conclusion

Even though more research needs to be done to fully understand the full picture of the direct CPD related health care costs, these findings indicate a direction for how temperatures can impact costs related to CPD morbidity; there seem to be a significant association between ambient air temperature exposure and CPD costs in Norway. Sex, age, and education levels all had a significant impact on the health care costs as well.

9. Practical implications, recommendations, further research

These findings can provide further incentive to act upon the knowledge of climate change's impact on human health and health care costs, in accordance to the Norwegian Government's strategy (Helsedirektoratet, 2021), as well as help with prioritizing in the planning of health care services, especially in terms of economic spending related to CDPs.

For further research it will be interesting to include data on hospitalization and medication use, as these will much likely impact the health care costs even more. Also, it would be interesting to look at air pollution in addition to ambient air temperature exposure, as these two are closely linked, and they seem to have synergistic effects on CPD outcomes (CICERO, n.d.). The combined effect of these exposures on economic outcomes will likely much greater than just ambient air temperature exposure alone. Seasonal variability would also be relevant to include in future research.

10.Literature

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Appendix 1: Article

Economic impact of cardiopulmonary morbidity due to ambient air temperature exposure in Norway

Christian Rikter-Ydse, Marte Kjøllesdal, Torbjørn Wisløff, Shilpa Rao, Terese Bekkevold

Norwegian University of Life Science, Norwegian Institute of Public Health

Background: The economic impact of cardiopulmonary diseases (CPDs) in Europe have been proven to be substantial. This study aimed to estimate the economic burden of CPDs in Norway, and to assess the relationship between ambient air temperature and the direct health care costs from the Norway Control and Payment of Health Reimbursements (KUHR). Associations between sex, age and socioeconomic factors and these costs were also assessed.

Methods: This retrospective cost-of-illness study was based on the Cohort of Norway (CONOR) cohort in the years 2008-2018 and linked to health care costs retrieved from KUHR and data on education and income from Statistics Norway. Data on daily mean ambient air temperature exposure was retrieved from the SeNorge2 dataset, with a grid spacing of 1km. Direct health care costs in 2018 Norwegian Kroner (NOK) were calculated by using reimbursement rates from KUHR, and a generalized linear model was applied to assess the costs related to ambient air temperature exposure, and sociodemographic factors.

Results: A total of 139 567 participants with a mean age of 68.2, was included. The total cost of CPD in the period 2008-2018 was NOK 1 512 651 719 (€ 157 million, 2018 value), of which 66.3% related to cardiovascular disease (CVD) visits, 31.2% to respiratory disease (RD) visits, and 2.4% for visits relating to both. A 1℃ increase in mean temperature the preceding week to a visit was associated with a 0.33% increase in cost ($p<0.001$). RD related costs increased with 0.55% ($p<0.001$). No association was found between temperature exposure and cost impact for CVD visits or visits with both. Sex, age, and education levels were significantly associated with changes in health care costs. Females had 7.36% ($p<0.001$) lower costs than males in total. RD costs increased with 0.72% ($p<0.001$) per year of age, but CVD costs decreased by 0.21% per year ($p<0.001$). Each level of higher education was associated with a 2.42% ($p<0.001$) decrease in RD costs, but a 2.76% ($p<0.001$) increase in CVD costs.

Conclusion: Direct costs of CPDs in primary health care amounted to a substantial economic impact, and ambient air temperature exposures seemed to increase direct health care costs related to CPDs. The total cost of CPD is likely much higher, when factoring in prescription costs, hospital visits and indirect costs.

Introduction

The Earth is warming at an even faster pace than ever registered, and global temperatures have now passed an increase in 1.1℃ compared to pre-industrial times (1). The occurrence of CPDs is closely linked with climate change (2), and studies show that anthropogenic global warming is responsible for 37% of all heat-related deaths worldwide (3). As temperatures continue to rise, we can expect an increase in people suffering from CPDs (2), which again can affect the health care expenditure.

CPDs are a group of diseases consisting of cardiovascular diseases (CVDs) and respiratory diseases (RDs), two disease groups that impact the human health substantially. CVDs are alone the global leading cause of death, killing an estimated 17.9 million people annually (32% of all deaths) (4). RDs also make up a significant burden - an estimated 235 million people worldwide suffer from asthma, and over 3 million people die annually from chronic obstructive pulmonary disease COPD alone (5, 6). CPDs are among the top contributors to mortality in Norway and make up five of the top ten causes of death, with ischemic heart disease, stroke and COPD all in the top four (7). CPDs make up a significant economic burden on society and have a combined impact of approximately €590 billion annually on a European scale (8, 9). Numbers from Norway estimate the total annual direct economic burden of these diseases at NOK 17.8 billion and NOK 11.1 billion for CVDs and RDs respectively (10).

The scale of CPD related economic impact in the coming years, will depend on how we meet the climate changes, and how we work towards mitigating them and their impact on human health (11). Since we need to prioritize public spending in this process, it requires us to quantify the burden of these diseases (12), and acting upon the knowledge we gain can potentially save substantial health care costs (11).

Aim

This study aims to estimate the direct economic burden of CPDs in Norway and assess how ambient air temperature exposure impact these costs. The impact of sex, age, education, and income on costs will also be assessed. By providing research on this topic, we hope to provide further incentive to work on mitigating climate change and its impact on economics and health.

Methods

Sample

The sample population was retrieved from CONOR, a cohort consisting of data from several Norwegian health surveys, with a quite heterogenous group with participants from a variety of geographical locations, socioeconomic- and age groups, and socioeconomic, with the possibility to link the participants to other health registries through their personal 11-digit ID (13). Data on health care costs were retrieved from the Norway Control and Payment of Health Reimbursements (KUHR), and socioeconomic data was retrieved from Statistics Norway (SSB), while daily mean temperatures were obtained from the SeNorge2 dataset (14). Datasets were linked to the participants of CONOR through an individual serial number and date. The total sample population was 139 567, while participants with available information on temperature (n=139 394), education (n=139 187) and household income (n=137 383) were included in their respective analyses.

Health care costs

The KUHR dataset gave information on reimbursement claims from health institutions, such as general practitioners, emergency rooms, and specialist doctors (15), and disease codes were given in both ICD-10 and ICPC-2 (16, 17). Only diagnoses containing "J" (respiratory) and "I" (circulatory) for ICD-10 and "R" (respiratory) and "K" (circulatory) for ICPC-2 were kept, as these contain the CPD relevant diagnoses. Some patients had more visits registered in the same day; these were collapsed, so one day would be considered one visit, and each visit was categorized as either cardiovascular, respiratory or both (i.e., cardiopulmonary).

Temperature data

Temperature data provided by the SeNorge2 dataset (14), gave information on daily mean temperatures for all of mainland Norway, with a high-resolution grid spacing of 1km. This data was linked to the CONOR participants by residential addresses. To obtain temperature information on days before a visit, a lag of 1-7 days was added, so information was retrieved for a total of 8 days (day of visit + 7 days). Mean temperature the preceding week of a visit was also calculated.

Socioeconomic variables

Socioeconomic variables retrieved from SSB, gave information on education levels and income. Education levels were registered as the highest level achieved by 1st of October the same year as the visit (18) and were divided into 6 groups and categorized as: "0 = no or undisclosed", "1 = primary school", "2 = high school", "3 = vocational school", "4 = university/college <4 years" and "5 = university/college ≥4 years". Household income was registered as household income divided by the number of consumer units by EU-standard (19).

Analyses

According to the Norwegian Medicines Agency, the recommended way of calculating the actual cost of a doctor's visit is by multiplying the reimbursement rate by 2 (20). A bottom-up cost-of-illness (COI) approach was utilized in this study, to first aggregate the total direct costs related to CPDs (21). Then, a generalized linear model was fitted to explore the association between direct health care costs the categorical variables sex and education and the continuous variables temperature exposure, age, and income. A generalized linear model is the preferred analytic tool for COI analyses, since it can be adjusted to handle the complexity of health care costs, by fitting a Gamma distribution and log link (22). The exponentiated results can then be interpreted as relative change, with "1" as a baseline. Hence, the changes are given in percentage and not in currency (22). Participants with missing were ignored by the generalized linear model. Confidence intervals were given in 95% and statistically significant results were defined with a p-value below 0.05.

Costs for all years were weighted to the annual average NOK for 2018 (23). As was median household income. Average exchange rate 2018 € to NOK was 9.59 (24)

All data processing was done in the free statistical software R Studio 4.12.

Results

Sample population

The included sample population of 139 567 consisted of a slightly higher proportion females (52.9%) than males (Table 1). The mean age was 68.27 years, median age 69, and median household income adjusted for consumer units NOK 353 041. Distribution of education indicated most participants with high school education, followed by primary school and then university/college ≤4 years. Mean all year temperature exposure was 4.99℃.

Table 1: Overview of sample population

The sample population	
Female (n= 73 862)	52.9 %
Male (n= 65 705)	47.1 %
Age	
Mean age	68.27
Median age	69
Min age	25
1st Q	58
3rd Q	80
Max age	108
Median household income per consumer unit (n= 137 419)	NOK 353 041
Education level distribution (n= 139 187)	0: 0.30%
0: No/undisclosed, 1: Primary school, 2: High school, 3:	1: 24.4%
Vocational school, 4: University/college < 4 years, 5:	2: 44.5%
University/college ≥ 4 years	3: 2.9%
	4: 21%
	5: 6.9%
Mean all year temperature exposure (n=139 304)	4.99℃

Aggregation of costs

The total aggregated direct costs amounted to NOK 1 512 651 719 (€157 million) (Table 2), of which CVDs were responsible for 66.29%, RDs 31.26% and visits with both/CPDs 2.45%. The annual cost of CPD increased from NOK 125 million in 2008 to NOK 132 million in 2018. The mean cost per visit increased from NOK 471 to NOK 502, while the median cost decreased from NOK 293 to NOK 238.

Table 2: Distribution and development of direct costs (all costs in Norwegian kroner (NOK))

Total aggregated costs by disease category 2008-2018 in NOK		
Disease category	Costs in NOK	%
CVDs	1 002 792 060	66.29%
RDs	472 806 156	31.26%
Both/CPDs	37 053 502	2.45%
Total	**1 512 651 719**	**100 %**

Development of CPD costs 2008-2018 in NOK			
Year	Total cost CPD	Mean cost/visit	Median cost/visit
2008	125 467 897	471	293
2009	125 801 880	452	264
2010	129 362 811	475	283
2011	137 172 787	483	297
2012	145 258 383	482	269
2013	146 937 829	485	264
2014	145 745 774	497	260
2015	144 876 511	497	253
2016	143 426 055	507	256
2017	136 437 477	510	253
2018	132 164 315	502	238
All years	**1 512 651 719**	**487,4**	**264,4**

Ambient air temperature exposure and CPD costs

Crude regression showed highest association between mean temperature over 8 days and total cost impact, as well as for CVDs and RD visits. The 7th day before a visit (lag7) had the highest impact on visits with both. After adjusting for the sociodemographic moderators, an increase of 1°C in mean temperature over 8 days was associated with an increase of total costs in all disease categories of 0.33% (95%CI [+0.18%, +0.48%, p <0.001) (Table 5). Age seemed to have a small, yet significant impact on the effect of temperature on cost with an increase of 0.01%, (p <0.001). Also, a significant association was found between increased temperatures and RD costs, with an increase of 0.55% (95%CI [+0.26%, +0.84%], p <0.001). Also here, age seemed to have a significant, yet marginal impact on the effect of temperature on costs, with an increase of 0.008% (p <0.018). No significant association was found between increase in temperature exposure and CVD costs (+0.08%, 95%CI [-0.10, +0.26%], p 0.35) or visits with both CVDs and RDs in one (-0.22% 95%CI [-1.30%, +0.86%], p 0.68).

Table 3: Associations between temperature exposure and direct CPD costs. From GLM regression

Temperature exposure and total direct CPD costs					
	All categories	β	Pr>(|t|)	Exp(β)	95%CI
Crude	Mean temperature 8 days	0.0114	<0.001	1.0115	1.0113, 1.0117
Adjusted	Mean temperature 8 days	0.0033	<0.001	1.0033	1.0018, 1.0048
	Meantemperature 8 days:age	0.0001	<0.001	1.0001	1.0000, 1.0001
	Mean temperature 8 days:sex	-0.0000	0.906	0.9999	0.9995, 1.0003
	Mean temperature 8 days:education	0.0001	0.237	1.0001	0.9999, 1.0002
	Mean temperature 8 days:income	0.0000	<0.001	1.0000	1.0000, 1.0000
Temperature exposure and direct CVD costs					
	CVD	β	Pr>(|t|)	Exp(β)	95%CI
Crude	Mean temperature 8 days	0.0123	<0.001	1.0123	1.0121, 1.0126
Adjusted	Mean temperature 8 days	0.0008	0.359	1.0008	0.9989, 1.0026
	Meantemperature 8 days:age	0.0001	<0.001	1.0001	1.0001, 1.0001
	Mean temperature 8 days:sex	-0.0004	0.064	0.9995	0.9990, 1.0000
	Mean temperature 8 days:education	-0.0001	0.077	0.9998	0.9995, 1.0000
	Mean temperature 8 days:income	0.0000	<0.001	1.0000	1.0000, 1.0000
Temperature exposure and direct RD costs					
	RD	β	Pr>(|t|)	Exp(β)	95%CI
Crude	Mean temperature 8 days	0.0099	<0.001	1.0099	1.0095, 1.0103
Adjusted	Mean temperature 8 days	0.0055	<0.001	1.0055	1.0026, 1.0084
	Mean temperature 8 days:age	0.0000	0.018	1.00008	1.0000, 1.0000
	Mean temperature 8 days:sex	0.0003	0.442	1.0003	0.9994, 1.0011
	Mean temperature 8 days:education	0.0002	0.139	1.0002	0.9999, 1.0006
	Mean temperature 8 days:income	0.0000	0.098	1.0000	1.0000, 1.0000
Temperature exposure and direct costs of visits with both/CPD					
	Both	β	Pr(>|t|)	Exp(β)	95%CI
Crude	Temperature lag7	0.0091	<0.001	1.0078	1.0078, 1.0104
Adjusted	Temperature lag7	-0.0022	0.684	0.9977	0.9869, 1.0086
	Temperature lag7:age	0.0000	0.186	1.0000	0.9999, 1.0001
	Temperature lag7:sex	0.0025	0.071	1.0025	0.9997, 1.0053
	Temperature lag7:education	0.0006	0.333	1.0006	0.9993, 1.0018
	Temperature lag7:income	0.0000	0.488	1.0000	1.0000, 1.0000

Sociodemographic factors and CPD costs

Sex was associated with differences in costs, and for females, a decrease in total CPD related costs of 7.36% (95%CI [-7.63, -7.1%]) was found, whereas the RD related costs was lower by 9.42% (95%CI [-9.9%, -8.91%]) than males (Table 3). Higher age was associated with higher total CPD costs, and RD related costs increased the most with each year of higher age with 0.7% (95%CI [+0.70, +0.75%]). However, CVD costs decreased with each year of higher age by 0.21% (95%CI [-0.22%, -0.19%]). Higher education levels were associated with increased CVD costs, with each level of education associated with an increase in costs by 2.7% (95%CI [+2.6%, +2.9%]). However, for RD related costs, education levels were associated with a decrease of 2.42% (95%CI [-2.64%, -2.20%]) for each level. Income levels were not associated with any effect on CPD costs.

Table 4: Associations between sex, age, education and income and costs. From GLM regression.

Sex				
All visits	β	Pr(>|t|)	Exp(β)	95%CI
Sex (male=1, female=2)	-0.0764	<0.001	0.9263	0.9237, 0.9290
CVD				
Sex (male=1, female=2)	-0.0622	<0.001	0.9396	0.9365, 0.9428
RD				
Sex (male=1, female=2)	-0.9893	<0.001	0.9058	0.9007, 0.9108
Both				
Sex (male=1, female=2)	-0.0440	<0.001	0.9569	0.9387, 0.9754
Age				
All visits	β	Pr(>|t|)	Exp(β)	95%CI
Age	0.0015	<0.001	1.001539	1.0014, 1.0016
CVD				
Age	-0.0020	<0.001	0.997929	0.9977, 0.9980
RD				
Age	0.0072	<0.001	1.007287	1.0070, 1.0074
Both				
Age	0.0019	<0.001	1.001193	1.0011, 1.0027
Education levels				
All visits	β	Pr(>|t|)	Exp(β)	95%CI
Education level	0.0079	<0.001	1.0079	1.0067, 1.0091
CVD				
Education level	0.0272	<0.001	1.0276	1.0261, 1.0290
RD				
Education level	-0.0245	<0.001	0.9757	0.9736, 0.9779
Both				
Education level	-0.0090	0.0343	0.9909	0.9827, 0.9993
Household income				
All visits	β	Pr(>|t|)	Exp(β)	95%CI
Income	0.0000	<0.001	1.000	1.0000, 1.0000
CVD				
Income	0.0000	<0.001	1.000	1.0000, 1.0000

RD				
Income	0.0000	<0.001	1.000	1.0000, 1.0000
Both				
Income	0.0000	0.79	1.000	1.0000, 1.0000

Discussion

Summary of results

Total direct costs for CPDs in Norway in the period 2008-2018 was NOK 1 512 651 719 (€157 million), with mean costs per visit increasing and median costs decreasing over the years. Regarding exposure to increased temperatures, costs for visits related to all disease categories and RD visits seemed to be significantly impacted. No significant association was found for CVD visits or visits with both CVDs and RDs in one. Further, direct costs seemed to vary significantly between sex, age, and education levels, but not for income.

Cost aggregation

Seeing the distribution of total costs by disease category seems quite consistent with the prevalence of CVDs and RDs in Norway. With an increase in mean costs over the years, while median costs decreased, indicate that the proportion of total costs increasingly consists of fewer, more high-cost visits compared to low-cost visits. Previous studies have found that the direct costs of CPDs primarily consists of hospitalization and medication use, and that the outpatient costs such as GP visits, make up a smaller fraction (8, 9, 25), and thus the total direct costs in this sample population is most likely much higher.

Ambient air temperature exposure and CPD costs

Our results suggest that increased temperatures were associated with increased total health care costs, and especially increased RD related costs. To put numbers into perspective, a 1℃ increase in temperature would amount to an increase of costs for the sample population in the period 2008-2018 of NOK 5 million (€521 000) for total costs, and NOK 2.6 million (€271 000) for RD related costs. Applying the results to the total cost of CPDs in the

Norwegian population found in another study (10), we could see annual increases of NOK 95 million (€9.9 million) in total costs and NOK61 million (€6.3 million) for RD related costs. Previous studies with similar outcome measures are hard to find, but one study from New York State associated increased costs of US$26-76 million related to CVD hospitalization due to excess temperatures of 1.9-5.9℃ (26), though hard to directly compare due to climatic differences, and since hospitalizations costs are typically much higher than GP costs (25). In a study from Sweden, no association was found between increased temperatures and morbidity or mortality (27); on the contrary, increased temperatures seemed to have a protective effect for the population sample, while extreme cold temperatures were associated with adverse cardiopulmonary effects. A study from Finland also found no association between increased temperatures and CVD hospitalization, and an inverse association between increased temperature and RD hospitalizations (28). The authors suggest that the absence of heat-related morbidity in Finland could be due to the generally mild summers, and that when heatwaves first occur, the most at-risk population die before reaching the hospital, thus becoming a part of the mortality statistics, and not the morbidity statistics. However, for long and intense heatwaves lasting over 10 days, an increase in RD hospitalizations for patients ≥75 was found, as well as a suggestive association for some CVDs (28). As the mean temperature the preceding week of a visit in this study had the highest association with cost impact, it would be interesting to extend the lag period, to see if even longer time periods could have higher impacts.

Sociodemographic factors and CPD costs

Females were associated with consistently lower health care costs, with a total decrease of 7.36%. Highest difference was for RDs, where females had 9.42% lower costs than males. This makes sense as the incidence of both CVDs and RDs are higher in males than in females (29, 30). Not surprisingly, increased age was associated with a general increase in costs, with the highest increase for RDs at 0.7% per year of age. The decrease in CVD related health care costs with age, seems contradictory to the increased incidence of CVD related to aging (31). Why this is, is not fully clear as previous studies have shown that CVD related cost tend to increase with comorbidities and age (32). However, it seems that for registered general practitioners' costs, the share of costs in the older age groups decrease, as the share of costs for hospitalization and nursing homes increase (33). It might be possible that the costs remaining for the general practitioners are related to low complex visits, with the more complex ones being handled in hospitals and nursing homes. In fact, a German study found that 74% of CVD related costs were due to hospitalization, while only 8% of costs were registered at general practitioners (25), and this picture of decreasing CVD costs with age could change if other costs were involved.

Income levels were not found to impact health care costs. In Norway, income seem to have a more prominent health impact within the lower socioeconomic groups, but the effect seems to decrease with higher income levels (34). Further, income levels can vary every year, and is not necessarily stable, and some argue that education levels, which applies to every adult and in fact is stable, are more robust measures of socioeconomic status (35). However, one cannot rule out that this picture would change if one were to include medication and hospitalization data. Education levels were associated with differences in direct health care costs; higher education was associated with lower RD related costs, but higher CVD related costs. In general, poor health, including prevalence of RDs and CVDs is more common in groups of lower socioeconomic status (36, 37). For instance, smoking is much more common among people with lower education (38), which could help explain the trend. However, information on alcohol consumption was not retrieved – a known major risk factor for adverse CVD outcomes, that seem to increase with education levels, and could be a confounding factor (36).

Strengths and limitations of the study

One strength of this study is its uniqueness, and that there are no other similar studies have been conducted in Norway. Further, the sample size and heterogeneity speak to the study’s generalizability to the Norwegian population. But the uniqueness also means that there are no studies to direct compare the results to.

As mentioned under Ambient air temperature exposure, both low and high temperatures could impact health and thus health related costs. With the present regression, either only a positive or a negative impact on cost was possible. This could further be extended to analyze added variables on extremely high or low temperatures, or by explicitly modelling the shape of impact of temperature on costs, such as through regression splines (39). It is also difficult to separate the variation in cost due to seasonal variability from the general increase in temperature. If longer follow-ups would be available, future studies could benefit from including this.

Some possible confounders were not available for inclusion, such as severity of disease, which has been proven to impact the cost of CPDs (32, 40, 41). It would have been interesting to see if potential comorbidities would have an association with the development of costs, in terms of increase of mean and decrease of median costs. Alcohol consumption is known to increase the risk for CVDs (36). Smoking is also a known risk factor for both CVDs and RDs (4, 5) that was not adjusted for. Finally, the effects of air pollution were not included. It is well known that air pollution exposure is closely linked to both CVDs and RDs (42).

Practical implications, recommendations, and further research

Even though more research needs to be done, these results could provide further incentive to act upon the knowledge of climate change's impact on human health and health care costs, in accordance with the Norwegian Government's strategy (43), as well as help with prioritizing in the planning of health care services, especially in terms of economic spending related to CPDs.

Further research should include data on hospitalization and medication use, as these will probably have a significant impact on health care costs. Also, it would be interesting to look at air pollution in addition to ambient air temperature exposure, as these two are closely linked, and they seem to have synergistic effects on CPD outcomes (44). The combined effect of these exposures on economic outcomes will likely much greater than just ambient air temperature exposure alone. It would also be of interest to look at other direct health care costs, such as prescription costs, as well as hospitalization costs.

Conclusion

This study suggests that the direct costs of CPDs in Norway imposes a substantial economic impact, with costs increasing over the last 11 years. Costs are likely much higher when including hospitalization and medication costs. Increased ambient air temperature was related to an increase in total direct health care costs related to CPDs, most notably for RDs. These costs could be explored more by adjusting for seasonal variability. Direct health care costs also varied by sex, age, and education, while no association was found for income.

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Norges miljø- og biovitenskapelige universitet
Noregs miljø- og biovitskapelege universitet
Norwegian University of Life Sciences

Postboks 5003
NO-1432 Ås
Norway