

Nadja K. Schreier

# The Influence of Weather, Season, Climate, and Disasters on Non-Communicable Diseases

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Nadja K. Schreier

# **The Influence of Weather, Season, Climate, and Disasters on Non-Communicable Diseases**

## **ACADEMIC DISSERTATION**

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To Tomi and the girls



## Abstract

Nadja Schreier. The Influence of Weather, Season, Climate, and Disasters on Non-Communicable Diseases. National Institute for Health and Welfare (THL), Research 136. 92 pages. Helsinki, Finland 2014.

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*Background.* The environment has a major impact on human beings. Extreme environmental conditions such as hot temperatures can have huge health impacts, as shown during the heat wave in Europe that occurred during the summer 2003. The main causes of death were non-communicable diseases (NCDs) such as respiratory and cardiovascular diseases. Natural and man-made disasters can cause the collapse of health infrastructure through a combination of marked increase in demand due to injuries, diseases and increased stress levels and the physical disruption/destruction of hospital buildings, roads and transport that follows such disasters. Extreme weather events and disasters are predicted to increase in the course of the ongoing climate change. Therefore, impacts on NCDs are very likely to increase, which raises the importance of the hitherto paucity of knowledge about this research area.

*Aims.* This study investigates the associations of weather conditions, temporal variations, in addition to the impact of a disaster, namely the bombings of Helsinki during the Second World War (WWII) on NCDs, specifically for coronary heart disease (CHD), cerebrovascular disease, type 1 diabetes mellitus (T1DM), hypertension, and obesity.

*Materials.* Three main data sets were used for this study: 1) All fatal and non-fatal coronary events in seven cities in Finland recorded in the years 1983, 1988, and 1993 (n=9243), 2) Data that originate from the Helsinki Birth Cohort Study (HBCS) include information about birth characteristics and about life-long disease outcomes in addition to deaths of subjects born in Helsinki between 1934-1944 (n=13 039), 3) Data that originate from the DiaMond project including standardized data from 112 centers in 56 countries of all children aged between 0-14 years with diagnosis of T1DM during 1990-1999 (n=31 091)

*Methods.* The following methods were used to achieve the specific aims: 1) Comparison of regression models with weather and temporal variation variables for the prediction of coronary events was implemented for the assessment of the influence on the case-fatality of the events, 2) Log-linear regression with Fourier terms were used to assess seasonal patterns for the incidence of childhood T1DM in different geographical locations, 3) Survival analysis and regression models were used to assess life-long health outcome due to exposure to bombings *in utero*, and to outdoor ambient temperature at the time of conception.

*Results.* Influences of temperature at the time of conception for hypertension and obesity were observed. Women who were conceived during the months with the



warmest mean temperatures of the time-series were found to have a significantly higher probability of developing hypertension in adult life. Furthermore, women conceived during those months with very low mean temperatures had lower BMI, lower risk of obesity and also lower fat percentage in adult life.

The seasonality of the incidence of the T1DM in children was demonstrated to be a global phenomenon. In addition it was shown that the further from the equator a location is in terms of latitude the higher is the probability of that location to exhibit a seasonality pattern for T1DM.

A slight positive influence for the life-long development of CHD and cerebrovascular disease was found for women who were *in utero* during the bombings of Helsinki in WWII. Furthermore, the case fatality of coronary events during the 1983-1993 period turned out to be negatively influenced by temporal variation. Case-fatality of CHD was higher in the December holidays and on Sundays. An attempt to predict coronary events on the basis of the weather forecast for the same study period appeared not to have any useful value.

*Conclusions.* This study contributes to the research of the fundamentals about the influence of weather, temporal variation, and disasters on NCDs. The results showed that hypertension, obesity, T1DM, CHD, and cerebrovascular disease were particularly affected by those factors. The ongoing climate change will potentially increase the impacts on NCDs. Preparedness for these increases - including the prevention of disease and the prevention of the further exacerbation of a disease – is an important task for the near future. Further, the collection of data in developing countries where data are sparse needs close collaboration between interdisciplinary scientific teams in order to address the complexity of this type of research and to contribute to the preparedness of health authorities in such challenging regions.

Keywords: climate, weather, season, temporal variation, non-communicable diseases, climate change, temperature, NCD, CHD, IHD, ischaemic heart disease, stroke, obesity, myocardial infarction, diabetes, conception, cerebrovascular disease, hypertension, fat percentage, BMI, disasters, heat wave, cold spell, coronary events

## Tiivistelmä

Nadja Schreier. Sään, vuodenaikojen, ilmaston ja katastrofien vaikutukset pitkäaikaissairauksiin. Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 136. 92 sivua. Helsinki 2014.

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*Tausta.* Ympäristön vaikutus ihmiseen on merkittävä. Vuoden 2003 lämpöaalto Euroopassa osoitti, että ääriolosuhteet, esimerkiksi kuuma lämpötila, voivat vaikuttaa terveyteen suuresti. Merkittävimmät kuolinsyyt liittyivät pitkäaikaissairauksiin, kuten hengityselinten ja sydän- ja verenkiertoelimistön sairauksiin. Lisäksi sekä ihmisen aiheuttamilla että luonnonkatastrofeilla – kuten aseellisilla yhteenotoilla sekä myös tulvilla ja myrskyillä – on äärimmäisiä vaikutuksia terveyteen, esimerkiksi kohonneiden stressitasojen ja terveyteen liittyvien infrastruktuurien luhistumisen välityksellä. Sään ääri-ilmiöiden ja katastrofien on ennustettu lisääntyvän ilmastonmuutoksen edetessä. Siksi myös vaikutukset pitkäaikaissairauksiin todennäköisesti lisääntyvät, mikä entisestään korostaa tutkimusaiheen merkitystä.

*Tavoitteet.* Tässä tutkimuksessa tarkastellaan sääolosuhteiden ja lämpötilan vaihtelun yhteyttä pitkäaikaissairauksiin, erityisesti sepelvaltimotautiin, aivoverenkiertosairauksiin, tyypin 1 diabetekseen, kohonneeseen verenpaineeseen ja liikalihavuuteen. Lisäksi tarkastellaan katastrofin – Helsingin toisen maailmansodan aikaisten pommitusten – vaikutuksia pitkäaikaissairauksiin.

*Aineistot.* Pääasiallinen tutkimusaineisto oli 1) kaikki sekä kuolemaan johtaneet että muut vuosina 1983, 1988 ja 1993 raportoidut sepelvaltimoperäiset sairauskohdat (n=9243) seitsemässä kaupungissa, 2) Helsingin syntymäkohortti (HBCS) -tutkimuksen aineisto, Helsingissä vuosina 1934–1944 syntyneet, mukaan lukien synnytyksiin liittyvät ominaispiirteet, myöhemmin havaitut sairaudet ja kuolemat (n=13039), 3) DiaMond-hankkeessa kerätty aineisto mukaan lukien 56 maan 112-keskuksen kaikki 0–14-vuotiaat, joilla todettiin tyypin 1 diabetes vuosina 1990–1999 (n=31091).

*Menetelmät.* Käytetyt menetelmät olivat 1) säää ja lämpötilanvaihteluita selittävinä tekijöinä käyttävien regressiomallien vertailu sydänkohtausten ennustamiseksi sekä tapausten kuolinriskin arvioimiseksi 2) Fourier-sarjan termejä sisältävä log-lineaarinen regressioanalyysi tarkasteltaessa asuinalueittain vuodenaikaisvaihtelun vaikutusta sairastuvuuteen lapsuusiän tyypin 1 diabeetikoilla 3) eloonjäämisanalyysi ja regressiomallit arvioitaessa sikiöaikaisen pommituksille altistumisen sekä hedelmöitymishetken ulkolämpötilan yhteyttä elinaikaisiin terveystuloksiin.

*Tulokset.* Hedelmöitymishetkellä vallinneen ulkoilman lämpötilan havaittiin vaikuttaneen kohonneeseen verenpaineeseen ja liikalihavuuteen. Naisten oli merkittävästi todennäköisempää sairastua kohonneeseen verenpaineeseen aikuisiällä, mikäli hedelmöitys oli tapahtunut kuukausina, jolloin ulkoilman keskilämpötila oli korkeimmillaan. Kylmimpinä kuukausina siitetyillä naisilla oli aikuisiällä mata-

lampi painoindeksi, pienempi liikalihavuusriski sekä alhaisempi rasvaprosentti kuin lämpiminä kuukausina syntyneillä naisilla.

Lapsilla vuodenaikaisvaihtelun, joka ilmenee sairastuvuudessa tyypin I diabetekseen, voitiin osoittaa olevan maailmanlaajuinen ilmiö. Asuinpaikkaan liittyvistä tekijöistä leveyspiiri näyttää vaikuttavan vuodenaikaisvaihtelun todennäköisyyteen.

Niillä naisilla, jotka olivat sikiökaudellaan altistuneet Helsingin toisen maailmansodan aikaisille pommituksille, havaittiin heikko positiivinen yhteys sepelvaltimotaudin ja aivoverenkiertosairauksien kehittymiseen aikuisiällä.

Kuolleisuus sepelvaltimotauteihin oli käänteisessä yhteydessä lämpötilan vaihteluun vuosina 1983–1993 – se oli korkeampi joulukuun juhlapyhien aikaan ja sunnuntaisin. Sepelvaltimotautiperäisiä sairaskohtauksia ei sen sijaan kyetty ennustamaan säätilan avulla samalla ajanjaksolla.

*Johtopäätökset.* Tässä tutkimuksessa tarkasteltiin sään, lämpötilavaihteluiden ja katastrofien vaikutuksia pitkäaikaissairauksiin. Tutkimuksessa voitiin osoittaa vaikutusta erityisesti kohonneen verenpaineen, liikalihavuuden, tyypin I diabeteksen, sepelvaltimotaudin ja aivoverenkiertosairauksien syntyyn. Meneillään oleva ilmastonmuutos saattaa lisätä vaikutuksia pitkäaikaissairauksiin. Lähitulevaisuudessa on tärkeää valmistautua vaikutusten lisääntymiseen niin sairauksien ennaltaehkäisyä kuin niiden pahenemista ajatellen. Tulevaisuuteen voidaan valmistautua keräämällä lisäaineistoa erityisesti kehitysmaista, joista sitä on saatavilla niukasti, sekä käyttämällä monitieteellisiä lähestymistapoja tämän monimutkaisen ilmiön tutkimiseksi.

Avainsanat: ilmasto, sää, vuodenaika, lämpötilan vaihtelu, pitkäaikaissairaudet, ilmastonmuutos, lämpötila, sepelvaltimotauti, aivohalvaus, liikalihavuus, sydäninfarkti, diabetes, hedelmöittyminen, aivoverenkiertosairaus, kohonnut verenpaine, rasvaprosentti, painoindeksi, katastrofit, lämpöaalto, sepelvaltimotautiperäisiä sairaskohtauksia

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## List of original papers

This thesis is based on the following five original publications referred to in the text by their Roman numerals:

- I Schreier NK, Molchanova EV, Puustinen NM. Prediction of daily coronary events based on the weather forecast: a case study from Finland. Submitted.
- II Schreier NK, Moltchanova EV, Lammi NM, Karvonen ML, Eriksson JG. Temporal variation in case fatality of acute myocardial infarction in Finland *Ann Med* 2009;41(1):73-80.
- III Moltchanova EV, Schreier N, Lammi N, Karvonen M. Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide *Diabet Med* 2009 Jul;26(7):673-678.
- IV Schreier NK, Moltchanova EV, Blomstedt PA, Kajantie E, Eriksson JG. Prenatal exposure to wartime stress: long-term effect on coronary heart disease in later life. *Ann Med* 2011;43(7):555-61.
- V Schreier N, Moltchanova E, Forsen T, Kajantie E, Eriksson JG. Seasonality and ambient temperature at time of conception in term-born individuals - influences on cardiovascular disease and obesity in adult life. *Int J Circumpolar Health* 2013 Oct 15;72:21466.

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## Abbreviations

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
BMI	Body mass index
BP	Blood pressure
CDR	Cause of Death Register
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DiaMond	Diabetes Mondiale
HBCS	Helsinki Birth Cohort Study
HDL	High density lipoprotein
HDR	Hospital Discharge Registry
HI	Haemorrhagic infarcts
ICH	Intracerebral haemorrhages
IPCC	Intergovernmental Panel on Climate Change
IS	Ischaemic stroke
LDL	Low density lipoprotein
ME	Mean error
MSE	Mean squared errors
NCD	Non-communicable disease
SAH	Subarachnoid haemorrhage
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UNEP	United Nations Environmental Program
UV	Ultraviolet
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio
WMO	World Meteorological Organization
WWII	Second World War

# Introduction

The environment has a major impact on the human being. Throughout their evolution, humans have had to cope with various conditions on Earth and to adapt to changes, be it on the physiological level or on other levels. An example of such a physiological adaptation is skin colouration. Starting with the same dark colour in Africa, the migration to the North resulted in a genetic selection towards lighter skin colour over thousands of years due to the better ability of lighter skin to generate cholecalciferol (Vitamin D<sub>3</sub>) (1,2). It does not take thousands of years for the environment to influence the ability to cope with other variations. For example, a child exposed to hot temperatures until the age of three will have a higher number of functioning sweat glands than a comparable child in a colder environment. The former will therefore be able to cope better with hot conditions in later life (3).

However, in the absence of adequate time for adaptation, the challenges to the body in the short term will overbalance and health problems will emerge. For example, abnormally hot conditions can have enormous immediate health impacts, as shown during the heat wave in Europe during the summer 2003. During this extremely hot summer, about 70 000 more deaths than usual occurred in Europe (4,5). The main causes of death were non-communicable diseases (NCDs) such as respiratory and cardiovascular diseases (6).

Predictions about the ongoing climate change imply along with the general global warming trend more extreme weather events and natural disasters such as heat waves, droughts, or floods. These changes happen with a speed that makes it impossible for the human being to adapt accordingly, thus the magnitude of such impacts on NCDs will increase. Therefore, it is important to study associations of weather, season, and climate, and also other natural or man-made disasters on health and disease outcome.

This study investigates the associations of weather conditions with coronary events and its temporal variation such as seasonality or weekly variation. Furthermore, seasonal patterns are compared in different climates for type 1 diabetes mellitus (T1DM). A large cohort of subjects born before and during the Second World War (WWII) makes it possible to explore prenatal influences on life-long health. In this matter, the study focuses on the influence of temperatures at time of conception on hypertension, coronary heart disease (CHD), cerebrovascular disease, and obesity, in addition to the *in utero* influence of a disaster on CHD and cerebrovascular disease.

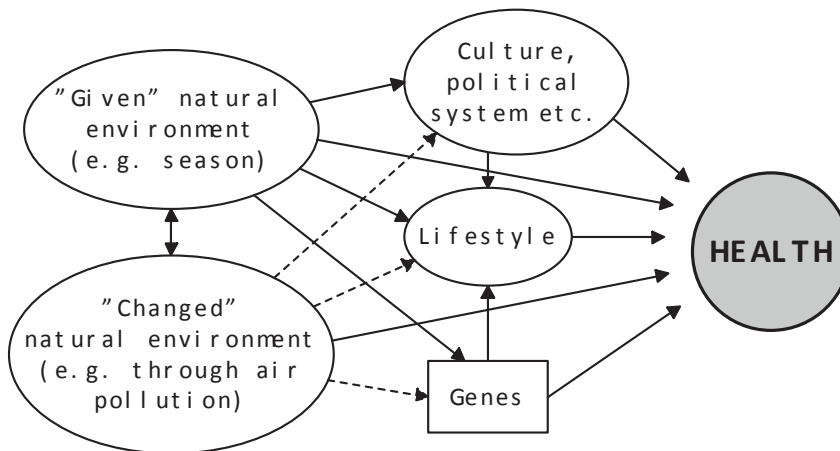




# 1 Review of the literature

## 1.1 Environmental risk factors for NCDs

The word “environment” in the health context is used very broadly. It conventionally refers to various external factors that may have an impact on human health through exposures that are common to members of groups, communities or whole populations. These environmental exposures are typically not under the control of the individuals, and are thought of as physical, chemical, and biological agents having an impact on us from the immediate surrounding environment (7,8). Lifestyle factors such as smoking, individual diet and exercise influence health substantially, and are in a broad sense also part of the environment. However, these factors will not be discussed in the review of the literature, since this work focuses on environmental factors with influence on a different scale, and which include weather, season, climate, and man-made or natural disasters (Fig.1 and Tab.1).



**Figure 1.** Some factors that influence health from an environmental perspective

Human beings and all other living beings on Earth have evolved to cope with the presence and absence of light, with heat and/or cold. These essentials are not uniformly distributed over the earth. The tilt of the earth’s axis and the rotation axis around the sun causes predictable patterns of climates with predictable patterns of vegetation (biomes) to be created, including different seasonal cycles in addition to typical or prevailing weather characteristics. Each biome is partially characterized by the species and life cycles of living organisms that range from mammals to

microbes (9). An example of the adaptation of human beings to these variations is skin colouration. Evidence indicates that the variations in skin colour are directly related to the geographical latitude and to ultraviolet (UV) radiation. Originally, all humans had the same skin colour. However, with the migration to more Northern parts of the Earth around 50 000 years ago, an advantageous selection of lighter skin over thousands of years happened which permits UVB-induced synthesis of cholecalciferol (Vitamin D<sub>3</sub>) to occur (1,2). An example of a more immediate adaptation to the environment is the number of sweat glands. The number of sweat glands that will become functional at the age of three depends on the temperature to which the child is exposed. Hence, a child who experienced hot conditions will be better equipped to adapt to similar conditions in later life, as a higher number of functioning sweat glands cools the body down more efficiently (3). In addition, the level of advancement of a culture plays a major role in how human beings alter their natural environment, including among other things housing, agriculture, nutritional culture, and status of infrastructure. Factors such as well-built waterproof housing, reliable food and safe water supply, and the health care systems especially in developed countries have meant that the natural environment as a factor for human health is often regarded as being of rather minor influence. These particular cultures were however substantially influenced by the natural environment in their development (9). The World Health Organisation (WHO) estimates that 24% of the global disease and 23% of all deaths can be attributed to environmental factors. Non-communicable diseases such as CHD, cerebrovascular disease, asthma, and lung cancer rank among the diseases with the largest environmental contribution (8).

Environmental factors that influence NCDs are manifold (Tab.1). There are factors that are strongly influenced by human beings; these are mainly connected to the contamination of air, water, and soil. Other factors such as weather and season have so far been regarded as natural factors. The recent wide acceptance of the anthropogenic component in the ongoing climate change implies that weather, season, and climate are to a certain extent influenced by the human being (10). Effects of the climate change include *inter alia* higher frequency of weather extremes such as hot or cold outdoor ambient temperatures, floods or droughts, and even shifts in climate zones, which forces human beings to adapt to their new natural environment or in certain circumstances even to migrate (9,11). Extreme forms of environmental factors are either man-made or natural disasters, which are mainly acute and have often substantial influence on the health status of the human beings involved, be it on a mental or physical level (12-15).

**Table 1.** Examples of human induced changes and differences in the natural environmental factors that influence health

	Environmental factor	Examples of sources	Exposures relevant to health
Human induced changes of the natural environment	Air pollution	Traffic, industry, electromagnetic fields, solid fuels	
	Water pollution	Traffic, industry, wastewater, farming	Chemicals, microbiological agents, radiation, toxins etc. through air, water or food consumption
	Soil contamination	Traffic, industry waste, farming, healthcare waste, warfare	
	Noise pollution	Traffic, industry	Chronic noise stress
<i>Extreme and acute forms of human induced changes are man-made disasters, e.g. oil spills, nuclear accidents, terrorist attacks or wars, fires etc.</i>			
Natural differences in environmental factors	Season and climate		
	Weather		Manifold influences, from extreme temperatures to Vitamin D deficiency, mineral content of the water, nutrition, viral infections etc.
	Geographical latitude		
	Topography		
	Soil properties		
<i>Extreme and acute forms of natural environmental impacts are natural disasters, e.g. earthquakes, avalanches, floods, tropical storms, tsunamis etc.</i>			

### 1.1.1 Weather

Weather can be thought of as the daily and weekly local variations of the atmospheric state for temperature, humidity, atmospheric pressure, wind, precipitation, and cloudiness (9).

The weather affects the human beings to a great extent; e.g. social behaviour, diet, mood, freezing and sweating differ according to its variation. Moreover, temperatures in a certain season may be colder or warmer than usual and affect our behaviour, our well-being and health in certain ways.

#### Ambient temperature

The impact of outdoor ambient temperatures on health is most obvious when the weather involves extremes of heat or cold.

Extended heat exposure causes increased peripheral circulation that causes the blood flow to move from the central organs towards the skin, which by itself can already be enough stress for the body to cause severe illness or even death (16). Furthermore, copious sweating can drain the body's electrolytes. The most consistent predictors of heat related mortality are mean ambient temperature and number of successive hot days (9). Risk factors include *inter alia* age, the presence of comorbid conditions, and living conditions (17).

Direct influences of hot temperature on NCDs have been studied extensively for the heat wave in Europe of the summer of 2003, during which almost 70 000 more people died than expected for a normal summer (4). Studies stated a general increase in the number of deaths, with the main excess deaths occurring in the age groups above 75 years of age (18-21). Studies on the causes of excess death from heat waves in big cities in Europe showed increased numbers especially for cardiovascular disease (CVD), cerebrovascular diseases, and respiratory disease (6).

Extended cold exposure causes hypothermia, defined as a body temperature below 35°C, caused by body heat loss to the environment (22). Hypothermia can cause a decrease in the heart and respiratory rate, a drop in blood pressure, failure of major organs, and can ultimately lead to death. The most consistent predictor of cold-related mortality is an exposure to cold ambient temperatures. Risk factors include very young or old age, the presence of comorbid conditions, and intoxication (22).

Direct influences of extended cold periods – cold spells – on certain diseases are less studied than heat waves, and their influence is more complex than the one from heat waves, as their effects are less direct and often confounded with other factors occurring in the winter months, such as acute respiratory infections or epidemics of influenza (23,24). Furthermore, people may take better protective

measures against cold than hot including e.g. clothing, heating, and avoiding travel (25). Influences of cold spells were found particularly for mortality from CVD, CHD, and respiratory diseases (24,26-30).

The influence of ambient temperature on a human being's life may start as early as conception. A study in reptiles showed that ambient temperature has an influence on the sex ratio of hatchlings (31). Furthermore, ambient temperature during pregnancy was shown to influence birth weight and/or length of gestation (32-34). These findings imply long-term health effects.

### **Atmospheric pressure**

Atmospheric pressure is the weight of the air pressing on the surface of the Earth. The air pressure changes with the weather and with the altitude. The atmospheric pressure changes are greater at higher altitudes altitudes (9).

The body of the human being consists of up to 75% of water, and also of air and other gases e.g. in lungs, intestines, joints, or ears. Variation in the atmospheric pressure affects the body's biochemistry in such a way that causes the body volume to expand slightly, which leads to a retention of water and therefore to an alteration of the electrolyte balance. These changes could possibly cause water retention in certain parts of the body, joint pain, glaucoma pain, increased blood pressure, and increased blood clotting (9). Studies on the influence of atmospheric pressure change and its impact on NCDs are rare and many show no detrimental effects on the health of humans. Associations have been found for CVD, whereby sudden drops in atmospheric pressure increased hospital admissions (35). U-shaped relationships with air pressure were found in relation to myocardial infarction (36), and acute or chronic vascular disease cases were reported to occur more often during increased air pressure conditions (37). Furthermore, increases in pain levels have been repeatedly associated with air pressure changes (38-40).

### **Wind**

Winds blow between the different atmospheric pressures that characterise air masses, and between zones of subsiding and rising air as part of the heating balancing of the atmospheric circulation (9). Strength, duration and frequency of winds vary greatly between places. Furthermore, the movement of air promotes the ionization i.e. the electric charging of atmospheric gases, especially in air of low humidity. In its extreme form this ionization is associated with the build-up of cumulus clouds whereby the segregation of electric charges results in lighting. Dry and warm winds have been associated with irritability, headaches, depression, strokes, and circulatory diseases, but the evidence is mostly anecdotal (9). The main cause for adverse health influences is currently suspected to be the ionization, and not the heat *per se*. Scientific studies are, however, rare and results are ambiguous (41-44).

## Relative Humidity

The effects of relative humidity alone were rarely compared and evaluated against adverse health outcomes directly. The combination of heat and humidity has been reported to add to the severity of the adverse health effects of heat (45,46). Furthermore, low indoor humidity is strongly correlated with low outdoor temperatures and is modified by the use of humidifiers. Low humidity has been associated with the exacerbation of asthma and the increase in respiratory infections, which are in turn associated with certain NCDs such as CHD or cerebrovascular disease (47-49).

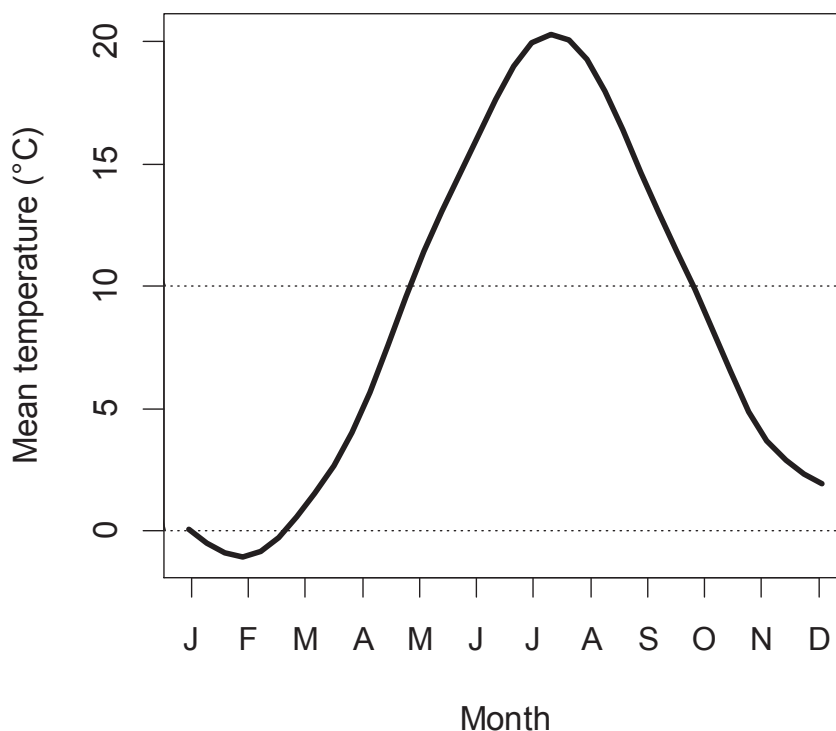
## Other meteorological factors

Direct impacts on NCDs of other meteorological factors such as precipitation and cloudiness are not studied well. For example, heavy snow fall has been associated with an increased incidence of acute myocardial infarction, but the mortality was mainly attributed to the exertion-related manual snow removal and not to the weather factor *per se* (50-52).

### 1.1.2 Temporal variation

Many phenomena such as temperature or diet are a function of time. Furthermore, many temporally variable phenomena are cyclical. Cycles may be annual, weekly, daily or a combination of all these. Examples of such cycles include holiday seasons, temperatures, and snow fall, with their typical characteristics concerning diet, stress, or physical activity.

The seasonality of a year is a good example of a temporal variation; it has one seasonal peak in summer and one trough in winter for outdoor ambient temperature or length of day light, which depend on the geographical latitude and other factors (Fig.2). The influence of season on human health may already begin during time of conception of an embryo. C.A. Mills (53) stated as early as 1941, that the season of conception has influence on the mental and physical development of a human being, which manifests as differences in college matriculation, different onsets of the menses in girls, and/or as differences in height and differences in weight. Furthermore, some forms of mental diseases such as depression or bipolar disorder have been found to be influenced seasonally: this is especially the case for seasonal affective disorder (54-57). Depression is in turn an established risk factor for mortality and cardiac morbidity in patients with CHD (58-62). Seasonal variations of mean ambient temperature, day length, amount of precipitation, nutrition, air pollution, and the occurrence of viral diseases are other plausible factors.



**Figure 2.** Example of a temporal variation: Mean outdoor ambient temperature throughout the year with one peak and one trough

Week days differ from the weekend days with regard to their activity patterns. For example weekends include potentially different behaviours concerning stress, diet, physical activity, and alcohol consumption. On weekends there might also be fewer personnel in health care centres and hospitals. All these factors may influence the onset, the pathological progression, and the subsequent treatment of certain diseases.

Annual holiday seasons are different from normal working weeks and weekends. Holiday seasons typically include different levels of stress, changes in diet, and usually increased alcohol consumption with potential health implications. It could also mean that persons having symptoms of a certain developing condition will delay seeking medical care and therefore diseases might exacerbate. Staffing in the health care centres and hospitals might be lower than at other times, which probably leads to delays in diagnose and treatments of diseases.



### 1.1.3 Climate and its change

Although the weather is understood to result from short-term atmospheric events including: variations in temperature, humidity, wind, atmospheric pressure, precipitation etc. at any given time, the climate can be described as “prevailing weather”. Therefore, it is the statistical description in terms of means and variation of relevant quantities for large areas mostly over a period of around 30 years or more (9,10,63). Certain patterns of weather predominate in a climate zone and these characteristics determine what crops will grow, what kind of insects live there, and the type of houses that are built etc. (9). Consequently, communicable diseases and NCDs will be influenced by the climate zone.

In the last 40 years, there has been a disruption and weakening of the world’s life-support systems and processes, which started to become evident. These disruptions of the natural systems of the earth on a global level are the results of increasing population size and of a high-consumption, energy-intensive, and waste-generating economy. One of the main global environmental changes is climate change, which has become a symbol of these large-scale environmental changes (7). In 1988, the Intergovernmental Panel on Climate Change (IPCC) was established by the United Nations Environmental Program (UNEP) and the World Meteorological organization (WMO). Its goal is to provide a clear scientific view of the current stage of knowledge about climate change by reviewing and assessing the most recent information from thousands of studies over the world (64). According to its most recent report, climate warming is a fact; as many of the observed changes since the 1950’s are unprecedented over decades or even millennia. The human influence on the climate system is also clear. The reason for these changes lays mainly in increased atmospheric concentrations of carbon dioxide (CO<sub>2</sub>) and other greenhouse gases such as methane (CH<sub>4</sub>) or nitrous oxide (N<sub>2</sub>O). Changes include warming of both atmosphere and ocean, continuously rising sea levels, and reduced amounts of snow and ice (65).

Even if the greenhouse gases and aerosols would be kept constant at the year-2000-levels, projections for the future include further global warming of around 0.1°C per decade. Snow cover is projected to contract further, sea ice to shrink in both the Arctic and Antarctic. Weather extremes, heat wave events and heavy precipitation are expected to get more frequent, tropical storms to become more intense - and their occurrence to extend further North. Furthermore, precipitation patterns are projected to change, so that there is more precipitation in certain areas, whereas other areas will suffer drought (64,65).

Climate change affects health by modifying social and environmental factors such as clean air, availability of safe drinking water, sufficient nutrition, and secure shelter (5). Furthermore, the occurrence of more extreme weather events creates an increasing threat to health. Climate change has a significant effect on this growing affected population, due to the increasing role of NCDs as a burden of global morbidity and mortality (16,66). For example, CVD is influenced through three main environmental exposures: 1) air pollution, 2) extreme temperatures, and 3)

changes in dietary options (16). Extreme hot temperatures tend to overload the cardiovascular system by increasing the core body temperature, which raises the heart rate, increases peripheral circulation, and enhances sweating with the associated outcome of dehydration. Furthermore, air pollution was shown to have significant adverse effects on cardiovascular diseases (67-72). An example is the influence of global warming on changing nutrition patterns that are currently facing the Inuit. The ongoing warming of the Arctic region has started to disturb traditional ways-of-life including hunting, which is forcing Inuit people to rely on imported goods that compromise mainly energy-dense processed food. This is potentially increasing the incidence of CVD (16).

#### 1.1.4 Disasters

Disasters involve a series of events that usually include a threat to health, safety, security, and/or wellbeing of a larger group of people. These crises are usually caused by one or more events, such as conflicts, epidemics, natural hazards and so on. Those events can be divided into man-made disasters such as wars, armed conflicts, or nuclear accidents, and natural disasters such as droughts, floods, earthquakes, or hail storms. The division between natural and man-made is not of any great importance, as the effects on health-related issues such as impaired sanitation or increased stress are similar. Furthermore, natural disasters can rarely be described as solely natural in reality, i.e. without the involvement of humans in the process. Accumulations of extreme weather events that cause droughts, floods, or avalanches have been recognized to be substantially influenced by humans (65).

Possible immediate health-related consequences of disasters involve injuries, acute mental and physical illnesses, collapse of health care infrastructures, destroyed waste disposal, and the sanitation infrastructure, shortage and/or bad quality of water, and loss or critical reduction of food production supply leading to food shortages. Possible non-immediate health consequences involve infectious disease epidemics, acute malnutrition, poor personal hygiene caused by poor housing, mental disorders, and exacerbation of chronic diseases, including NCDs (12-14). Disasters are widely accepted to put individuals with NCDs at risk, in addition to increased risks of NCD incidence (12,73,74). The increasing impact of the NCDs as a health burden is evident, as they have already become the leading cause of death worldwide.

The most vulnerable groups include uneducated, malnourished and homeless people, elderly, disabled, people with chronic illness, and children (15). The smallest human beings affected are the unborn. Studies on the influences of birth outcomes after the World Trade Centre disaster in 2001 showed that birth weight in full-term-births was significantly lower for those living close to the event site (75,76). Similar results were found for the Belgrade bombings in 1999 (77). Low birth weight in term borns may be linked to non-optimal growth *in utero*, which in turn

has been connected among others to an increased risk of CHD, hypertension, type 2 diabetes mellitus (T2DM), and metabolic syndrome in adult life (78-83).

## 1.2 Hypertension

Hypertension occurs when the blood in the circulation that is being pumped by the heart is under constant pressure that exceeds normal limits (84). The blood pressure (BP) varies for both minimum (diastolic) and a maximum (systolic) range during each heart beat (85). Normal adult BP is defined as being around 120 mm Hg systolic and 80 mm Hg diastolic (Tab.2). In Finland, the diagnosis of hypertension is based on double measurements on at least four subsequent occasions in a sitting position. BP measurements above 90 mm Hg (diastolic), and/or above 140 mm Hg (systolic) indicate hypertension (86,87). The use of hypertension medication is indicated, when 1) the systolic BP is above 159 mm Hg or the diastolic BP is above 99 mm Hg, or 2) the systolic BP is above 139 mm Hg or above 89 mm Hg diastolic BP, and the patient has diabetes, kidney disease, target organ damage, or clinically relevant heart disease or angiopathy (86). Treatment strategies include both medication and lifestyle modification.

Hypertension is a major risk factor for atherosclerosis, which is the main cause for changes in the arteries that lead to CHD and cerebrovascular disease (85,88,89).

**Table 2.** Detailed classification of hypertension and normal blood pressure (86,90)

		Systolic (mm Hg)		Diastolic (mm Hg)
Normal	Optimal blood pressure	<120	and	<80
	Normal blood pressure	<130	and	<85
	High normal blood pressure	130-139	and	85-89
Hypertension	Mild hypertension	140-159	or	90-99
	Moderate hypertension	160-179	or	100-109
	Severe hypertension	≥180	or	≥110
	Hypertensive crisis	≥200	or	≥130
	Isolated systolic hypertension	≥140	and	<90

Hypertension is estimated to cause about 12.8% of all deaths worldwide. The global prevalence of hypertension was around 40% in 2008. Despite a modest decrease since the mid-1980s, the proportion of the world's population with uncontrolled hypertension has increased due to population growth and ageing (91).

In Finland, the estimated prevalence of hypertension is above the world mean, with 52% in men and 46% women according to the WHO (92). The FINRISK study *inter alia* compared hypertension in participants aged 25-64 years in three different regions of Finland from 1982-2007 and came to the conclusion that the prevalence of hypertension dropped from 63 to 52% in men, and from 48 to 34% in women since the mid-1980s (93). According to the same study, antihypertensive drug treatment has increased between 1982-2007 from 8-12% to 11-19% varying by sex and region. The percentage of drug treatment increased steeply between the years 1982 and 2002, and then levelled-out in the 2002-2007 period.

### 1.2.1 Established risk factors

Established risk factors for hypertension include mainly dietary and lifestyle factors. Age, gender and genes are also risk factors. Additionally, hypertension can result from certain chronic conditions or medication (Tab.3).

### 1.2.2 Examples of environmental risk factors

Influences of weather, climate, and temporal variation on hypertension are relatively well studied. Weather and climate influence hypertension mainly through changes in air pressure and temperature (9,94,95). Hypertension has been found to generally occur more frequently in winter than in the summer months (96-98). Air pollution has also been found to increase blood pressure and the risk of becoming hypertensive, especially in subjects with underlying CVD (69,70,99).

**Table 3.** Major risk factors for hypertension (87,100-103)

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Age
Genes or family history
Overweight/obesity
Physical inactivity
Smoking
High sodium intake
Low potassium intake
Low magnesium intake
Low calcium intake
Low intake of fish fatty-acids

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### 1.3 Coronary heart disease

Coronary heart disease (CHD) is characterized by atherosclerosis, a condition in which atheromatous plaques build up inside the coronary arteries over many years. The plaques consist of fatty cores within the arterial wall that are covered by fibrous caps, and these structures narrow the space within the artery. They accumulate and grow throughout life and become only symptomatic when target organs such as the heart become affected. The supply of oxygen-rich blood to the heart muscle is reduced or may even be completely blocked (84,89). Manifestations of CHD include chronic and acute states. Acute manifestations are categorized under the name acute coronary syndrome (ACS), which refers to any group of clinical symptoms compatible with acute myocardial ischaemia (insufficient blood supply) (104). It includes unstable angina and also myocardial infarction.

In the case of myocardial infarction, rapid treatment of the blockage is essential, as the portion of the heart muscle fed by the occluded artery begins to die. Healthy tissue is replaced by scar tissue and may cause severe or long-lasting problems. Angina is characterized by chest pain or discomfort in an area with insufficient oxygen-rich blood flow in the heart muscle (ischaemia). It is a symptom of the underlying problem and in contrast to myocardial infarction does not damage the heart muscle (105).

**Table 4.** Coronary and cerebrovascular disease events in Finland 1991 and 2011 (106)

Events ( 100 000 per year)					
		Coronary heart events		Cerebrovascular disease	
	Age group	1991	2011	1991	2011
<b>MEN</b>	35-44	332	131	145	116
	45-54	1494	603	441	364
	55-64	4077	1715	1335	922
	65-74	8408	4050	3590	1970
<b>WOMEN</b>	35-44	53	25	79	106
	45-54	343	154	216	260
	55-64	1431	425	673	519
	65-74	4472	1477	2088	1199

CHD is one leading cause of death globally and accounts for 12.2 % of all deaths. It also ranks as the sixth most common disability worldwide as measured in disability-adjusted life years (DALYs) (107-109). Projections for the year 2030 predict even further increases in CHD as a cause of death and disability in all regions of the world. This expected increase will largely be due to the projected population ageing, an increase in the prevalence of type 2 diabetes, growing affluence, and climate change (107). CHD is also the leading cause of death in Finland. Despite a slight decrease in the death rate in the recent decades, more than every fifth death (22%) in Finland is caused by the disease (106). Table 4 shows coronary event rates in Finland.

The 28-day case fatality, i.e. the probability of dying within 28 days after the occurrence of the event, was found to have generally decreased between 1994 and 2002 as reported in a nation-wide study on acute myocardial infarction (AMI) in Finland. Case fatalities in the age group of <55 years were around 35% for 1994-1996 vs. 33% for the years 2000-2002, whereas in the older age group  $\geq 55$  years 54% (1994-1996) vs. 50% (2000-2002) were found. One-year fatalities decreased from around 35.5% in 1994-1996 to 34.5% in 2000-2002 in the younger age group, and from 63% to 60.5% in the older age group (110).

### 1.3.1 Established risk factors

Established major risk factors for developing CHD are mainly modifiable risk factors in addition to age, gender and family history (Tab.5).

**Table 5.** Major risk factors for CHD (111-113)

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Age
Gender
Family history
Overweight/Obesity
Physical inactivity
Smoking
High blood pressure
High LDL Cholesterol
Low LDL Cholesterol
Diabetes
Low vegetable and fruit intake / high saturated fat intake

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### 1.3.2 Examples of environmental risk factors

A large body of mainly new studies has confirmed the influence of both cold and hot temperature on the incidence of coronary events (36,114-117). Furthermore, air pollution has been implicated as a risk factor for coronary event incidence and mortality (67,71,72,118,119).

## 1.4 Cerebrovascular disease

Cerebrovascular diseases originate in the vessels that supply or drain the brain. Artherosclerosis develops over many years. Atheromatous plaque builds up inside the arteries and this event is the main cause for changes in the large arteries that supply the brain. Middle-sized and also intracerebral arteries can be affected by acute or chronic vascular diseases of inflammatory origin. Inflammation often results from infections that range from chronic to subacute in intensity. They can also arise from collagen disorders and other vascular disorders. All these diseases may cause obstruction, and lead to thrombosis and embolisms (89). The acute manifestation of cerebrovascular disease is stroke. The WHO defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”(120). There are two major types of stroke: ischaemic and haemorrhagic.

Ischaemic stroke (IS) is the most common type of stroke and is caused by a critical reduction of regional cerebral blood flow. If this blood supply shortage lasts long enough, a stroke develops. This can happen in two ways: either through atherothrombotic changes, where a clot is formed where an artery is already narrow, or through cerebral embolism, where clots, embolus, from other parts of the body travel up to the brain. The pathological substrate of these strokes is ischaemic infarction, where brain tissue dies from anoxia. The size, location and shape of these dead tissue areas vary considerably (89).

Haemorrhagic infarcts (HI) are defined as ischaemic infarcts in which varying amounts of blood cells are found within the necrotic tissue. In a healthy brain, neurones do not come into contact with blood. The brain is supplied by nutrients and oxygen through the thin walls of capillaries. The blood cells originate from a leakage from damaged vessels. This can be due to increased vascular permeability or vascular rupture secondary to ischemia. HIs can be divided in two categories: intraaxial: inside the brain - and extraaxial: inside the skull but not within the brain. Subarachnoid haemorrhage (SAH), epidural haematoma, and subdural haematoma are main types of extraaxial infarcts, whereas intracerebral haemorrhages (ICH) are intraaxial. ICH occurs as a result of bleeding from an arterial source directly into the brain. Most of those strokes originate from the rupture of small, deep arteries. These changes in the small vessels lead to a weakening of the vessel wall, microaneurysms, and consecutive small local bleedings. These can also be followed by a cascade of secondary ruptures of the enlarging haematoma. This

bleeding can continue for several hours and enlarge the haematoma continuously (89). An SAH occurs when a blood vessel on the surface of the brain leaks or ruptures. This type of haemorrhage often does not cause any damage to the brain (120). Impacts of stroke vary from no symptoms to temporary or permanent loss of function of certain body parts due to the disruption of the blood supply to nerve cells, and may also lead to death (84).

Cerebrovascular disease ranks second in the leading causes of death in the world, and accounts for 9.2% of all deaths. Furthermore, it ranks seventh in leading causes for DALYs (109). Projections for the year 2030 predict a further increase in cerebrovascular disease worldwide, especially due to increases in cerebrovascular disease in middle- and low-income countries (107). The case-fatality and the DALYs of the disease highly depend on the time to treatment as well as on the quality of the treatment. Improvements in care and education have caused a decrease in stroke case-fatality and disability over the past decades in high income countries. In Finland, the 28-day case-fatality for IS between 1999 and 2008 was at 10-13%, for ICH 27-34%, and SAH 20-25%, with a tendency to decrease in IS and ICH (121). The same applies for the 1-year case-fatality data that show in IS: 22-27%, in ICH: 42-45%, and in SAH: 27-33%. Cerebrovascular disease events in general have decreased during the last 20 years, especially in the older age groups (Tab.4). Despite this decrease, cerebrovascular disease still ranks number four on the list of the causes of death in Finland (106).

#### 1.4.1 Established risk factors

Similar to CHD, established major risk factors for developing cerebrovascular disease include age and family history mainly in addition to several modifiable risk factors (Tab.6). The risk of cerebrovascular disease is about equal in men and women (113).

**Table 6.** Major risk factors for cerebrovascular disease (113)

Age
Family history
Physical inactivity
Smoking
High blood pressure
High LDL Cholesterol
Low LDL Cholesterol
Diabetes
Low vegetable and fruit intake / high saturated fat intake



### 1.4.2 Examples of environmental risk factors

Seasonal studies of cerebrovascular disease mainly concentrate on hospital admissions and mortality. Generally, deaths and hospitalizations appear to occur less frequently in the summer months. However, results are ambiguous (122-125). Both hot and cold temperatures have been associated with increased stroke mortality (115,117). Similar to that for coronary events, air pollution has been also found to raise stroke mortality (68,126,127). Similar to that for coronary events, air pollution has been also found to raise stroke mortality (68).

## 1.5 Type I diabetes mellitus

T1DM is an autoimmune disorder, and occurs when the immune system misidentifies the insulin secreting  $\beta$ -cells in the Islets of Langerhans of the pancreas as being foreign and destroys them (84,128). It is characterized by hyperglycaemia which is resulting from defects in insulin secretion, insulin action or a combination of both (129). It is of importance to replace the lacking hormone with insulin injections in order to maintain blood glucose concentrations and overall survival. Care also includes a harmonization of insulin treatment, diet, physical activity, and close self-monitoring of the blood glucose level throughout the day. Acute and severe complications include ketoacidosis and hyperosmolar hyperglycaemic states (128,130).

Despite the availability of sophisticated care such as that given in Finland, T1DM is a life-long disease, which often causes complications in the long term. The most common complications are the following:

- 1) Nephropathy, a kidney disease that potentially leads to dialysis treatment and kidney transplantation, and a high risk of cardiovascular mortality attributed to the disease. An estimated 30% of T1DM patients develop nephropathy.
- 2) Retinopathy, which may lead to blindness if untreated. As much as 80% of T1DM patients develop retinal changes within 20 years.
- 3) Arteriosclerosis and obstructions of the coronary and cerebral arteries, which can cause myocardial infarction or stroke, are more common in T1DM patients, and their severity is usually exacerbated.
- 4) Neuropathy includes symptoms such as pain, sensory loss, balance disorders, foot ulcers and foot injuries, which lead to an increased risk for lower-limb amputation (128).

**Table 7.** Centres arranged by countries in descending incidence of T1DM in children ≤ 14 years of age (means of the centres in each country, age-standardized), and the annual change of incidence in per cent (131)

Country (centre-based, not country-wide)	Incidence of T1DM	Annual change of incidence (%)
Finland	40.9	4.2
Sweden	30	3.6
Canada	22.8	5.1
Kuwait	22.3	7
Norway	20.8	-0.9
UK	19.7	4
New Zealand	18	2.8
Denmark	16.6	15
USA	15.9	5.5
Australia	14.5	4.1
Germany	14	2.3
Portugal	13.1	2
The Netherlands	13	3.4
Czech Republic	12.7	9.6
Spain	12.4	-1.9
Switzerland	12	2.1
Estonia	11.7	3.7
Belgium	11.7	1.5
Luxembourg	11.3	-0.1
Italy (Sardinia*)	10.2 (37.8)	0.9 (1.4)
Greece	10	0.9
Austria	9.9	2.1
Hungary	9.7	2.6
Slovakia	9.7	6.3
Bulgaria	9.4	5.1
Libya	9	-0.9
Slovenia	8.9	3.3
Algeria	8.6	11.6
France	8.5	4.8
Lithuania	7.9	3.1
Argentina	7.6	0.4
Brazil	7.5	-16
Latvia	7.4	3.1
Tunisia	7.4	0.7
Poland	7.1	7.6
Russia	6.9	6.6
Israel	6	7.6
Dominica	5.7	-46.1
Romania	5.3	2.8
FYR Macedonia	4.2	9.7
Chile	3.7	7.5
Cuba	2.3	-10.8
Japan	1.7	-3.5
Mauritius	1.3	-2.2
Paraguay	0.9	-0.5
China	0.9	-0.1
Dominican Republic	0.5	12.6
Peru	0.5	12.1
Pakistan	0.5	-5.6
Venezuela	0.1	-6.8

\*Sardinia is an autonomous region of Italy and has a much higher incidence of T1DM than the other regions of that country; therefore it is tabulated separately in brackets

T1DM has its highest incidence between 10 and 14 years of age, and is the most frequent cause of chronic disease in children below 16 years of age (130). The first organisation to establish population-based registries in a standardized way was Diabetes Epidemiology Research International. This organisation created the opportunity to compare the incidence of T1DM between countries (132). Later on, the EURODIAB ACE project enabled a comparison of T1DM with onset in childhood between European countries (133), and in 1990 the WHO launched the Di-aMond (Diabetes Mondiale) project in order to compare variation in childhood-onset T1DM worldwide (131,134). The WHO found great variations in the incidence of T1DM in Europe and worldwide. The highest incidence was found in Finland with 40.9 cases per 100 000/year, and the lowest was found in Venezuela with 0.1 cases per 100 000/year (Tab.7) (131). However, there is paucity of data in large regions of the world, especially Africa, Asia, and South America.

The incidence of T1DM with the onset in childhood has been increasing in most countries. In Finland, the incidence has more than doubled since the 1960s, and the newest data show an incidence as high as 57 cases per 100 000/year (135,136). The Di-aMond data show a mean annual increase of 2.8% for the years 1990-1999 for all included centres. In many centres, the incidence increase has been markedly larger in younger children (137). Predictions indicate a further increase of cases for the next ten years, especially in children below 5 years of age. In Europe, the prevalence of cases in these age groups may increase by as much as 70% (138,139).

### 1.5.1 Established risk factors

Confirmed risk factors for the development of T1DM are genetic predisposition and young age. Other possible risk factors are mainly environmental, including microbial, perinatal, and dietary factors (137).

### 1.5.2 Examples of environmental risk factors

Two different types of seasonality have been attributed to the incidence of T1DM; seasonality of birth and seasonality of the onset of the disease. Seasonality of birth involves seasonal environmental factors that affect the development *in utero*, such as viral infections or the mother's intake of Vitamin D (140,141). Seasonal variation of the onset of the disease has been studied extensively, with conflicting results (142-146). A study associated cold ambient temperatures at birth with increased insulin resistance and dyslipidaemia, which can result from prolonged elevation of insulin levels (147).

## 1.6 Obesity

Obesity is a condition whereby an excess of body fat has accumulated to such an extent that it becomes a health risk (148). This accumulation usually happens as a result of an imbalance of energy intake and energy expenditure. In Finland, obesity is diagnosed when the body mass index (BMI) exceeds  $30 \text{ kg/m}^2$ , and the waist circumference exceeds 100 cm for men and 90 cm for women. Overweight is defined as  $\text{BMI} \geq 25 \text{ kg/m}^2$ . BMI is the weight of an individual in kilograms divided by the squared height of that individual in kilograms per squaremeters. Additionally, the measures of waist-to-hip ratio (WHR) and the waist circumference (WC) have been used to define obesity, as the distribution of the accumulated fat affects the risks associated with obesity, and the potential associated disease risk (148). Additional methods also include different measures of body composition. However, these other methods are usually costly and difficult to carry out in practice, and therefore not usually used in general practice. Treatment includes primarily lifestyle interventions; reduction of calorie intake and increase of physical exercise. In addition, drug treatment can also be used. Surgical interventions such as bariatric surgery are only performed when the lifestyle interventions do not lead to sufficient weight loss (86).

Being overweight or obese increases an individuals risk of getting diseases such as type 2 diabetes mellitus, CHD, cerebrovascular disease, hypertension, musculoskeletal disorders, certain types of cancers, or psychosocial problems. The global prevalence of obesity has more than doubled since the 1980s, and even tripled in Europe (149,150). The prevalence of obesity in women for the year 2008 was estimated to be 14% worldwide, 23% in Europe, and 23% in Finland. The prevalence of obesity in men in 2008 was estimated to be 10% worldwide, 20% in Europe, and 23% in Finland (151,152). Predictions for the future indicate even further global and local increases in the incidence of the condition (153).

### 1.6.1 Established risk factors

The obesity and overweight states are usually a long-term consequence of an energy imbalance, whereby the energy intake exceeds the energy expenditure. The recent epidemiological trends of global obesity and overweight suggest that mainly environmental and behavioural changes can be attributed to this change. Genetic, biological and other interacting factors such as smoking cessation, sex and age determine the weight gain of the individual (148).

**Table 8.** Estimated relative risk of health problems associated with obesity (modified after (148))

<b>Very high relative risk (&gt; 3)</b>	<b>Moderately increased relative risk (2-3)</b>	<b>Slightly increased relative risk (1-2)</b>
T2DM mellitus	CHD	Cancer (breast cancer in postmenopausal women, endometrial and colon cancer)
Gallbladder disease	Hypertension	Reproductive hormone abnormalities Polycystic ovary syndrome
Dyslipidaemia Insulin resistance Breathlessness Sleep apnoea	Osteoarthritis (knees) Hyperuricaemia and gout	Impaired fertility Lower back pain Increases risk of anaesthesia complications Foetal defects associated with maternal obesity

### 1.6.2 Examples of environmental risk factors

The influences of temperature and season around the time of birth on adulthood obesity have been studied. However, studies are rare and the few that exist show ambiguous results. Exposure to cold temperatures around the time of birth has been suspected to increase the probability of becoming obese in adult life (154,155). Seasonality and either lower or higher outdoor ambient temperatures during pregnancy have been repeatedly associated with low birth weight, which in turn has been associated with obesity (33,34,156-158).

## 1.7 Gene-environmental interactions

The individual responses to various environmental risk factors differ largely partly due to underlying genetic factors. Therefore, gene-environmental interactions influence the individual responses to various stressors. It is also known that epigenetic factors which are often induced by environmental factors influence gene expression and consequently later health and disease risks. These factors will not be discussed in this work however.



## 2 Aims of the study

The aims of the study were to examine the influence of certain types of weather, season, and also the impact of a disaster on the incidence of NCDs.

The specific aims of the study were as follows:

1. To determine the usefulness of the daily weather forecast in the prediction of coronary events (Paper I),
2. To determine the influence of temporal variation and variations in the daily weather conditions on the 28-day case-fatality of coronary events (Paper II),
3. To compare temporal variation patterns on the incidence of T1DM globally (Paper III),
4. To determine the prenatal influence of the bombings of Helsinki during WWII on the incidence of CHD and cerebrovascular disease in adult life (Paper IV),
5. To determine the prenatal influence of temperature and season on the incidence of cardiovascular disease, CHD, cerebrovascular disease, and obesity in adult life (Paper V).





# 3 Materials and methods

## 3.1 Study subjects

### Papers I-II

#### *Epidemiological data*

The data set includes all fatal and non-fatal coronary events recorded in the years 1983, 1988, and 1993 in the Finnish cities namely: Helsinki, Jyväskylä, Kuopio, Rovaniemi, Tampere, Turku, and Oulu (n=9243, including first and recurrent cases). Data were obtained from two nationwide registries: the Cause of Death Register (CDR), and the Hospital Discharge Registry (HDR). International Classification of Diseases (ICD) version ICD-9 was used in both registries between 1986 and 1995. The ICD-9 codes used for coronary events were 410-414.

The HDR is maintained by the National Institute for Health and Welfare. It has record of all discharges from hospitals in Finland since 1967. The records include individual clinical and administrative data such as discharge diagnoses, surgical procedures, dates of admission and discharge, and data on the attending hospital. In Finland there are no medical record abstractors, so clinicians who take care of patients are also responsible for recording and coding their patients conditions (159,160).

The CDR is maintained by Statistics Finland, Helsinki. It is compiled from data obtained from death certificates, and supplemented with data from the population information system of the Population Register Centre. The CDR covers all persons who died in Finland or abroad while they were domiciled in Finland. It details causes of deaths, age, gender, marital status and other demographic variables (161). The underlying cause of death is registered in the death certificate, with the possibility of stating two intervening causes of death, one terminal cause of death, and four contributing causes of death (106).

The personal social security number assigned to all Finnish residents was used to execute a computerized record linkage between the two separate data sets, and thereby obtain all the deaths and hospitalizations due to coronary events for those years. HDR was checked for any previous mention of coronary events in order to distinguish between first and recurrent coronary events. The sex-age-municipality-specific population data were obtained from Statistics Finland, to determine the residence of the patient at the time of diagnosis.

### *Weather data*

The weather variables were obtained from the European Centre for Medium-Range Weather Forecasts ERA-40 project, and consists of interpolated measurements of air pressure, air temperature, and wind speed, at six hour intervals (162). Locally available meteorological data for the cities of Oulu and Helsinki were highly correlated with the ERA-40 project data in a comparison.

### **Paper III**

The WHO DiaMond incidence study was a 10-year project that lasted from 1990 to 1999 and which provided a consistent framework for the collection and analysis of T1DM incidence data by using a well-defined population-based registry. The goals of the study were to determine the existence of seasonal patterns in childhood T1DM internationally, provide a uniform basis for standardized studies of risk factors for T1DM, collect standard information on risk factors and mortality associated with T1DM, evaluate the efficiency and effectiveness of health care and the economics of diabetes, and to begin the building up of national and international training programs in diabetes epidemiology (131,163). Data were collected from 112 centres in 56 countries for two specific study periods from 1990-1994, and from 1995-1999 (Tab.9) (131). Each centre was led by a local principal investigator who was responsible for data collection. Every centre had to have a well-defined population-based registry, where the incidence could be assessed accurately as a criterion for being able to participate in the WHO DIAMOND study. Each centre had its own local methods of operation for the incidence study, though every centre followed the framework provided by the WHO DIAMOND study. The centres provided a description of the population base, design of the registry, the sources of data, data items, data management, and the time schedule for data collection. Participating centers submitted annual incidence data to the WHO DiaMond centre located in Helsinki, Finland, using standardized forms. The database included information on sex, ethnic group, date of birth, date of first insulin administration, and source of family history of diabetes (134). The cases include all children aged  $\leq 14$  years with a diagnosis of T1DM during 1990-1999. The diagnosis was based on the 1985 WHO classification of diabetes and diagnostics criteria, and this also covered T1DM diagnosed children in the present study's area. The study area was defined geographically to correspond with administrative and census boundaries (164). The denominator for the analysis were 84 million children per year, and the number of children diagnosed with T1DM over the years was 43 013 (131).

**Table 9.** The location of the 112 centres collected in the DiaMond study.

<b>Continent</b>	<b>Country</b>
Africa	Algeria, Libya, Mauritius, Sudan, Tunisia
Asia	China, Hong Kong, Israel, Japan, Kuwait, Pakistan, Russia, South Korea
Australia	Australia, New Zealand
Europe	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania, Republic of Macedonia, Slovakia, Slovenia, Spain, Switzerland, The Netherlands, United Kingdom
North America	Barbados, Canada, Cuba, Dominica, Dominican Republic, Mexico, USA
South America	Argentina, Brazil, Chile, Colombia, Paraguay, Peru, Uruguay, Venezuela

## Papers IV-V

### *The register cohort and the clinical study sample*

The Helsinki Birth Cohort Study (HBCS) includes 6975 men and 6370 women born in Helsinki, Finland between 1934 and 1944. They were either born in the University Central Hospital or in the Maternity Hospital, and attended child welfare clinics in Helsinki, and were residents in Finland 1971. The year 1971 was when a unique personal identification social security number was assigned to every resident of the country. The data consist of detailed growth information from birth until 12 years of age, birth characteristics such as parity and last menstrual period of the mother, and information on socio-economic factors such as the occupation of the father, apartment size and condition (165). This information was collected from birth records, child welfare and school records. The personal identification number enabled the data to be linked with the national Cause of Death Register (CDR), which was computerized in 1971, as well as with the Hospital Discharge Registry (HDR) for all hospital admissions (see materials and methods Papers I-II). The cohort has been followed up from 1971 until the present to provide reliable information on both mortality and morbidity (165). The following ICD codes were used in our studies: CHD, ICD-8 and 9: 410-414, and ICD-10

I21-I25, and cerebrovascular disease: ICD-8 and ICD-9: 430-438, ICD-10 I60-I69. For hypertension, we used the data of subjects who were entitled to special reimbursement for antihypertensive medication from the Social Insurance Institution of Finland. In Finland, entitlement to special reimbursement is determined by a physician at the National Social Insurance Institution who assesses a clinician's statement based on set criteria.

A sample of the records with more detailed and updated information was obtained by selecting a subset of people from the cohort using random-number tables for the year 2001. Out of 7078 subjects still alive and living in Finland, 2902 were invited to attend a clinical examination. A total of 928 men and 1075 women underwent the examination. The measurements were performed by three trained research nurses between August 2001 and March 2004. Weight and height were recorded to the nearest 0.1 kg, and 0.1 cm, respectively. Both measurements were carried out with the subjects wearing light indoor clothing, without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Information on socio-economic status was derived from the census in 1980 (166). Bioelectrical impedance analysis was performed with the eight-polar tactile electrode system to assess body composition (InBody 3.0, Biospace Co Ltd, Seoul, Korea). Bioelectrical impedance estimates lean body mass and percentage body fat by segmental multifrequency analysis (5,50,250, and 500 kHz), separately from each limb and trunk. The lightly clothed subjects stood on the 4-foot electrodes on the platform of the analyser during the resistance measurements, and gripped the two palm and thumb electrodes (166). Subjects were asked to state their highest BMI in their lifetime - except for the BMI in pregnancy - for maximum lifetime BMI. In our study, we took the highest BMI from either the self-reported variable or from the measured BMI. Subjects were classified as obese with a BMI  $\geq 30$  kg/m<sup>2</sup>.

The study was approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa. Every subject gave a written informed consent before any examinations were carried out for the clinical examination subset (167).

### ***Bombing data (Paper IV)***

Historical sources and archived records from military archives were used to collect the exact times and dates of the bombing raids on Helsinki during 1939-1944. Further information on damage and destruction of buildings, number of injured, and loss of human lives were also gathered from historical sources (168,169).

The bombing raids of Helsinki took place during WWII, were divided into the Winter War (November 1939-March 1940) and the Continuation War (June 1941-September 1944) phases in Finland. There were two bombing raids during the

Winter War; the first was a very intensive raid starting in November 1939, which also initiated this war, and a second was a raid in January 1941. The number of deaths of these two raids was 97, and 260 were injured. The Continuation War consisted of more frequent but less intense bombing rates. In 1941 there were nine raids, 17 in 1942, and 13 in 1943, with a total of 104 dead and 398 wounded (169). In February 1944, three very intensive raids occurred within a short time span. The number of injured (n=364) and dead (n=146) could be kept relatively low due to the successful air defence of Helsinki (168).

### *Temperature data (Paper V)*

The mean monthly temperature data (1923-1944) were available from the Helsinki weather station in Kaisaniemi (170).

## 3.2 Statistical methods

### **Paper I**

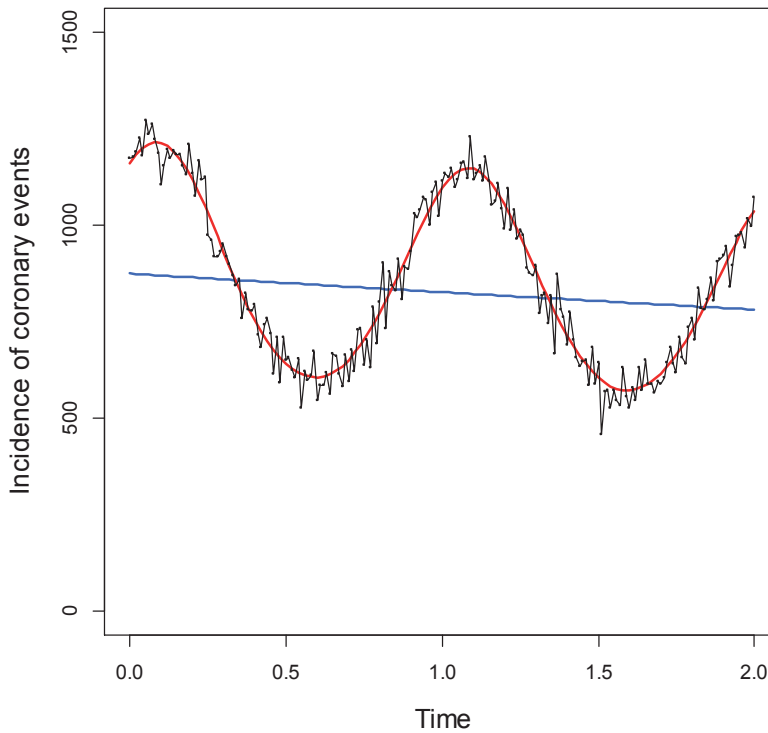
Four generalized linear models of increasing complexity were compared to find a model that potentially predicted the daily numbers of coronary events (Tab.10). The models were fitted separately for the first and recurrent coronary event, sex, and age group (25-54, 55-64, and 65-74 years).

The linear trend found was used to determine that coronary events declined due to risk factor reductions and/or due to improved treatments in a linear fashion during the time span of our data base (1983-1993) (171).

**Table 10.** Regression models that assess the predictability of coronary events from daily weather forecasts

<b>Name</b>	<b>Content</b>	<b>Shows</b>
LT	Model only with linear trend	
FS	Model with linear trend, and Fourier terms (up to four harmonics, and a weekday harmonic) (172)	Temporal influence
DW	Model with linear trend, and daily weather covariates	Weather influence
FW	Model with linear trend, daily weather covariates, and Fourier terms (as above)	Weather and temporal influence combined

Fourier Temporal Analysis is based on the mathematics devised by Joseph Fourier, who lived in the 19<sup>th</sup> century. He showed that any periodic observation can be represented by a combination of sine and cosine curves. Fourier terms therefore allow the modelling of temporal variation, and the number of harmonics corresponds to the number of peaks and troughs in one phase.



**Figure 3.** Example of how the curves of the models could look for: 1) A linear trend (blue) with e.g. decreasing cases over the years. 2) Temporal curves within a year (red) with e.g. summer peaks and winter troughs. 3) Curves on a smaller time scale (black) with e.g. daily temperatures.

## Paper II

The influence of temporal variation and/or weather on the 28-day case-fatality of coronary events was assessed by five regression models of increasing complexity, which were compared to each other (Tab.11).

The covariates of sex and age were significant ( $p=0.03$ ) upon a preliminary analysis, and were therefore retained in all the models. In contrast, the linear trend that almost showed for age in the graphical analysis but was non-significant ( $p=0.71$ ) was left out in all other models than LT.

We assessed how accurately the predictive model would perform in practice by using the leave-one-out cross-validation procedure (in our case one-day-out). For the validation, mean squared errors (MSE) were evaluated, whereby smaller MSE indicated a higher accuracy of the predictive model.



The time of the coronary event was assumed to be the time of hospital admission or the time of death. The weather variables finally included in the W0 and FW model were daily temperature and the square of the daily temperature. The square of temperature was added to detect a possible U-shaped relationship in order to evaluate whether cold and hot temperatures had influences on the outcome.

**Table 11.** Regression models assess the influence of weather and temporal variation on the 28-day case-fatality of coronary events.

Name	Content	Shows
NT	Model only with the covariates of sex and age	
LT	Model with covariates, and a linear trend	
FS	Model with covariates, and temporal Fourier terms (up to four harmonics, and a weekday harmonic) (172)	Influence of temporal variation
W0	Model with covariates, daily weather covariates	Influence of weather without temporal variation
FW	Model with covariates, Fourier terms, and weather covariates	Influence of weather combined with temporal variation

### Paper III

We subdivided the data into three age groups of 0-4, 5-9 and 10-14 years to assess the temporal patterns for each study centre. The monthly numbers of cases were assumed to follow a Poisson distribution. The Poisson distribution is often used to model counts of rare events in large populations. Its purpose is to predict the spread around the mean rate of occurrence. The distribution mean was modelled using a log-linear regression with Fourier terms, with zero to six harmonics, for which zero corresponded to no temporal variation and six meant that each month has its own risk level. The optimal harmonic for each centre was chosen by finding the one with the smallest Akaike criterion. Additionally, a pooled model was run without taking sex and age into account.

Patterns were estimated, and peaks and troughs studied for those centres that exhibited a significant temporal pattern.

The association of the coordinates with temporal/non-temporal variation were tested by running a logistic regression with the geographical latitude and a binary variable for the presence or absence of a temporal variation. Similarly, the association of temporal variation/non-temporal variation with the level of incidence was tested.

#### Paper IV

The influence of severe prenatal stress on the lifelong health outcome was assessed by dividing individual study subject's exposures to bombings when they were *in utero*. These exposures were measured starting from two weeks after the last menstrual period of the subject's mother up until the date of the subject's birth. Bombings were divided into "major bombings" and "all bombings". Major bombings include only bombing days that caused massive damage and destruction of buildings, loss of human lives, and large numbers of injured persons. Major bombings are included in the "all bombings" data (Tab.12).

**Table 12.** The dates of bombings in the city of Helsinki during WWII

Year	All bombings	Major bombings
1939	Nov 30 / Dec 1,2,19,22	Nov 30
1940	Jan 13,14	
1941	Jun 25,26 / Jul 6,7,9,12,22 / Sep 28 / Nov 2,4	Jul 9
1942	Jan 20-24 / March 7,8 / May: 16 / Aug 24,29 / Oct 4,28 / Nov 8, 21-24	
1943	Feb 15,23, 24 / March 15,20-23 / Sep 5,10,11	
1944	Feb 6,7,16,26	Feb 6,7,16,26

The incidences of CHD and of cerebrovascular disease were assumed to follow a Weibull hazard model. A Bayesian conditional autoregressive model was fitted to the Weibull median with time of birth as spatial co-ordinate. The model assumed that people who are born closer in time to each other would have a more similar exposure profile than people born further apart in time from each other. The Weibull model was estimated separately for each group, by gender. Adjustments were made for birth weight, socio-economic status, and parity. The survival curves

were evaluated together with the corresponding pointwise age-specific 95% credible intervals. Credible intervals are the Bayesian equivalent of confidence intervals.

**Paper V**

BMI, maximum lifetime BMI, and obesity linear regression models were all fitted to assess the association of ambient temperature and seasonality with birth weight. Survival analysis was used to assess CHD and cerebrovascular disease (Tab.13).

In addition to the continuous temperature influences, two grouped temperature variables were formed and were evaluated as temperature quartiles:

In the first group called “TempQuart overall”, each month was assigned to one of the three groups (Q1, Q3-Q1 and Q3) on the basis of where its recorded mean monthly ambient temperature lays.

The second group named “TempQuart month-specific” was based on season-specific quartiles. For example, January of 1939 had a mean ambient temperature of -5.5° and therefore it lies within Q1 compared to all annual mean temperatures measured in the time period 1923-1944, but it also lies within in Q3 relative to all January mean temperatures measured over the time period of 1923-1944.

**Table 13.** Methods and adjustment variables to assess the influence of temperature and seasonality

Relationships to be examined		Method	Adjustments
Birth weight, BMI, maximum lifetime BMI	- Month of birth	Linear regression	- Gestational age
	- Month of conception		
Obesity (BMI ≥ 30)	- Mean temperature of birth month	Logistic linear regression	- Sex
	- Mean temperature of conception month		- Father’s occupation
CHD, cerebrovascular disease	- Temperature quartiles	Survival analysis (Cox regression)	- Parity - (Birth weight)

# 4 Results

## 4.1 Prediction of coronary event rates based on the weather forecast

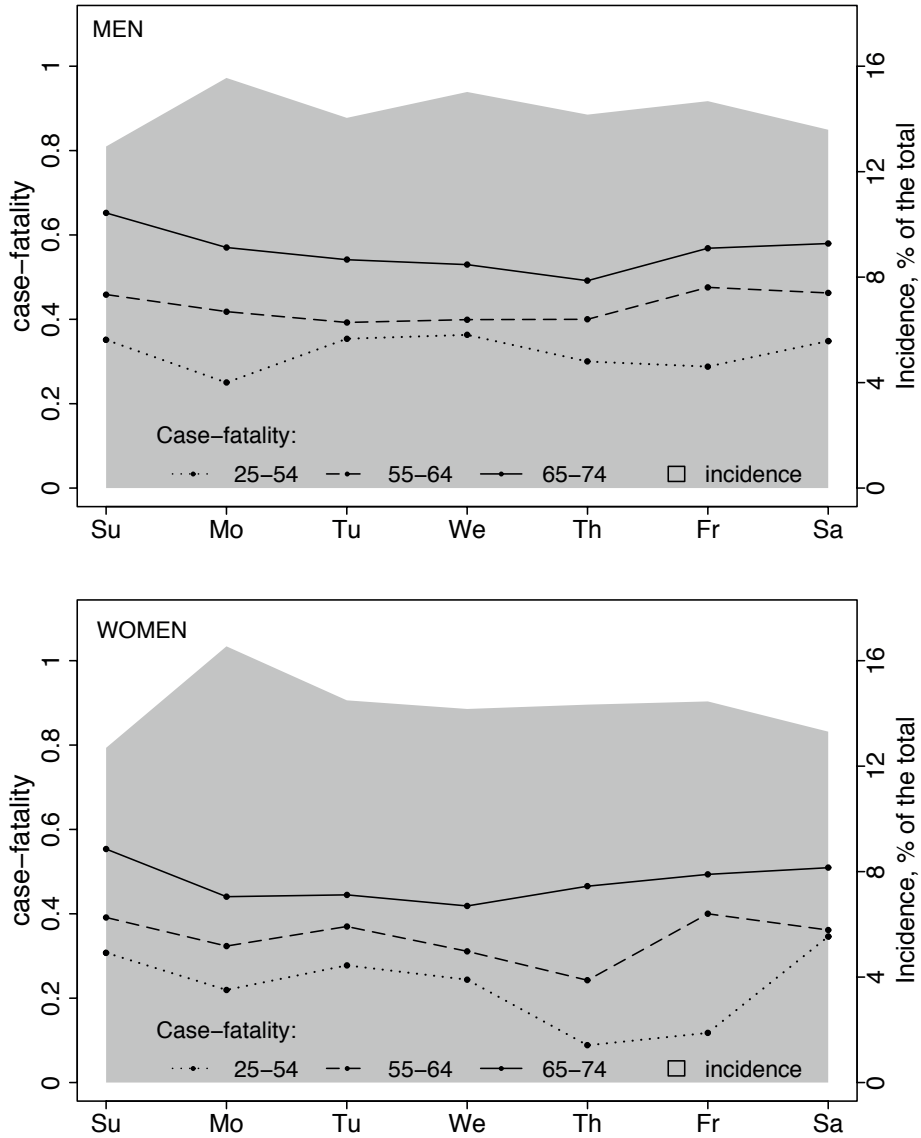
In the seven Finnish cities included in the analysis 9243 cases of first and recurrent coronary events were registered for the years 1983, 1988, and 1993. Over the time period of 1983-1993, there was some minor variation in the number of cases between the municipalities. The mean daily temperatures varied from -25°C to +25°C within the 90% interquartile range (-13;17.6).

There was a consistently significant linear trend, with decreasing numbers of cases during the 1983-1993 time period. An exception was the category of recurrent coronary events in women aged 25-54 years. This was however most likely due to the small number of cases. The estimated decrease in first coronary events varied from 2.4-6.3% within age and gender groups, and in recurrent coronary events from 5.5-11.2%.

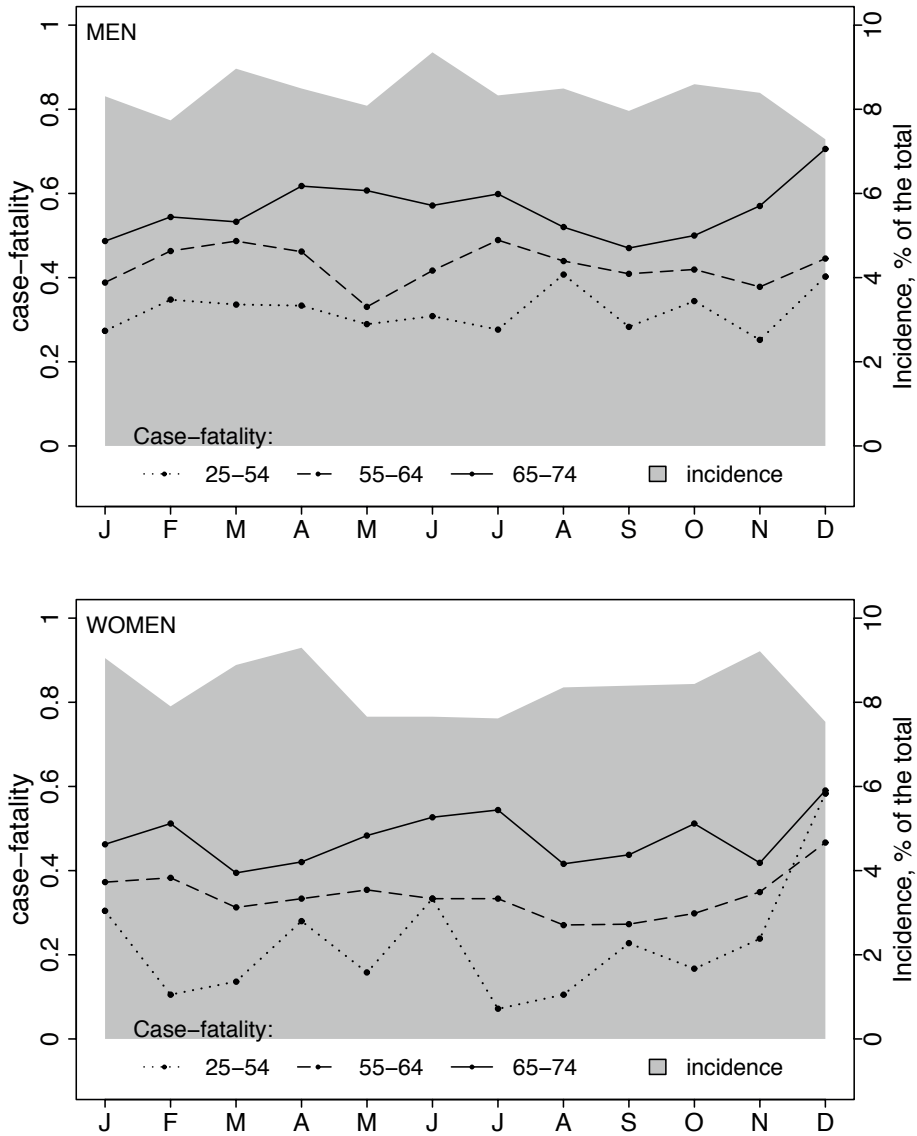
None of the weather variables improved the prediction of the daily incidence rate of coronary events based on one-out and five-out crossvalidation. The weather variables that were evaluated included the following: ambient temperature, squared ambient temperature, variation of ambient temperature, variation of ambient temperature within seven days, air pressure, and wind speed. Neither the addition of the temporal variation component nor the temporal variation on its own showed an improvement of the prediction.

## 4.2 Temporal variation in the case fatality of coronary events

There were 7328 cases of first coronary event registered in the years 1983, 1988, and 1993 in the seven Finnish cities included in the analysis. The overall 28-day case fatality was 44%, as 3196 subjects died within 28 days of their coronary event. The lowest case fatality was found in women of the 25-54 cohort (22%, CI 14-32%), whereas the highest was found in men for the 65-74 cohort (55%, CI 52-60%). In general, older age predicted higher case fatality; the numbers were generally lower for women, though. The variation between the study years was not significant.



**Figure 4.** Observed weekly variation of first coronary event incidence and first coronary event case fatality rates by age group and sex for the years 1983, 1988, and 1993. This figure is reproduced with permission of Informa Healthcare.



**Figure 5.** Observed monthly variation of first coronary event incidence and first coronary event case fatality rates by age group and sex for the years 1983, 1988, and 1993. This figure is reproduced with permission of Informa Healthcare.

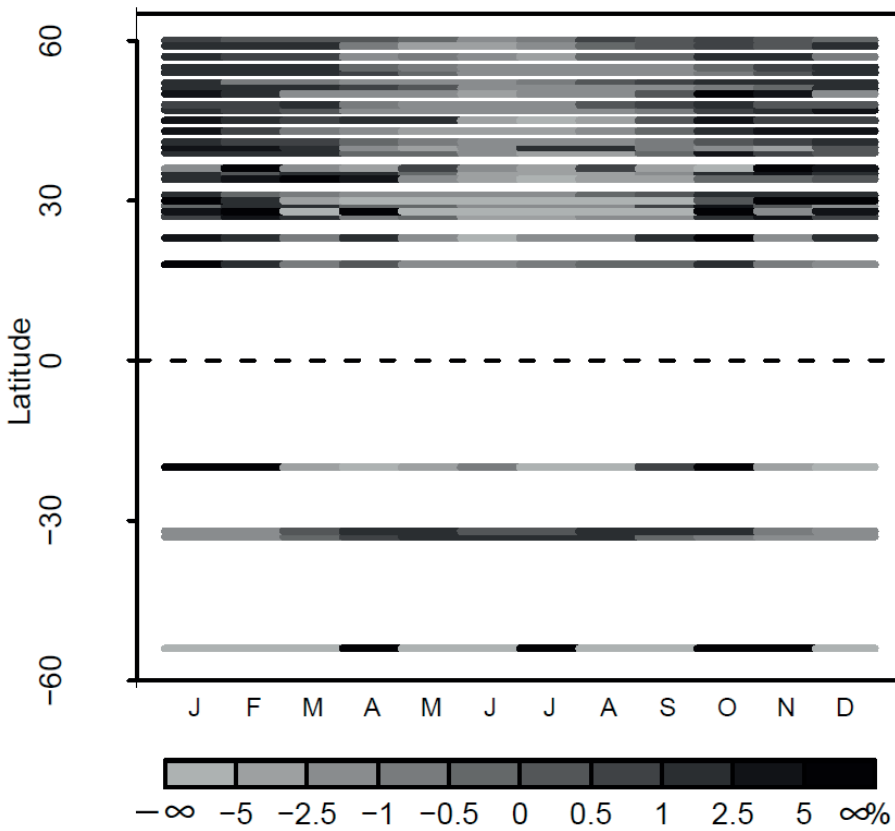
Variation by month and by day of the week was significant (Fig.4 and 5). The case fatality rates of the month December proved to be significantly higher than the mean of the rest of the year ( $p<0.05$ ). However, the risk did not differ significantly from the next highest risk month. The Christmas season - defined as 23<sup>rd</sup>-31<sup>st</sup> of December - proved to be the riskiest time period, with significantly higher case fatality rates for all except young men (25-54 years of age), and older women (65-74 years of age). Sunday was the day of the week found to have the highest case fatality rates, but only for the oldest age group ( $p<0.01$ ).

Cross-validation analysis revealed that the best prediction of case fatality was accomplished by a model fitted with temporal variation influences, but without the weather covariables (model FS, see materials and methods). However, the MSE were big compared to the NT model (only with covariates sex and age), so neither the temporal variation nor the weather variables were of use in the prediction of case fatality.

### 4.3 Seasonal variation of diagnosis of T1DM in children

After exclusion of the centres without sufficient data from at least one year, 105 centres from 53 countries remained. Of these, 42 centres showed significant temporal variation in the incidence of T1DM ( $p<0.05$ ), when the data were pooled for sex and age. The nature of the temporal variation was seasonal, as 28 centres had peaks in the winter months (October-January), and 33 had troughs in the summer months (June-August). The four centres with statistically significant patterns in the Southern hemisphere did not show exactly mirror images of the pattern in the Northern hemisphere, but two centres had a generally higher incidence of T1DM in children during the southern winter months and a trough in the incidence in the summer months (Fig.6).

Centres further away from the equator were more likely to have a significant seasonal pattern ( $p<0.001$ ). However, the geographical location according to the longitude had no influence. When data were divided into males and females, higher numbers of centres manifested with significant seasonal patterns for males than in females (33 vs. 26 centres). Furthermore, division into cohorts of 0-4, 5-9, and 5-14 years of age had more significant seasonal patterns in the two older age groups.



**Figure 6.** Estimated seasonality patterns for T1DM incidence in the centres with significant seasonality, arranged by latitude. Notes: The shades of grey reflect the difference between the annual incident cases estimated to occur in each month. Darker shades of grey correspond to annual peaks and lighter shades to troughs. This figure is reproduced with permission of John Wiley & Sons, Inc.



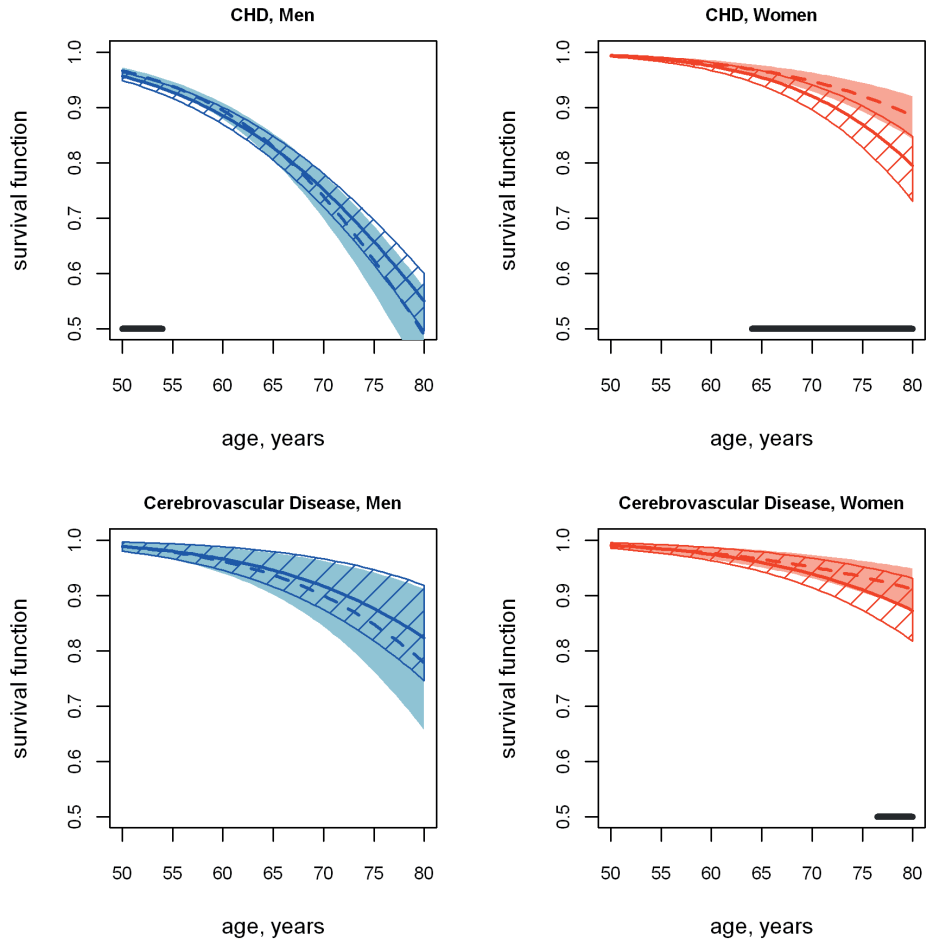
#### 4.4 Prenatal exposure to wartime stress and its influences on diseases in adult life

A total number of 13 039 records were used for the analysis. As much as 57% of the subjects were exposed to at least one bombing while *in utero*, and 40% were also exposed to at least one major bombing. The 12 209 records included information on the father's occupation and parity.

No differences between exposed and unexposed subjects for birth weight, gestational age, birth weight adjusted for gestational age, ponderal index, or length at birth were detected. There were minor differences in the distribution of father's occupation and parity. In further analysis, parity was found to have no influence on the risk of either developing CHD or cerebrovascular disease. However, the male offspring of labourers showed to have a higher risk of developing both CHD and cerebrovascular disease in later life than male offspring of non-manual workers. Additionally, birth weight had only an influence on CHD risk in men ( $p=0.0013$ ).

A graphical analysis of the mean-age-to-event CHD plotted against the time points of the bombings showed no tendencies of either adverse or protecting influences of the bombings. A similar graph for cerebrovascular disease neither showed any tendencies.

We detected better survival rates for CHD and cerebrovascular disease of subjects who were exposed to bombings when fitting curves for CHD and cerebrovascular disease separately by sex and age. Higher survival rates for CHD were found for women between 63 and 80 years of age, and for men between 50 and 54 years of age, when exposed to all bombings (Fig.7). In the "major bombings" group, only women between 62 and 80 years were affected. Regarding the incidence of cerebrovascular disease, women between 76 and 80 years of age were affected in the major bombing group, and from 70 to 80 years in the "all bombings" group.



**Figure 7.** Posterior 95% envelopes and mean survival curves of CHD and cerebrovascular disease adjusted for birth weight, parity and father’s occupation. Envelopes were fitted separately for individuals unexposed (solid line) and exposed (dashed line) to **all** bombing events. The thick horizontal lines indicate significant differences in survival. This figure is reproduced with permission of Informa Healthcare.

## 4.5 Influences of temperature at time of conception on diseases in adult life

A total number of 11 237 records in the register-based sample were used for the analysis of birth weight, CHD, hypertension, and cerebrovascular disease. A total of 1678 records were used from the clinical study sample for the analysis of obesity-related variables.

Women who were conceived during the warmest temperatures of the time-series in the 1923-1944 period were found to have significantly higher probability of getting hypertension in adult life (Tab.14). An increase of temperature was also generally associated with hypertension in women.

**Table 14.** ANOVA p-values to assess the association between season/temperature and birth weight/CHD/cerebrovascular disease in the register cohort sample

	Season	Temperature (continuous)	TempQuart overall	TempQuart month- specific
<b>MEN</b>				
Birth weight	0.64	0.45	0.24	0.34
CHD	0.59	0.26	0.22	0.90
Cerebrovascular disease	0.34	0.67	0.88	0.52
Hypertension	0.19	0.97	0.96	0.77
<b>WOMEN</b>				
Birth weight	0.74	0.78	0.98	0.20
CHD	0.49	0.25	0.08	0.36
Cerebrovascular disease	0.16	0.65	0.77	0.79
Hypertension	0.06	<b>0.001</b>	<b>0.04</b>	0.42

statistically significant in bold / TempQuart: temperature quartiles

Men who were conceived during the warmest months in the 1923-1944 time series (Q3, TempQuart overall) had a lower mean BMI in adult life (Tab.15).

Women who were conceived during a specific month with mean temperatures in the lowest quartile within the 1923-1944 period (Q1, TempQuart month-specific) had a lower mean BMI, a lower risk of obesity and also a lower fat percentage in adult life (Tab.15).

There were no temperature associations found for birth weight, CHD, or cerebrovascular disease. Season had no apparent influences on the outcomes studied.

**Table 15.** ANOVA p-values to assess the association between season/temperature and obesity variables in the clinical study sample. Significant p-values indicate that the given factor has an influence on the respective outcome.

<b>MEN</b>	<b>Season</b>	<b>Temperature (continuous)</b>	<b>TempQuart overall</b>	<b>TempQuart month- specific</b>
BMI	0.07	0.36	<b>0.03</b>	0.63
Obesity	0.58	0.30	0.14	0.54
Fat percentage	0.65	0.24	0.29	0.41
<b>WOMEN</b>				
BMI	0.63	0.84	0.66	<b>0.02</b>
Obesity	0.41	0.82	0.87	<b>0.02</b>
Fat percentage	0.77	0.75	0.77	<b>0.03</b>

statistically significant in bold / TempQuart: temperature quartiles



# 5 Discussion

The environment has a major impact on the human being. Predictions concerning the ongoing climate change indicate more extreme weather situations and natural disasters in addition to the global warming trend *per se*. This study investigated the associations of weather conditions, temporal variations, and the impact of a disaster on certain diseases. It shows that these factors influence certain NCDs – more specifically T1DM, CHD, cerebrovascular disease, hypertension, and obesity - and therefore such data contributes to the knowledge of this increasingly important research field.

## 5.1 Prediction of coronary event rates based on the weather forecast

The factors measured included linear trend, weather conditions, and seasonal variations, of which the linear trend turned out to be the single most significant influence on the incidence of coronary events. The factors of weather conditions and seasonal variations did not improve the predictive power of the model for the available Finnish data.

Studies on the influence of cold outdoor ambient temperature on coronary events show ambiguous results. One study performed in Minnesota (USA) which has similar mean monthly temperatures over the year as in Finland investigated the influence of daily weather conditions in relation to myocardial infarction. No significant influence was reported (173). Studies that emanated from Sweden and Kazakhstan – with very cold mean temperatures – and a study from Switzerland produced similar results as the study in Minnesota (41,116,174). In contrast, several studies reported adverse influences of cold temperature on coronary events, among them a study from Eastern Siberia (Russia), Moscow (Russia), a few studies from the UK and Germany and studies from countries with warmer climates such as Florence (Italy), Beijing (China), and Taiwan (117,175-180). The adverse influence of hot temperatures on coronary events is well documented and was found in studies done in warm and also cold climates (114,115,180-182).

Periods of elevated temperature have possibly a greater impact in Northern areas than do periods of very cold temperatures. Adaptations to cold temperatures over the centuries may decrease potential health impacts of the cold regardless of whether they are physiological or behavioural. On the other hand, inhabitants of these higher latitudes are not appropriately acclimatized to periods of high temperatures. Two studies that originate in Sweden and Moscow showed that heat may have a greater impact on health than cold temperatures in their respective latitudes

(179,181). The study periods (1998-2003 and 2000-2005) of those two publications included very hot summers, whereas there were no remarkable hot summers in our study period. Consequently, the potential heat wave impact on health in Finland was not apparent in our models.

The influence of temperatures on coronary events can also lag. “Lagged” means that there is a time interval between cause and effect. For example if the impact of a few successive hot days would manifest as a health effect only many days later. Several studies found influences of lags (175,178,181). We studied these influences on cold and hot temperature with lags up to seven days, but we did not find any influence.

## 5.2 Temporal variation in the case fatality of coronary events

We studied the influence of temporal variation and weather conditions on the case fatality of coronary events. We observed significant influence of weekly and monthly variation in case fatality, whereas we did not find any influence of weather conditions.

The highest case fatality rates were observed for Sundays. Another study reported significantly higher mortality in patients admitted to the hospital on weekends compared to those admitted during the week (183). Patients who were admitted during weekends were less likely to undergo invasive treatments especially in the first days after admission than patients admitted during week days. Such invasive treatments include percutaneous coronary intervention and coronary bypass surgery. Furthermore, the time between admission and subsequent invasive treatment was significantly longer in patients with a weekend admission. The reason for that might be the shortage of specialized hospital staff during weekends. Lower staffing also applies to the December holiday period, during which we also observed increased coronary event case fatality.

The month of December had the highest coronary event case fatality rate. Two other studies also focused on case fatality and found increased rates in winter (184,185). Another two studies investigated the seasonality of incidence and also of mortality of AMI (186,187). Both found winter peaks in the incidence and in the mortality of AMI. One Scottish study that analysed incidence and mortality of AMI distinguished by month and found December and January had the highest incidence and mortality rates. In an Italian study, the case fatality was clearly higher in winter than in the summer, whereas autumn and spring were about even. Thus, higher mortality in winter might originate from both higher incidence and higher case fatality.

Possible reasons for seasonal variation of case fatality of coronary events may originate from several factors. For example, the direct physiological impact of weather and season from temperature, air pressure, or air pollutants is one factor (185,188,189). However, in our study there was no statistically significant influence of temperature in case fatality detected. Concomitant diseases such as influenza, other viruses and respiratory diseases might also underlie seasonal fluctuations and add to the case fatality of coronary events. However, those diseases do not appear exclusively in December, and therefore cannot fully explain the peak detected. Another factor is the time to treatment interval in winter. The time taken due to travelling from the place of the incident to reaching hospital might be increased due to bad traffic conditions caused by snowfall or black ice, and therefore this delay potentially exacerbates the condition of the patient. Again, those situations are not typically worse in December than in the other winter months. Two studies found a peak of fatal coronary events during the December holiday season. One suggested a superimposing of respiratory diseases, behavioural changes in the consumption of food, salt, and alcohol, and the emotional and psychological stresses of those holidays (190). The other study proposed that persons with symptoms would inappropriately delay seeking medical care in their holidays and therefore the risk of death would be much higher during this time (191). Together with the low specialized hospital staffing during the holiday season, these might be the reasons for the peak case fatality found in December.

### 5.3 Seasonal variation of diagnosis of T1DM in children

Temporal variation in the incidence of T1DM was studied for different climates. We found that 42 out of 105 centres of 53 countries had a significant temporal variation in the incidence of T1DM. The nature of the temporal variation was seasonal, as 28 centres had peaks in winter, and 33 had troughs in the summer months.

The underlying reasons for those seasonal patterns are numerous. Viral infections are suspected to either affect the incidence level or to change the seasonal pattern itself (192). Glucagon secretion by pancreatic cells raises the level of blood glucose, and was found to cause higher plasma levels in winter compared to summer (193). Elevated adrenalin levels, which raise the blood glucose level in the 'flight or fight' response, were also found to exert a greater influence in winter (194). Similar findings have been found for growth hormone, thyroid hormone, and steroid hormones (195-197). There are also suggestions that behavioural differences in summer and winter including diet and exercise might have an influence. Furthermore, the summer holidays were reported to provide a rest from school stresses for Scottish children and more opportunities for exercising (186). These hormonal changes in the human body together with the seasonal dietary and exercise



changes, and the occurrence of viral infections during the colder months may explain the seasonal patterns of the diagnosis of T1DM.

A higher incidence of T1DM was generally found in children who lived in a region that had significant seasonality. The interpretation of the results is therefore difficult, as the probability of detecting seasonality increases with the number of cases per year. Thus, seasonality might be only found in populations with a high incidence of T1DM. This may partially explain why seasonal patterns are often found among the older group and/or among boys, as the incidence is generally highest in these groups.

#### **5.4 Prenatal exposure to wartime stress and its influences on diseases in adult life**

We observed higher CHD survival rates among *in utero* subjects exposed to bombings for women at 64 years of age and older, and for men between 50 and 54 years of age. There were no significant differences in birth weight, birth weight adjusted for gestational age, ponderal index, gestational age, and length at birth between the exposed and unexposed groups.

We divided the bombings into two categories, where major bombings only included bombing dates in which there were considerably more casualties and damages to buildings than during the other bombings. The expectation was that major bombings would be more stressful and therefore would show a potential influence on health more clearly. However, no such influence was observed.

Some studies on the effects of the terrorist attacks on the World Trade Centres in New York in 2001 and the Belgrade bombings in 1999 reported decreased birth weights (75-77). This would suggest a restriction of growth when exposed to stress in utero. However, we did not find such an influence in our study.

Miscarriages that were caused by stress may affect 'genetically weaker' embryos and fetuses (198). As the stress of the bombings was severe, miscarriages could have occurred more frequently and therefore lead to a selection bias in our sample. According to this hypothesis, stronger and therefore healthier embryos and fetuses would have more likely survived. The same applies to CHD. However, there is a lack of data on miscarriages, thus it is not possible to test this hypothesis, and the bias might be too small to influence the results significantly.

Contrary to our hypothesis, we found higher CHD survival rates in subjects exposed to bombings *in utero*. Studies including the Dutch Hunger Winter study, the Leningrad Siege study, and the Channel Island famine study focused mainly on the influences of malnutrition on the unborn child and its impact on adult health

(199-202). However, the findings varied among those studies. In the Leningrad study and the Channel Island Study only small influences were observed, whereas the Dutch Hunger Winter study suggested adverse long-term influences of malnutrition during prenatal life on the risk of getting CHD and T2DM in later life. A Cuban study focused on the impact on health caused by the economic crisis including food and medicine restriction due to the US embargo. Despite those shortages, Cuba showed health improvements mediated by lowered infant and maternal mortality, and also a reduction of other diseases (203). This indicates that milder food shortages may also be protective regarding long-term health.

We focused on CHD and cerebrovascular disease which usually occur late in adulthood. At the time of the study, most of the subjects were between 60 and 70 years of age. A longer follow-up would therefore increase the statistical power of the study.

## **5.5 Influences of temperature at time of conception on diseases in adult life**

We observed a higher probability of getting hypertension in adult life in women who were conceived during the warmest temperatures of the study period. Furthermore women who were conceived during a relatively cold month compared to the same month in the 1923-1944 time period had lower BMI, obesity risk, and lower fat percentage in adult life. Men who had been exposed to the warmest months of the time-series had a lower mean BMI.

We found an association between the exposure to relatively cold months during conception with lower obesity-related variables in women. When a month is colder than usual, this usually requires some form of adaptation. Such an adaptation can include clothing and/or in the colder month the increasing heating indoors. Such adaptation usually takes a certain time, during which prolonged cold exposure and therefore a lowering of the core temperature is possible. This lowering of the core temperature could have an impact on the conceived embryo or even the selection of the sperm that fuses with the ovum.

We also observed associations of warmer temperatures at conception with lower BMI in men and a higher risk of hypertension in women. People living in northern latitudes such as the Helsinki area are not acclimatized to heat, and will therefore be easily overheated/stressed during a period of higher temperatures or even a heat wave. Additionally, the housing in Helsinki is built for cold conditions, which means that the insulation will keep the heat inside and in many homes the heat persists even if it cools down outdoors. The exact underlying mechanisms for our findings are unknown and require more research.

Many other stressors were involved during war time, including nutritional restrictions, concern for family members at the front, threat of invasion by the enemy, and related war strains. There was food rationing for many consumables in Helsinki. Furthermore, the quality and quantity of the food was occasionally insufficient to meet the nutrient requirements of the population (204). In the framework of this study, the influence of nutritional restrictions could not be investigated, as this would need extensive research. Previous studies focused upon the influence of prenatal nutrition on CHD and CVD in adult life (199-202), with ambiguous results. Only the Dutch Hunger Winter study showed increased risks of CHD, hypertension, and T2DM. The Channel Island Famine Study and the Leningrad Siege study did not find such associations. In conclusion, the influences of the hardships of the war are very hard to estimate. (The same applies for Paper IV.)

## 5.6 Strengths and limitations of the data sets

For a detailed description of the data sets see chapter 4: materials and methods.

### **Epidemiological data of Papers I-II**

The personal social security number assigned to all Finnish residents was used to perform a computerized record linkage of individuals for the HDR and CDR data sets. This unique personal number enables a linkage of extraordinary precision. Furthermore, the agreement in diagnosis concerning the ICD-9 codes of coronary events in the combined registry was found to vary between 87-100%, which is a very good level of agreement (205).

Although there has been a decrease in the incidence of coronary events since the mid-1980s, Finland still belongs to the high incidence countries. However, a total population of 5.3 million people at time of making this study may not provide enough statistical power to detect potential weather influences.

The results of our studies cannot be generalized for older age groups, as there is a lack of data for the age group above 74 years. There is no reason, however, to expect that the results would not be relevant in a higher age group as well.

### **Weather data of Papers I-II**

The weather data of the ERA-40 project was intentionally chosen as it is free of charge and globally available. In this way, the generalized model formulated in our study could easily be reused in other regions of the world using local weather data from the same source.

### **The WHO DiaMond data of Paper III**

The strength of the DiaMond data is certainly its standardized global collection procedure for the incidence, mortality, and health care aspects of childhood T1DM.

The set-up and maintenance of population-based registries in low-income countries is very challenging. Furthermore, the assumed low incidence in countries and regions around equator latitudes would require an even larger surveillance population to obtain stable estimates for T1DM incidence and mortality. In our study, centres further away from the equator tended to show more seasonality than centres closer to it. However, due to the sparse data from Asia, and Africa, and the Southern hemisphere in general, this association is not conclusive.

### **The register cohort and the clinical study sample of Papers IV and V**

The participants of the HBCS study were born at the Helsinki University Central Hospital and their attendance at the child welfare clinics was voluntary. Therefore those subjects might not be fully representative of all people born in Helsinki at the same time. However, the distribution of social class at birth in the data set – indicated by the father’s occupation- was similar to that of the whole city.

### **Bombing data of Papers IV and V**

Additional information about bomb false alarms i.e. where there were no actual bombings was available. However, it is hard to estimate to what extent these false alarms also caused stress on their own. For this reason, we decided not to include the alarms, because actual bombings would definitely have a higher impact than false alarms.

Although the bombings were not distributed evenly throughout the city, Helsinki during 1934-1944 was limited to a peninsula surrounded by the sea. Therefore, we can assume that the threat of losing one’s life, friends and family, or property was shared equally amongst all 275 000 inhabitants during that time (206).

### **Weather data of Paper V**

We used mean monthly temperature data for the study, because daily measurements were not available. The study could be refined using daily temperatures due to the smoothing out of extremes when calculating means. However, we would not expect the results to change much with daily data, as e.g. a heat wave which lasts

for one week would conceivably increase the monthly mean ambient temperature, except when that same month included an unusually cold week.

# 6 Conclusions

This study contributes to the research on the fundamentals of the influences of weather, temporal variation, and disasters on NCDs. Associations with those factors were found for CHD, cerebrovascular disease, T1DM, hypertension, and obesity.

The conclusions related to the specific aims are:

The daily weather forecast did not improve the predictive power of the models in the case of Finland.

There were significant weekly and monthly variations in the case fatality of coronary events in Finland, with the highest case fatalities occurring during the December holiday season and also on Sundays. Weather conditions were not found to have an influence.

The seasonality of the incidence of T1DM in children is a genuine phenomenon globally, which has been now demonstrated by this large standardized study. The geographical latitude appears to influence the probability that a location exhibits a seasonality pattern.

A slight protective influence for the life-long development of CHD and cerebrovascular disease was detected for women who were *in utero* when the bombings in Helsinki in WWII occurred.

Temperatures at conception were found to have long-term influences on the outcomes of hypertension, overweight, and obesity.



# 7 Future Directions

The ongoing climate change is predicted to increase extreme weather events and therefore potentially increase its overall impact on NCDs.

A generalized linear model that includes both Fourier terms and meteorological covariates may prove to be of use in predicting increased risk situations in future, such as that formulated for Paper I.

Seasonality patterns of diabetes might become more evident and may also shift with climate change. Data should also be collected in future, including additional data from low-income countries in order to monitor these changes and prepare for potential interventions.

Disaster preparedness is becoming increasingly important in geographical areas which hitherto have not been affected. Preparedness should help to ensure the prevention of disease and lessen the aftermaths of disease and thereby also provide economic savings. In Northern countries, the focus should especially be on cumulative heat periods in the near future.

In order to do justice to this complex theme with manifold factors, future work should preferably consist of interdisciplinary scientific teams including physicians, gene specialists, geographers, statisticians, biologists etc. This would ensure more objective and therefore more reliable studies.





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