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Seasonal variation in incidence of acute myocardial infarction and cardiovascular disease risk factors in a subarctic population

The Tromsø Study

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“Whoever wants to pursue properly in the science of medicine must proceed thus. First he ought to consider what effects each season of the year can produce; for the seasons are not all alike, but differ widely both in themselves and at their changes.”

Hippocrates

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CONTENTS

SUMMARY

A seasonal pattern with winter peak in acute myocardial infarction incidence and cardiovascular disease risk factors is observed in studies worldwide. However, several previous studies have methodical limitations and few are performed in cold climate areas. The aim of this thesis is to assess the effect of season and meteorological factors on first-ever myocardial infarction and the seasonal variation in cardiovascular disease risk factors in a subarctic adult population with long-term follow-up, using appropriate methods with adjudicated outcomes and well-defined exposures.

The population-based Tromsø Study consists of more than 40,000 individuals living in a subarctic climate in Northern Norway. The cohort members have been examined up to nine times in six repeated health surveys in the years between 1974 and 2008. Data on myocardial infarction and risk factors have been collected throughout follow-up. The thesis consists of three studies. The first study is an analysis of the seasonal variation in fatal and non-fatal incident myocardial infarction. The second study is an analysis of the effect of temperature, wind, atmospheric pressure, humidity and snowfall on incident myocardial infarction. The third study is an analysis of the seasonal variation in systolic and diastolic blood pressure, heart rate, body weight, total cholesterol, triglycerides, high density lipoprotein cholesterol, C-reactive protein and fibrinogen.

The results from the present studies show that there is a seasonal variation with increased risk of myocardial infarction in the darkest winter months, however small compared to what has been observed in other populations, especially those in warmer climates. There is little effect of weather variables, although cold temperatures and heavy snowfall may increase the risk of myocardial infarction among older individuals. Cardiovascular disease risk factors have a seasonal pattern, although the sizes of the seasonal changes are likely too small to contribute to acute cardiovascular disease events.

The findings implies that, compared to populations in warmer climates, this subarctic populations is little effected by season and weather, probably due to long-term adaption to a harsh climate, mainly through behavioural protection.

SAMMENDRAG

Årstidsvariasjon med topp om vinteren i akutt hjerteinfarkt insidens og risikofaktorer for hjertekarsykdom er observert i studier verden over. Mange tidligere studier har metodiske begrensninger og få er utført i områder med kaldere klima. Hensikten med denne avhandlingen er å undersøke effekt av årstid og meteorologiske faktorer på insidens av førstegangs hjerteinfarkt samt årstidsvariasjon i risikofaktorer for hjertekarsykdom i en subarktisk befolkning med lang oppfølgingstid, ved bruk av adekvate metoder med validerte endepunkt og veldefinerte eksponeringsvariabler.

Den befolkningsbaserte Tromsøundersøkelsen består av over 40,000 mennesker bosatt i et subarktisk klima i Nord-Norge. Studiedeltagerne har blitt undersøkt opp til ni ganger i seks repeterte helseundersøkelser i årene mellom 1974 og 2008, der det har blitt samlet inn informasjon om hjerteinfarkt og risikofaktorer. Avhandlingen består av tre studier. Den første studien er en analyse av årstidsvariasjon i insidens av fatale og ikke-fatale hjerteinfarkt. Den andre studien er en analyse av effekt av temperatur, vind, atmosfærisk trykk, fuktighet og snøfall på hjerteinfarktinsidens. Den tredje studien er en analyse av årstidsvariasjon i systolisk og diastolisk blodtrykk, hjertefrekvens, kroppsvekt, totalkolesterol, triglyserider, high density lipoprotein kolesterol, C-reaktivt protein og fibrinogen.

Resultatene fra disse studiene viser at det er en årstidsvariasjon med økt risiko for førstegangs hjerteinfarkt i de mørkeste vintermånedene, men at denne er liten sammenlignet med økningen om vinteren sett i land med varmere klima. Effekten av værvariabler er generelt liten, men hos eldre er det økt risiko for førstegangs hjerteinfarkt ved kulde og etter store snøfall. Risikofaktorer for hjertekarsykdom har et årstidsmønster, men størrelsen på variasjonen gjennom året er liten og vil lite trolig kunne bidra til akutt hjertekarsykdom.

Funnene viser at denne subarktiske befolkningen er lite påvirket av årstid og vær sammenlignet med befolkninger i varmere områder, antagelig på grunn av langtids adapsjon til et barskt klima, hovedsakelig via beskyttende atferd.

LIST OF PAPERS

This thesis is based on the following three papers, referred to in the text as paper 1, 2 and 3.

Paper 1

Hopstock LA, Wilsgaard T, Njølstad I, Mannsverk J, Mathiesen EB, Løchen ML, Bønaa KH. **Seasonal variation in incidence in acute myocardial infarction in a sub-Arctic population: the Tromsø Study 1974–2004.** *European Journal of Cardiovascular Prevention and Rehabilitation* 2011;18(2):320-325.

Paper 2

Hopstock LA, Fors AS, Bønaa KH, Mannsverk J, Njølstad I, Wilsgaard T. **The effect of daily weather conditions on myocardial infarction incidence in a subarctic population: the Tromsø Study 1974–2004.** *Journal of Epidemiology and Community Health* 2012;66:815-820.

Paper 3

Hopstock LA, Barnett AG, Bønaa KH, Mannsverk J, Njølstad I, Wilsgaard T. **Seasonal variation in cardiovascular disease risk factors in a subarctic population: the Tromsø Study 1979–2008.** *Journal of Epidemiology and Community Health* 2012; doi 10.1136/jech-2012-201547 [Online August 2, 2012].

ABBREVIATIONS

A	autumn
ACS	acute coronary syndrome
AF	atrial fibrillation
AP	angina pectoris
ASAT	aspartate aminotransferase
ASHD	arteriosclerotic heart disease
°C	degrees Celsius
CA	cardiac arrest
CAD	coronary artery disease
CCU	coronary care unit
CD	coronary disease
CHD	coronary heart disease
CICU	coronary intensive care unit
CK/CK-MB	creatine kinase
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
ECCO	echocardiography
ECG	electrocardiogram
g/L	gram per litre
GP	general practitioner
HF	heart failure
ICD	international classification of diseases
IHD	ischemic heart disease
HDL	high-density lipoprotein
HR	heart rate
LD	lactate dehydrogenase
LIA	limited available information
kg	kilogram
MeSH	Medical Subject Headings
MI	myocardial infarction
mmHg	millimetre mercury
mmol/L	millimol per litre
NIA	no information available
PCI	percutaneous coronary intervention
ROSC	return of spontaneous circulation
SBP	systolic blood pressure
SCD	sudden cardiac death
Sp	spring
Su	summer
SV	seasonal variation
UV	ultraviolet
W	winter
WHO	World Health Organization
yrs	years

LIST OF TABLES AND FIGURES

1. INTRODUCTION – A REVIEW OF THE LITERATURE

This thesis includes an introduction to the theme seasonal variation and weather effects on morbidity and mortality from myocardial infarction (MI), and seasonal variation in cardiovascular disease (CVD) risk factors, based on a systematic review and a discussion of the findings pointing out the rationale for the thesis. The aims, methods and results of the thesis will then be presented, before the study limitations and study findings will be discussed, ending with future perspectives for this field of research.

1.1 A historical perspective

The knowledge of effects of season and weather on human health has probably existed in all cultures throughout history. The first known written source describing this is from Hippocrates [1]. In his work "Airs Water Places" he stresses the importance of recognizing that geographical conditions and climate influence health. The work is partly medical and partly ethnographical [1], describing climate- and season-related diseases among populations living in different geographical areas. In the Nordic countries, the Swedish astronomer Pehr Wargentin was the first to describe the seasonal pattern in mortality with his report from 1767 [2]. Increased winter mortality from "acute coronary occlusion" was first described in 1926 [3] whereas the relationship between "coronary artery thrombosis" and meteorological variables was first described in 1938 [4]. Seasonal [5] and monthly [6] variation in blood pressure was first described in 1921 and 1930. Recent years' focus on global climate change and impact on human health [7] and valuation of so-called local, traditional or indigenous knowledge [8] has renewed the interest in this area of research.

1.2 Seasonal variation – the burden of disease

Winter excess mortality is a worldwide phenomenon [9]. In the European countries Spain, Italy, Portugal, Greece and the UK, the estimated total excess winter all-cause mortality is approximately 100,000 deaths, i.e. 16-28 % winter excess mortality [10], where the UK alone has 30,000-37,000 annual winter excess deaths, i.e. 18 % winter excess mortality [10, 11]. In Norway the corresponding number is 2,600 deaths or 12 % excess mortality in winter [12]. Winter excess mortality is mainly due to CVD [12, 13]. Various studies from Europe [14, 15], USA [16-19] and Oceania [20, 21] report the morbidity or mortality from MI to be 22-70 % greater in winter than in summer.

1.3 A systematic review

Systematic literature reviews were performed both before initiation of, as well as regularly during, this PhD work. This particular systematic review will be an attempt to be a scan of the English literature in this research area found in PubMed registered medical journals, from the period before this PhD work was carried out. A systematic review allows an objective appraisal in contrast to traditional narrative reviews, that are prone to bias and error [22]. To meet the criterion for a systematic review [23], a protocol was prepared before the literature search was performed, and consisted of a formulation of the review question, an a priori definition of eligibility criteria, and a plan for the comprehensive search and for assessment of the methodological quality of the studies. The results will provide information on the extensiveness of the literature with a superficial review of possible shortcoming in existing knowledge without in-depth details on methodology or results for each study. The short discussion of the results will lead to a rationale for performing a new study in this field of research.

1.3.1 Objectives of the review

There were three objectives, which made the basis of three systematic reviews with two different exposures and two different outcomes:

To consider the effect of season on MI morbidity and/or mortality.

To consider the effect of temperature, wind, atmospheric pressure, humidity and snowfall on MI morbidity and/or mortality.

To consider the effect of season on systolic and diastolic blood pressure, heart rate, body weight, cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein (CRP) and fibrinogen.

1.3.2 The search strategy

Three main literature searches were performed. Medline via OvidSP was searched March 19, 2012 for the period from 1946 (Medline archive start) to end of 2007 (PhD project start) for the following U.S. National Library of Medicine Medical Subject Headings (MeSH) terms (based on the tree structure): “death, sudden, cardiac”, “acute coronary syndrome”, “coronary disease”, “coronary artery disease”, “myocardial infarction” AND “seasons” respectively “weather”, and for: “blood pressure”, “heart rate”, “body weight” , “cholesterol”, “triglycerides”, “cholesterol, HDL”, “C-reactive protein”, “fibrinogen” AND “seasons”. All subheadings were included and the searches were limited to studies of humans, adults over 19 years, published in English.

1.3.3 Inclusion and exclusion criteria

Studies were included when MI, respectively the various CVD risk factors, were included as outcome, and season, respectively weather, was included as exposure. To retrieve information from studies of mortality suspected to origin from MI or from the period before MI was a commonly used concept, studies using the following terms as outcomes were included: morbidity or mortality from acute coronary syndrome (ACS), combinations of MI and angina pectoris (AP), coronary disease (CD) and coronary artery disease (CAD), including terms like “arteriosclerotic heart disease”, “coronary thrombosis”, “coronary artery occlusion” and “coronary insufficiency”, or mortality from ischemic heart disease (IHD), coronary heart disease (CHD), sudden cardiac death (SCD) or cardiac arrest (CA). If several outcomes were studied, only results from analysis of MI are presented here. Results of sub-group analyses (gender, age, et cetera) are not presented here unless only results from sub-analyses were reported.

Studies were excluded if investigating seasonality of specific MI outcomes (S-T elevation versus non S-T elevation MI, fatal versus non-fatal MI, et cetera). Studies were also excluded if they were not original research articles (comments, letters, editorials or conference abstracts) or were a case report or review study, or did not conclude with the question of interest by reporting an association or non-association. In addition, studies were excluded if they, for the association with season, included one season analysis only, or, for the association with weather, included non-meteorological variables or other meteorological variables than temperature, wind, atmospheric pressure, humidity or precipitation as snow. Studies were also excluded if they included mixes of meteorological variables (weather-types), only one extreme weather event, or were controlled experiments (cold-exposure in a laboratory setting or controlled diets in cross-over designs, et cetera). Studies reporting results for persons with seasonal affective disorder only were also excluded.

Reference lists for all included studies, as well as for identified review studies, were searched for any further studies, and also worked as a test of fit of the main search. This included an investigation of the search terms for all additional studies, to see if there were other search terms that should have been added to the main search. These references were processed in the same way as studies from the main search. Only references from 1946 and forward were included, in accordance with the main search.

1.3.4 Procedure

After the search, titles and abstracts were screened for relevance based on the inclusion and exclusion criteria. If the content of the title and abstract was not extensive enough to decide if the study should be included or excluded, or if the abstract were missing, a full-text version of the paper

was obtained and superficially reviewed for final decision. For studies where an interpretable title or abstract were missing (for decision of study inclusion or exclusion) and a full text version was not available in Medline, both a Google search and a Bibsys library search (to order the article via international library resources) were performed for retrieving of full text version.

Due to the extensiveness of the search of seasonal pattern in CVD risk factors, a modification was made for this search. Here, only studies available in full-text found in the main search were included, and reference lists were not searched for further studies. This means that both if an interpretable title or abstract were missing (for decision of study inclusion or exclusion) and for studies likely to be included based on the available abstract content; if a full text version was not available in Medline or Google, the full-text version was not ordered via library resources.

For each included study from the three searches, the full text version (either found as an electronic version in Medline, or, for the two first searches, obtained electronically via Google or ordered and received as print per mail via library resources) was scanned and the following information was obtained: study design, time-period or follow-up time, number of subjects included, study population, geographical area, and definition of outcome and exposure, as well as a short description of the result of the study.

1.3.5 Results

A total of 74 studies meet the inclusion criteria for reviewing the association between season and MI (table 1) and 56 studies for the association between weather and MI (table 2). There are 22 studies reporting both seasonal and weather effects on MI, and these exist in both table 1 and table 2, reporting only the exposure of interest for the specific search. A total of 72 studies meet the inclusion criteria for reviewing the association between season and the various CVD risk factors (table 3).

1.3.5.1 Seasonal variation in myocardial infarction morbidity and mortality

In 51 [11, 14-21, 24-65] of 74 (69 %) studies there is a seasonal variation in MI morbidity or mortality, and from these, 30 [11, 14-16, 18-21, 24-45] (59 %) studies report a winter peak only.

1.3.5.2 Effect of weather on myocardial infarction morbidity and mortality

Among the 56 studies of effect of weather on MI morbidity or mortality, an effect is found for temperature in 42 [13-15, 17, 20, 34, 36, 40-42, 60, 61, 66-95] of 49 (86 %) studies, for wind in 2 [24, 41] of 4 (50 %), for atmospheric pressure in 5 [24, 57, 66, 75, 96] of 16 (31 %), for humidity in 8 [14, 41, 67, 69, 72, 77, 78, 84] of 17 (47 %), and for precipitation as snow in 6 [24, 41, 80, 87, 97, 98] of 9 (67 %) studies. For those studies finding an effect, MI morbidity or mortality is positively associated with wind and snowfall, positively, inversely,

U- or V-shapely associated with atmospheric pressure and humidity, and generally (83 %) inversely associated with temperature, except from 7 studies of temperature and MI that report a positive [70, 71, 74] or a U-shaped [14, 69, 95, 99] relationship.

1.3.5.3 Seasonal variation in cardiovascular disease risk factors

Several studies investigate the seasonal pattern in more than one risk factor. Seasonal variation is investigated in 32 studies for systolic blood pressure, 31 for diastolic blood pressure, 4 for heart rate, 12 for body weight, 27 for cholesterol, 23 for triglycerides, 19 for HDL cholesterol, 7 for CRP and 11 for fibrinogen.

Systolic blood pressure has a seasonal pattern in 28 [100-127] (87.5 %) studies, and from these a winter peak is reported in 23 [100-105, 108-113, 115-123, 125, 126] (82 %). Diastolic blood pressure has a seasonal pattern in 26 [100, 101, 103-122, 124, 125, 127, 128] (84 %) studies, with a winter peak in 20 [100, 101, 103-105, 108-113, 115-122, 125] (77 %). Heart rate has a seasonal pattern in 1 [107] (25 %) study, peaking in summer. Body weight has a seasonal pattern in 7 [111, 117, 129-133] (58 %) studies, all with a winter peak. Cholesterol has a seasonal pattern in 21 [105, 106, 109, 115, 116, 127, 130-132, 134-145] (78 %) studies, and from these a winter peak is reported in 17 [105, 109, 115, 116, 127, 130-132, 134-138, 142-145] (81 %). Triglycerides has a seasonal pattern in 14 [105, 106, 109, 115, 116, 127, 131, 132, 134, 135, 139, 140, 145, 146] (61 %) studies, with a winter peak in 2 [106, 109] (14 %). HDL cholesterol has a seasonal pattern in 16 [105, 106, 115, 116, 130-132, 134-136, 138, 139, 142-144, 147] (84 %) studies, with a winter peak in 11 [105, 115, 116, 131, 132, 134-136, 138, 142, 144] (69 %). CRP has a seasonal pattern in 5 [106, 142, 148-150] (71 %) studies, with winter peak reported in 2 [142, 148] (40 %). Fibrinogen has a seasonal pattern in 9 [142, 148-155] (82 %) studies, and from these there is a winter peak in 6 [142, 148-150, 152, 153] (67 %) studies.

1.3.5.4 Methodological considerations – the review

From the 108 studies investigating the effect of season and/or weather on MI 5 [50, 156-159] (5 %) report first-ever MI. A total of 8 [28, 43, 63, 72, 74, 75, 95, 156] (7 %) studies include separately reviewed cases with a description of a validation-of-event protocol with diagnostic criteria, while the remaining used routinely collected statistics from mortality registers or hospital discharge databases. There is a lack of information on time-period of study conduction in 8 [15, 20, 64, 65, 74, 81, 88, 157] (7 %) studies, number of included subjects in 22 [11, 13, 15, 16, 19, 21, 32, 36, 42, 70, 71, 76, 79-81, 85-87, 90, 92, 98, 160] (20 %) studies and geographical area in 1 [157] (1 %) study. A total of 35 [11, 13, 14, 16, 17, 19, 21, 25, 26, 30-33, 36, 37, 41, 42, 46, 51, 69, 76, 79-82, 85-87, 90, 92, 98, 99, 109, 160, 161] (32 %) studies report mortality only. From the 73 studies reporting morbidity (included combinations of morbidity and mortality) 14 [14, 20, 29, 43, 50, 60, 61, 68, 74, 75, 91, 156, 162, 163] (19%) claim to be population-based while the remaining studies include events from hospital admissions data only. In 5 [53, 57, 157, 159, 164] (7 %) of the morbidity studies the information of data source lack or the available information is too limited to classify as population-based or not. From the 43 studies

reporting the seasonal distribution (i.e. not monthly only) of mortality or morbidity 20 [15, 19, 28, 31, 32, 35, 39, 45, 46, 48, 49, 52, 54, 57, 60, 61, 65, 78, 83, 162] (46.5 %) do not define the seasons.

From the 72 studies investigating seasonal variation in CVD risk factors, 12 [102, 103, 109, 118, 126, 127, 146, 147, 165-168] (17 %) claim to be population-based or partly population-based. In 3 [105, 134, 153] (4 %) studies the information lack or is too limited to classify as population-based or not. A total of 16 [102-106, 112, 124, 126, 127, 134, 141, 146, 147, 152, 154, 165] (22 %) studies use only one measurement per individual or the available information is too limited to classify as repeated measurements or not. A total of 16 [122, 128, 137-140, 145, 148, 155, 168-174] (22 %) studies have fewer than 30 subjects, and 48 [100, 101, 104, 107, 108, 110-117, 119-124, 127, 128, 130-132, 136, 137, 142, 144, 146-152, 154, 165, 167-177] (67 %) studies report findings from populations of patients on certain treatment, very limited age-ranges or one sex only. There is a lack of information on time-period of study conduction in 19 [100, 112, 115, 116, 120-122, 125, 129, 131, 132, 136, 138, 139, 148, 170, 171, 174, 178] (26 %) studies, number of subjects in 2 [154, 179] (3 %) studies and geographical area in 14 [100, 107, 115, 116, 120, 121, 136, 148, 171, 173, 174, 176, 178, 179] (19 %) studies. From the 42 studies reporting the seasonal distribution (i.e. not monthly only) of risk factors 17 [100, 102, 108, 120, 121, 126, 127, 131, 132, 134, 136, 141, 143, 153, 165, 171, 175] (40.5 %) do not define the seasons.

1.3.5.5 Geographical differences – the review

By roughly dividing the studies into broad different geographical areas there are more studies reporting seasonal variation in MI with winter peaks in the UK [11, 15, 26, 30, 40, 42, 43, 45, 60, 61], the Mediterranean countries [14, 27, 34, 48], Southern hemisphere countries [20, 21, 29, 32, 33] and the USA as a whole [16, 18, 25, 38, 41, 44, 64, 65]. Inconsistency in results is found in reports from Canada [37, 42, 162], Japan [28, 35, 36, 47, 180, 181] and Southern USA [19, 62, 63]. Lack of seasonal variation in MI is more often reported from the Nordic countries [159, 163, 182-184], Northern USA [18, 156, 161, 185] and countries close to the Equator [83, 186, 187].

Similarly, studies from the UK [15, 40, 60, 61, 76, 77, 85, 86, 90-92, 94, 160], the Mediterranean countries [34, 48, 67, 72] and Southern hemisphere countries [20, 79, 81, 88] more often report inverse relationships between MI events and temperature. Temperature is more often reported to be U-shapely associated with MI events in countries close to Equator [69, 99]. For studies reporting from several countries, areas with colder climates show less effect of temperature on MI events than areas with milder climates [13, 42, 68, 80]. For risk factors, the geographical differences are not that evident, and studies from most areas report a seasonal pattern with a winter peak. However, in a study reporting from several countries, populations in areas with colder climates show less seasonal variation in systolic blood pressure than populations in milder climates [102]. Similarly, studies from USA show larger seasonal variation in cholesterol levels in Southern compared to Northern areas [131, 132].

1.3.5.6 Limitations of the review

From the two searches investigating seasonal variation or weather effects on MI, 46 studies were found in reference lists after the main search. From these, 26 had search terms matching the main searches, and why they were not found in the main search cannot be explained. The rest had other MeSH terms or other combinations of MeSH terms. From these, 3 studies had the term "myocardial infarction" combined with search terms other than "weather" ("meteorological concepts", "hot temperature" or "climate", or "atmospheric pressure" which was not included in the term "weather") and 4 studies had no term for "season" nor "weather". In addition to this, among the older (i.e. from around 1960 and earlier) studies, 5 had only one MeSH term ("myocardium" or "periodicity") and 6 did not exist in Medline. Further, 1 study was incorrectly marked as Spanish even if it was an English version, and 1 study was incorrectly marked with the term "cerebrovascular disorders" even if this was not among the study endpoints. In total, from both main searches and reference searches, 27 studies were not available in full text versions in Medline or Google, and were ordered from the library via Bibsys.

From the search of studies investigating seasonal variation in CVD risk factors, 30 studies were not found in full text versions and therefore excluded. These were both studies that should have been included based on the available information in the title and abstract, and studies that lacked this information to evaluate whether to be included or not.

As described above the review is fairly extensive for the first two searches, but more limited for the search on risk factors. Most studies of interest were identified, and the investigation of search terms in studies found in references lists and not in the main searches did not reveal a large number of search terms that should have been added to the main search. There are, however, limitations for the review as a whole. First, only one database was searched. Further, there is a possibility of language bias, negative publication bias as well as limitations due to the time-frame (i.e. exclusion of studies before 1946, as these do not exist in Medline). However, the main limitation of this review is the lack of in-depth methodological considerations of the various studies, especially the lack of investigation of the statistical methods and a discussion of their quality and appropriateness. Even if a meta-analysis was not possible to perform due to the large variation in methods, some kind of comparison of effect, especially between the observed differences in different geographical areas, would have been of interest. An investigation of possible time trends in seasonal variation could have been an additional issue of interest.

1.3.6 Discussion with rationale for the thesis

The literature review shows that the main body of studies reports a seasonal pattern with winter peak in morbidity and mortality from MI and in levels of CVD risk factors, and that this has been studied extensively in the last half century. This calls for a rationale for this thesis. Epidemiological studies must progress from descriptive to analytical and further to studies of effectiveness, which leads to public health prevention programs, but there is a tendency in epidemiology to a stagnation in development of study design, leading to rediscover evidence from past studies – so-called circular epidemiology [188].

The argument for a new study in this area of research is based on the limitations in previous study methods. Firstly, few studies are population-based, but are based on hospital discharge registers (for MI) or measurements within special subgroups (for risk factors), which can result in selection bias. Excluding non-hospitalized MI events does not mirror the population numerator and thus does not account for all events in a community. A non-defined population (denominator) gives an unknown number of individuals at risk, and factors like seasonal migration may change the population during the year [189]. Secondly, few studies of MI are based on validated events, but use routine statistics, which can result in misclassifications. Many studies are based on mortality data only, and for those investigating morbidity, few distinguish between first and recurrent events, which may have different incidence patterns [190] due to medical treatment that influence the physiological effects to seasonal exposure or patient advice that changes the behavioural pattern. Several studies of risk factors do not use repeated measurements in the same individual, which is important as individual and population seasonal patterns may differ [191]. Further, few studies define the exposure season, which can give different results depending on how season is defined [192, 193]. Lastly, it seems to be different impacts of season and weather in different geographic and/or climatic areas, and few studies are conducted in high latitude and/or cold climate areas.

To perform circular epidemiology by identical replication is a stagnation [188], but research with improved and innovative methods to minimize bias should be performed on relatively established research findings [194]. The limitations mentioned here could have been met by using unique personal identity numbers to search population-, disease- and death registers and thereby follow a defined general population of all ages and both sexes with person-time as denominator and well-validated endpoints as numerator. The rationale for this thesis is therefore the attempt to investigate seasonal and meteorological impact on the specific endpoint of validated first-ever MI and seasonal variation in repeated measurements of risk factors for this disease in a well-defined population in a subarctic area.

2. AIMS OF THE THESIS

The overall aim of the thesis is to describe the seasonal pattern in MI incidence and in CVD risk factors in a subarctic population. In order to fulfil the overall aim, three more specific objectives were formulated. These objectives made the basis for the data analysis in three different studies based on data from the subarctic cohort study the Tromsø Study;

To investigate the seasonal variation in first-ever non-fatal and fatal MI (paper 1).

To investigate the impact of daily meteorological variables on first-ever MI (paper 2).

To investigate the seasonal variation in CVD risk factors in repeated measurements (paper 3).

3. METHODS

3.1 Tromsø – location, climate and seasons

Tromsø is the regional centre of Northern Norway, situated 400 km north of the Arctic Circle at 69°39'N. The municipality has approximately 70,000 inhabitants. Tromsø has extreme seasonal variation in daylight. From approximately May 18 to July 26 the sun does not set, which gives two months of 24 hours daylight or so-called "midnight sun" during the summer. From approximately November 28 to January 14 the sun is below the horizon, which gives two months of dark winter season or so-called "polar night". The climate is harsh and the weather is constantly changing, but because of the Gulf Stream, the climate is generally mild compared to other areas at the same latitude. Therefore, even if Tromsø is located above the Article Circle, the climate is subarctic as defined by the Köppen climate classification [195]. The city centre of Tromsø is situated on an island, with no industry causing air pollution. On certain days in autumn and spring there is a risk of increase in air pollution due to the winter use of studded tires on cars, but because of the local geographic with frequent replacements of air, accumulation of air pollution is not likely [196].

The astronomical seasons are the same in Tromsø as for all geographical areas on the Northern hemisphere, where the spring (usually March 21) and autumn equinox (usually September 23) [197] define the winter and summer season, with winter in the darkest months (November-January), summer in the lightest months (May-July) and spring (February-April, increasing daylight) and autumn (August-October, decreasing daylight) between these. The meteorological definitions of seasons depend on geographical area. Months with a daily mean temperature below 0°C is defined as winter, months with daily mean temperature above 10°C is defined as summer, and months with a daily mean temperature between 0°C and 10°C are defined as spring (increasing temperature) and autumn (decreasing temperature) [197]. For Tromsø, the meteorological definitions of seasons are as follows; winter: November 6-April 13, spring: April 14-June 22, summer: June 23- August 18, and autumn: August 19-November 5 [197]. For this thesis, data on meteorological variables from the Tromsø Weather Station were collected from the official Norwegian Meteorology Institute webpage Eklima [198].

3.1.1 Meteorological data and definitions of seasons used in paper 1-3

In paper 1, the seasonal pattern in MI incidence was investigated in a Cosinor model based on time as month (month adjusted to 30.4375 day length) with one cycle per year. To describe the local climate, the monthly mean values of various meteorological variables were calculated for the 31 year period as a whole, based on monthly means from January 1974 to December 2004. These values also

estimated the seasons, based on the definitions described above. Whole months were used to model season, for both astronomical and meteorological season models. This is a simplified version of seasons than those described above, which use accurate dates. The astronomical season model divided the year into four three-months seasons depending on seasonal light (winter season as November-January). The meteorological season model divided the year into four seasons depending on monthly mean of daily mean temperatures (winter: November-March, spring: April-May, summer: June-August, autumn: September-October). April was close to be included as a winter month, as the first day of spring is April 14, but still with more days of spring. June had a monthly mean of daily mean temperature of 9.2 °C, but was included as a summer month because the temperature value was closer to the summer month temperatures than to the spring month temperatures. For both the definitions of season, a model dividing the months into winter and non-winter (spring, summer and autumn) season was also included.

In paper 2, meteorological data for each day of follow-up were linked to person-years at risk and number of events. Based on assessment of possible time-lag phenomenon, a three-day average (the weather on the date of the event and the two previous days) of each meteorological variable was used as exposure variables. In addition to that, to describe the local climate, the yearly mean values of various daily meteorological variables was calculated for the 31 year period as a whole, based on daily values from February 14, 1974 to December 31, 2004, the total period of follow-up. The meteorological defined seasons using the accurate dates as described above was used to perform separate analysis for winter season for the weather variable precipitation as snow, to investigate if there was any difference in MI incidence after snowfall in winter compared to snowfall in other seasons.

In paper 3, the seasonal pattern in CVD risk factors was investigated in Cosinor models based on time as date of screening as the main exposure variable with one cycle per year. Here, meteorologically defined seasons using the accurate dates as described above were used only to describe the results. Likewise, to describe the local climate the monthly mean values of various meteorological variables were calculated for the 30 year period as a whole based on monthly means from January 1979 to December 2008.

3.2 Study population – The Tromsø Study

The Tromsø Study is a single-centre, population-based, prospective health study conducted in the municipality of Tromsø. The Tromsø Study consists of six repeated health surveys (Tromsø 1: 1974, Tromsø 2: 1979–80, Tromsø 3: 1986–87, Tromsø 4: 1994–95, Tromsø 5: 2001–02 and Tromsø 6:

2007–08) including a second extended subsample-screening after the first visit in the three last surveys (Tromsø 4 visit 2, Tromsø 5 visit 2 and Tromsø 6 visit 2). Both total birth cohorts and random samples of Tromsø inhabitants were invited by written mail-sent invitations. The overall participation rate ranged from 66-85 % (when adjusting for deaths and emigration), and were even higher for the second visit screenings [199]. The Tromsø Study has been approved by the Norwegian data Inspectorate and recommended by the Regional Committee of Research Ethics. In Tromsø 4–6, the participants signed a written consent. Participants are free to withdraw their consent at any time and also to give new consent later, therefore the number of participants with valid consent may vary over time. An overview over the Tromsø Study sample is given in table 4, numbers of examinations attended is given in table 5 and a flowchart for the subsamples used in paper 1–3 is given in figure 1. Further information about the Tromsø Study, including the invitation letters, consent forms and questionnaires for each survey is available at the study web pages www.tromsoundersokelsen.no [200].

3.2.1 Study population used in paper 1–3

Paper 1 is a follow-up study of MI incidence among all participants from the first five surveys (Tromsø 1-5: 1974–2002). They were followed from enrolment (first date of examination) to December 31, 2004. This gave a total of 38,164 participants, where 160 subjects were excluded because of emigration from Tromsø before start of follow-up, 222 because of non-consent and 390 because of prevalent MI, which resulted in 37,392 participants for inclusion in the analysis. New participants from the last survey (Tromsø 6: 2007–2008) could not be included, as end point validation was only complete until the end of 2004. Median length of follow up was 15.7 years.

Paper 2 is a follow-up study of MI incidence among all participants from the first five surveys (Tromsø 1-5: 1974–2002). They were followed from enrolment (first date of examination) to December 31, 2004. This gave a total of 38,164 participants, where 160 subjects were excluded because of emigration from Tromsø before start of follow-up, 222 because of non-consent, 390 because of prevalent MI and 5,282 because they were younger than 35 years at the end of follow-up, which resulted in 32,110 participants for inclusion in the analysis. To have complete age-groups throughout the follow-up period, subjects younger than 35 at the end of follow-up were excluded, as this age-group grew older without including new participants as years passed by. As for the study in paper 1, new participants from the last survey (Tromsø 6: 2007–2008) could not be included, as end point validation was only complete until the end of 2004. Median length of follow was 17 years.

Paper 3 is a study of repeated measurements of CVD risk factors in participants from the second to the last survey (Tromsø 2-6: 1979–2008), included visit 2 (a second and more extensive screening) in Tromsø 4-6. This gave a total of 39,059 participants, where 224 subjects were excluded because of

non-consent, 6 because of missing attendance date in 1979–80, 7 because of attendance without invitation and 785 because they were younger than 20 years at enrolment, which resulted in 38,037 participants for inclusion in the analysis. Subjects younger than 20 at enrolment were excluded because of participation in Tromsø 3 only – if they were invited again (older than 20 years), they were included. Measurements from the first survey were not included due to inconsistency in measurement methods compared to later surveys. For participants included, 41% had at least 3 or more examinations, and 28% had between 4 and 8 examinations with repeated risk factor measurements. There were various numbers of measurements for each risk factor; from 92,641 measurements of cholesterol in 37,986 participants, to 25,421 measurements of fibrinogen in 16,450 participants, i.e. not all risk factors were measured in each survey and not all measurements were performed in all participants.

3.3 Myocardial infarction case identification and definition used in paper 1 and 2

A huge work to identify and define each case of MI among the Tromsø Study participants is being performed by the Tromsø Study endpoint committee. To identify hospitalized cases of fatal or non-fatal MI among study participants the discharge diagnosis register at the University Hospital of North Norway (UNN), the only local hospital serving the Tromsø population, was searched. To identify out-of-hospital cases of fatal MI the study participant list was linked with the Norwegian Causes of Death Register. The unique personal identification system in Norway makes exact matching in register sources possible. For event ascertainment the endpoint committee followed a detailed protocol and examined all available medical records (including medical records from other hospitals and pre-hospital records from ambulance service, general practitioners, nursing homes and death certificates). Among the cases 4 % were observed at another hospital than UNN, and of these 25 % were observed at a hospital in Northern Norway. Diagnostic criteria were based on clinical presentation, electrocardiograms, levels of myocardial biomarkers, echocardiograms, results from angiography and/or autopsy. Fatal MI was defined both as death on the same date as the event and death within 28 days.

3.4 Cardiovascular disease risk factors measurements used in paper 3

Each survey followed a standardized examination protocol, and the methods used for physical examination (blood pressure, measurements of body weight and heart rate) and blood sampling were almost identical for all surveys. For blood pressure, there were some inconsistencies in measurement methods. In Tromsø 3-6 blood pressure and heart rate were measured with an automatic device, while in Tromsø 2 blood pressure was measured manually with a mercury

sphygmomanometer. Previous validated methods [201] were used to transform the recordings from the automatic device, to adjust for this change in measurement method. The mean of the final 2 of the 3 readings in Tromsø 3-6 and the 2 readings in Tromsø 2 were used in the analysis. Weight was measured with subjects wearing light clothes and no shoes. Blood samples were analysed (for total cholesterol, triglycerides, HDL cholesterol, CRP and fibrinogen) by standard methods at the Department of Laboratory Medicine at the University Hospital of Northern Norway (names have changed for both department and hospital during survey period). Participants were not requested to fast. All data collection was performed by trained personnel.

3.5 Data from questionnaires used in paper 1

Self-reported data on smoking for Tromsø 1-5 was collected from questionnaires[200] for purpose of stratified analyses of smoking status (current smoker or non-smoker) in paper 1. Definition was made by reported smoking status in the latest questionnaire available, and for cases, the latest available questionnaire before the event.

3.6 Statistical analyses

3.6.1 Cosinor

In paper 1 and 3 a sinusoidal seasonal pattern was fitted using cosine and sine terms to monthly incidence (paper 1) or date of screening (paper 3), known as the Cosinor procedure. The Cosinor analysis was developed by Halberg, Tong and Johnson [202] and determines how much of the seasonal variation can be explained by a sinusoidal curve, a common method for analysing seasonality in health data [191]. Cosinor analysis has the assumption that a cycle exists and that the cycle length is known [203]. Using the Cosinor procedure helps determine the characteristics of this cycle; the acrophase or phase (the time point at which maximum values occur, i.e. peak time point), the mesor (the mean of the fitted curve) and the amplitude of the wave form (the peak to mesor difference, i.e. the size of the seasonal change from the seasonal mean) [203]. A linear regression model using the Cosinor procedure can be described by the following equation:

$$y = \beta_0 + \beta_1 \cos(2\pi\, t/\mathrm{P}) + \beta_2 \sin(2\pi\, t/\mathrm{P}) + e$$

where y is the dependent variable of interest (the outcome variable), βs are regression coefficients, t is the time point, P is length of period, cos is cosine, sin is sine and e is the residual variation term. A Cosinor curve with parameters as described above is shown in figure 1.

3.6.2 Statistical models used in paper 1-3

In paper 1, data was arranged as survival time data with month of the year as time unit, where each subject was followed month by month (records of the data file were months of follow-up). Seasonality in incidence was assessed with the Cosinor procedure in a Poisson regression model using the following equation:

$$\log \mu = \log(t) + \beta_0 + \beta_1 \cos(month * 2\pi/12) + \beta_2 \sin(month * 2\pi/12)$$

where μ is the expected incidence rate, βs are regression coefficients, t is length of observation time in month for each record and *month* is the month under observation ranging from 1 to 12. In addition to the Cosinor analysis, four different Poisson models were used to assess seasonal patterns. These were two four-season models defined earlier (an astronomical and a meteorological season model) and, for both of these, a winter and non-winter model.

In paper 2, association between MI incidence and meteorological variables were assessed with Poisson regression. The meteorological variables were modelled using fractional polynomials. The records of the data file were dates of follow-up. When temperature (temp) was the independent variable, the best fitting fractional polynomials of degree two gave powers equal to (-2, -2). The following model was used:

$$\log \mu = \beta_0 + \beta_1 * temp^{-2} + \beta_2 * temp^{-2} * \log(temp)$$

where μ is the expected incidence rate and βs are regression coefficients for temperature. The fractional polynomial models were also used to assess the relative risk of MI between upper and lower limits of the distribution of each meteorological variable.

In order to assess possible effects of unusual weather (unusual for the season), z-scores were calculated for all meteorological variables (except for snowfall that seldom occur in summer) for each week of the year. The association between the z-scores and MI were assessed in similar fractional polynomial models as for the models above.

A linear model was used to estimate the percentage change in risk of MI per standard deviation increase in each meteorological variable. For the variable temperature (temp) the following model was used:

$$\log \mu = \beta_0 + \beta_1 temp$$

In paper 3, data was arranged with one record for each observation. The seasonality in the risk factors was assessed using a linear mixed model. Regression analysis was fitted by restricted

maximum likelihood. The models were specified as random coefficients or multilevel models (thereby controlling for repeated measurements). Two models were used. For the population model, time unit was day of the year, with cosine and sine functions as fixed effects and a random intercept for each individual. For the individual model random terms of the cosine and sine effects were added. Both models included fixed effects of age and sex.

The population model had the following equation:

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 \text{age} + \beta_4 \text{sex} + \beta_5 \text{time} + \sum_{i=1}^{7} \lambda_i \text{survey}_i + u + e$$

The individual model had the following equation:

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 \text{age} + \beta_4 \text{sex} + \beta_5 \text{time} + \sum_{i=1}^{7} \lambda_i \text{survey}_i + u + V_1 + V_2 + e$$

where y is the risk factor (the outcome variable), X_1, X_2, age, sex, time, and survey_i are fixed effects independent variables , where X_1 = cos(day of year*2π/365.25), X_2 = sin(day of year*2π/365.25), survey_i are indicator variables of survey number, βs and λ_is are regression coefficients, u is the random intercept, V_1 and V_2 are random effects for the Cosinor variables X_1 and X_2 and *e* is the residual variation term.

For all papers two-sided p-values < 0.05 were considered statistically significant. Analyses were performed using stratifications by sex (paper 1, 2 and 3), age (paper 1 and 2), smoking status (paper 1), and/or models included adjustment for sex and age (paper 3), season (paper 2) or time as survey number (paper 3). Effect modification was assessed for the variables time as calendar year (paper 1) or calendar days (paper 2), sex (paper 1 and 2), age (paper 1 and 2) and smoking status (paper 1) by including cross-product terms for the effect modifier with the two Cosinor functions of month (paper 1) or with each meteorological variable (paper 2). Assessment of circadian and weekly variation in examination time and association with month of year was investigated descriptively (paper 3). Analyses was performed using STATA (Stata Corp LP) version 10 (paper 1) and 11 (paper 2), and R (www.r-project.org) version 2.13.2 using the lme4, circular and season packages (paper 3).

In paper 1, the Wald test was used to assess seasonality (the seasonal terms; sine and cosine) in the Poisson model. The likelihood ratio test was used to assess the effect of season when season was categorized in 4 levels. A power calculation was performed to assess the possibility to detect a seasonal pattern. Given a sample size of 37,392 subjects and an incidence rate of 2.7 per 1,000 there

was an 80% power to detect a rate ratio of 1.27 change in amplitude from the mesor in the Cosinor model.

In paper 2, the likelihood ratio test was used to assess the association between MI incidence and each meteorological variable expressed as fractional polynomial terms (untransformed and as week-specific z-scores). Confidence intervals were used to assess the impact on MI of each meteorological variable expressed as linear terms.

In paper 3, the likelihood ratio test was used to assess seasonality by comparing models with and without seasonal terms. This tests compared the model with or without seasonal terms as a fixed effect (test of seasonality on the population level) or as a random effects (test of seasonality on the individual level).

4. RESULTS – SUMMARY OF PAPERS

4.1 Paper 1

Seasonal variation in incidence in acute myocardial infarction in a subarctic population: The Tromsø Study 1974–2004

The aim of the study was to investigate the monthly and seasonal variation in first-ever non-fatal and fatal MI in the Tromsø Study cohort, with season defined by light and by temperature.

Among the 37,392 cohort members followed between 1974 and 2004, a total of 1,893 incident MIs were registered and analysed for seasonality.

The lowest incidence (fatal and non-fatal MI combined) occurred in July (2.88 per 1,000 person-years) and the highest in December (3.63 per 1,000 person-years). There was an 11% increase in risk of MI during the darkest winter months (November-January) compared with non-winter seasons. Other seasonal models did not show significant seasonality in MI incidence.

There was no statistically significant interaction between monthly variation in MI incidence and time period, sex, age or smoking status.

The conclusion was that there was little seasonal variation in incident MI events in this subarctic population.

4.2 Paper 2

The effect of daily weather conditions on myocardial infarction incidence in a subarctic population: The Tromsø Study 1974–2004

The aim of the study was to investigate the impact of daily meteorological factors on first-ever MI in the Tromsø Study cohort.

Among the 32,110 cohort members followed between 1974 and 2004, a total of 1,882 incident MIs were registered and linked with daily weather variables.

In the total population, wind speed had an inverse U-shaped (p=0.004) and humidity a U-shaped (p=0.004) association with MI incidence. MI incidence was not affected by changes in atmospheric pressure. There was an increase in risk of first-ever MI with decreasing temperatures (p=0.016) and with increasing snowfall (p=0.030) among individuals aged 65 years or older. In this age-group, the risk increased by 47% when comparing days with -10°C to days with 20°C, and by 44% comparing winter days with 10 mm snowfall with winter days without snowfall. Among those aged 35-64 there was no association with temperature, while snowfall showed a borderline significant inverse

association with MI (p=0.048). In women, a positive association was observed between MI and snowfall (p=0.035), while no association was observed in men.

There was no statistically significant interaction between the meteorological variables and time period, sex or age, except for snowfall and age (p= 0.0057), and snowfall and sex (p=0.023). Results were similar when including month as an adjustment for season.

The conclusion was that in this subarctic population the MI incidence was little affected by the weather, although older people should take extra precautions at cold temperatures and after heavy snowfall.

4.3 Paper 3

Seasonal variation in cardiovascular disease risk factors in a subarctic population: The Tromsø Study 1979–2008

The aim of the study was to investigate the seasonal variation in CVD risk factors in repeated measurements among the participants in the Tromsø Study.

From the 38,037 study participants examined in up to 8 screenings from 1979 to 2008, the seasonal pattern in 7 traditional CVD risk factors and 2 acute phase proteins associated with CVD was analysed.

Systolic and diastolic blood pressure, heart rate, body weight, total cholesterol and HDL cholesterol peaked in winter while triglycerides peaked in autumn, and CRP and fibrinogen peaked in spring. The seasonal pattern was significant for all risk factors ($p<0.001$). Maximum seasonal variation was 2 mmHg for systolic and 1 mmHg for diastolic blood pressure, 1.5 beats per minute for heart rate, 1 kg for body weight, 0.26 mmol/L for total cholesterol, 6 % for triglycerides, 0.062 mmol/L for HDL cholesterol, 12.8 % for CRP and 0.11 g/L for fibrinogen.

Results were similar in analyses stratified by sex. No association was found between month of year and day of week or time of day for the examination time.

The conclusion was that the seasonal variation in risk factors was highly statistically significant, but clinically likely too small to cause a seasonal pattern in CVD events in this subarctic population.

5. DISCUSSION – METHODOLOGY

The discussion of methodology is divided in two, firstly an overview over general methodological considerations and secondly considerations concerning each paper.

5.1 Overall considerations of internal validity

5.1.1 Study design

The Tromsø Study is defined as a prospective cohort study, as individuals are screened for risk factors prior to disease and followed up by repeated screenings. However, the design of the present studies was not pre-specified at the start of follow-up. Therefore the design can be called prospective non-concurrent data collection of exposure and outcome, as both the exposure (season or weather) and outcome status (MI or CVD risk factors) is not assembled during follow-up, but later. For paper 3, a short discussion of the appropriateness of the study design is included in the section about paper 3.

5.1.2 Study population – selection bias, non-response bias and loss to follow-up

Participation in the Tromsø Study is voluntarily and there is a possibility for selection bias, although the general participation rate is high (around 80% for the first five surveys, 65% for the latest survey, table 4). Differences in motivation (for example little interest in health screenings, which could give lower participation rates among younger individuals - a trend in the Tromsø Study [199] as well as in other population studies in Norway and internationally) or other obstacles (for example physical impediment among older, chronic ill or bedridden patients) to participate can produce a non-response bias among certain subgroups. Age should be controlled for here, either by stratifying, or by adjusting for, or by assessing the interaction. A lack of inclusion of all age-groups would limit the generalizability but not alter the results on seasonal distribution of disease. Differently, the lack of inclusion of for example homeless people might alter the results as they could be more exposed to seasonal meteorological factors. However, in Norway there is generally high socio-economic equality [204] and a welfare system covering all citizens[205], and few individuals live on the street. Loss to follow-up is not of a major concern in the Tromsø Study, quite contradictory; the attendance rate in repetitive surveys is high among previous participants [199]. However, migration may create some loss to follow-up.

5.1.3 Measurement of outcome – misclassification bias

For paper 1 and 2, the use of MI as an endpoint gives possibilities for misclassification. In spite of thorough efforts to perform an accurate validation of each possible case, the decision lies with the researcher investigating the available information. Despite a strict protocol and researcher expertise, the final judgment is a subjective matter and therefore measurement errors like misclassification (or

more broadly called information bias[206]) may occur. However, the validations of endpoints for these analyses were completed by a separate working group before the present studies were initiated and are not suspected to be differential, and therefore believed not to influence on the seasonal variation of the incidence.

5.1.4 Measurement of exposure – construct validity

The exposure variable season has a large geographical variation and is not straightforwardly defined. For paper 1 and paper 3, the use of season as an exposure is not problematic per se, as season can be defined a priori as combinations of months. However, in the interpretation of the results, the question of what is actually measured may arise. When investigating a seasonal pattern in risk factors or disease, the possible association with a seasonal pattern may be associated with environmental factors like temperature or sunlight, lifestyle factors like diet, physical activity or smoking patterns, acute infections or circannual rhythms [207]. The relationship between season and human biology, pathophysiology of CVD and local culture will be elaborated on in the discussion of results.

5.1.5 Measurement of exposure – misclassification bias

Data on migration from Tromsø was available, but data on shorter non-temporary absence from Tromsø was not. Thus, in paper 1 and 2, for some individuals the exposure to season and weather may be non-differentially misclassified. However, for cases, data on number of MIs observed at other hospitals and geographical location of the hospital was available. This showed that only a minor part of the cases (4 %) was observed at hospitals outside Tromsø, and from these, 25 % was observed at other North Norwegian hospitals, which should give exposure status somewhat similar to cases present in Tromsø.

5.1.6 Statistical methods – validity

The judgment of whether or not there exists an association between the exposure (season or weather) and the outcome (MI or level of CVD risk factors) are based on statistical analyses using methods which might be inappropriate. For example, in paper 1 and paper 3 the Cosinor procedure was chosen as it was a well-known method [191] for analysing seasonal patterns in health data. The Cosinor procedure assume one cycle per year with a symmetric peak and trough. The test of whether a sinusoidal pattern exists in the data is a test of this symmetric wave-form, which does not allow other seasonal patterns. However, analyses of differences between months and categorising season in different levels (additional analyses in paper 1) do not assume a functional form.

5.1.7 The preconception of the researcher – bias in analysis, interpretation and presentation

The preconception of the researcher could influence the analysis and interpretation of the results [206], and not even quantitatively oriented epidemiological research can be strictly objective. Likewise, this can influence which findings that are reported or highlighted [206]. An a priori aim as described in the introduction of this thesis could contribute to limit this bias. Another attempt to minimize this bias was to include collaborators from various disciplines, but none of this can totally rule out possible bias produced by the subjective view of the researcher(s).

5.2 Paper 1

5.2.1 Bias in analysis, interpretation and presentation

As described in the introduction, using several definitions of season was decided after a review of the literature, where the shortage of definitions of season, or justifications of using a certain definition of season, was common in previous studies. Therefore, using several well-defined models of season was prior to analysis considered as a strength of the study. In the light of potential causes of bias and errors in epidemiological research, when interpreting and presenting the results, such an approach could seem to rather increase the risk of making a type I error, which is more likely in a large data set [206]. Only one of several models of assessing the association between MI incidence and season was statistically significant, which could be chance. In the possible eagerness of presenting a positive result, this one finding is highlighted instead of faded down. However, the analyses were not fishing expeditions or data dredging; hypothesis, models and significance level were planned a priori.

5.3 Paper 2

5.3.1 Measurement of exposure – misclassification bias

The actual individual exposure to the weather conditions, both to the outdoor exposure and the possible following indoor effect is not known. In the same way as in other studies in this field [208], the outdoor meteorological factors, measured at an adjacent weather station, is used as a surrogate for the individual exposure. The validity of the surrogate measurement could be tested by comparing personal exposure values with values from the surrogate measurement [209], but such data was not available. The chosen surrogate marker may lead to non-differential misclassification, which in turn can lead to an underestimation of the association between exposure and disease, as the groups (here; MI or not) get more similar [210]. As will be elaborated on in the discussion of results, other factors than information on outdoor exposure, like information on behavioural protection and quality of housing heating and insulation, may be another important consideration.

5.3.2 Confounding

Season might be a confounder or mix-up of effect for the exposure variable weather (the opposite is also possible, but considered more a part of the content of the exposure and therefore not discussed further). Season is associated with both the disease (here; MI), and the exposure (here; weather) and is not an intermediate step in the causal path between the exposure and the disease, and therefore a possible confounder [211]. Another factor is the correlation between meteorological factors. Confounding can be controlled for in the statistical analyses [211], and in the statistical model adjustment were made for season, but not for other meteorological variables. Another confounder could be air pollution. Such data were not included in the analysis as levels of air pollution generally are considered low in Tromsø [196], although few data exist.

5.4 Paper 3

5.4.1 Study design

Among the 38,037 participants 39% were screened only once and thus had only one time point of measurement. Among those having more measurements, they were not necessarily evenly distributed throughout the year, and no measurements were performed in the vacation month of July. Besides this, the variables CRP and fibrinogen were measured only in a subset of participants in Tromsø 4-6. These shortcomings show that the design of this study was not optimal. A better design could have been to invite a random sample (with sample size based on power calculations) within the Tromsø Study cohort for repeated measurements (preferably monthly) of risk factors during one year. Possible cohort effects [210] would then also be ruled out. Trends in CVD risk factors have changed considerably over the last three decades in this population [200], although adjusting for time should minimize the effect of possible time trends in seasonal variation in risk factors. However, due to economical and timeframe considerations of the project, a new data collection project was not possible. By using available measurements, the cohort investigated for seasonal and meteorological effects on MI incidence and for seasonal pattern in CVD risk factors were the same and within the same period of follow-up.

5.4.2 Measurement of outcome – measurement error and biological variation

The possibility of measurement errors and of confounding from biological variation [206] is present when investigating the seasonal variation in risk factors. To minimize measurement errors, the measurements from both physical examinations and laboratory analysis have been performed by standard methods and the protocol has been similar in all surveys. However, possible imprecise or unequal measurements are not suspected to be systematically performed and therefore not influence the seasonal pattern. Biological variation, like circadian and weekly variation in the risk

factor blood pressure, could be a confounder for the seasonal variation, if the examination time of day and day of week was not evenly distributed throughout the year. However, the examination time and weekday was found not to be associated with month.

5.5 External validity

In spite of the limitations discussed here, the overall consideration of internal validity should be satisfactory, which is a requirement of external validity [211]. The major threat to external validity, the representativeness of the study participants, should be satisfactory here. Therefore, for a population that could be comparable to the participants in the Tromsø Study, i.e. a society with generally high living standards and equality in socio-economic status adapted to living in a similar climate with cool summers and cold to severe winters, a similar result should be held true and a generalization possible. Comparison between different populations will be further elaborated on in the discussion of the results.

6. DISCUSSION - RESULTS

As stated in the rationale for the thesis, the design and methods used in the studies which this thesis is based on has been an attempt to be an improvement of the limitations in designs and methods in previous studies. A consideration of the methods used in the three papers show that there are methodological limitations tied also to the present studies. Bearing these limitations in mind, stringing together the main results in these papers with the research existing at the time of study start and updated findings from recent research might still give an important contribution to this field of research.

6.1 Seasonal variation – geographical differences

In the Tromsø population the impact of season and weather on MI and CVD risk factors was small compared to what has been found in other populations, especially those in warmer climates.

Geographical differences in impact of season and meteorological factors on MI and CVD risk factors were suggested already in the literature review given in the introduction to the thesis. Seasonal variation in less specific outcomes like all-cause mortality or CVD mortality also shows geographical differences. Such studies comparing populations in different geographical areas within the same time period have been performed. Greater excess winter mortality in populations living in milder climates compared with populations in colder climates has been called "The paradox of excess winter mortality" [9, 10], a paradox because higher mortality rates are found in milder climates with less severe winters, where there should be less potential for cold-related mortality. Such differences in effect of season or weather between populations have been reported for both all-cause [10, 13, 212, 213], CVD [13, 81, 213, 214] and IHD [13] mortality, and for MI morbidity [215]. An analysis of latitude-related differences in seasonal mortality including countries of all continents and both hemispheres [216] showed that the amplitude of seasonality was greatest in mid-latitude areas around 35° while low or absent near the Equator and subarctic regions. Comparing European countries, the Nordic countries have the lowest while the Mediterranean countries and the UK have the greatest excess winter mortality [9, 13, 212, 213, 217].

The main contribution from the three present studies in this thesis is the support to previous studies suggesting a geographical difference in seasonal variation, and the following discussion will emphasise the possible originations of such differences, with respect to both biology and culture.

6.2 The biology

6.2.1 Physiological and pathophysiological responses to season and weather

The seasons are effects of the Earth's axis being tilted to its orbital plane giving differences in day length [195]. Seasonal changes from effect of sun radiation and the following fluctuations of weather [218] change living conditions for humans as well as other animals and plants. Thus, the observed effects on MI and CVD risk factors have been associated with, among others, seasonal patterns in behavioural factors, infections, circannual rhythms and environmental factors [207].

Human behaviour changes with season in various ways. Yearly events like the Christmas holiday period could for example change the eating and drinking behaviour. There is a known seasonal pattern in diet, physical activity and smoking activity [207]. Increased fat intake [115] and reduced physical activity [115, 219, 220] in winter may increase blood lipids and body weight [115]. Acute respiratory infections peak in winter and can be triggers of CVD events [221, 222]. Circannual rhythms have been found in a number of hormones [207] and in the human circadian rhythms [223, 224], although factors like a strict work schedule reset the sleep and activity rhythm [223], which would be expected in a modern society.

Among the environmental variables changing with season are the meteorological factors. Ultraviolet (UV) radiation increase 25-hydroxyvitamin D giving subarctic populations like the Tromsø inhabitants a clear seasonal pattern in D-vitamin status [225]. However, the possible effect of UV-radiation on blood lipids and coagulation factors is not evident [226]. Both cold and hot temperatures increase various CVD risk factors. Cold activate the sympathetic nervous system, increasing the blood levels of epinephrine and norepinephrine [227] giving cardiovascular responses like increased blood pressure [227-229], which may lead to plaque rupture and thrombosis, increasing the risk of SCD, stroke or MI [221]. Cold also increase the total plasma cholesterol concentration, mainly because of increase in low density lipoprotein cholesterol, but also in HDL cholesterol [230]. Acute phase proteins like CRP and fibrinogen [230, 231] increase in cold temperatures and cold also decrease plasma volume [230] and increase the levels of factor VII [150, 151], thromboxane B_2 [232], t-PA [233], platelet count [230, 234, 235], red cell count [230, 232] and whole-blood viscosity [230, 235], which may lead to a hyper-coagulate condition, increasing the risk of a thrombotic event like SCD, stroke or MI[221]. The effects of relative humidity [236] and atmospheric pressure [237, 238] on CVD risk factors are unclear. This could be because of the high correlation with other meteorological variables like temperature, which should be considered in data analysis [237]. Wind is known to exacerbate symptoms of AP, which could be partly explained by the increase in cardiac output, stroke volume, diastolic blood pressure and oxygen uptake when exposed to a stream of cold air [239]. Snowfall may increase the risk of MI probably via the (sometimes heavy)

exertion of snow shovelling. Snow shovelling increase the heart rate and blood pressure [240] and a study report that this activity is continued despite symptoms of chest pain [241].

The presented effects of season and weather on the human body can be summarized to physiological changes like reflex effects from cold exposure, haemoconcentration- and trombogenic effects from cold exposure or infections and behavioural changes both from reactions to natural environmental changes but also from cultural changes like yearly holiday periods. Some of these seasonally or meteorologically dependent changes can act as triggers for acute MI. Both physiological and cultural factors may differ with populations and will be discussed further.

6.2.1.1 Association and causality

Epidemiological research search to provide a broad perspective on causes of disease [206], and with the many complex known and unknown mechanisms behind the development of MI and risk factors for CVD, the present studies are investigations of associations, not causality. However, there might exist causal relationships (based on the criteria of causality from Hill [242]) between variables presented here. This could be true for for example for the relationship between temperature and blood pressure. However, an observed relationship between season and MI is a statistical and not a causal association.

6.2.2 Adaptation and acclimatization

Adaptation are changes that reduce the physiological stress produced by exposures in the total environment, which may occur within the lifetime of an organism (phenotypic) or be a result of genetic selection in a species or subspecies (genotypic) which favours survival in a particular environment [243]. Acclimatization (in the natural environment) or acclimation (in an experimental or laboratory setting) is a phenotypic adaptation to specific climatic components [243].

Man is originally a tropical mammal with a critical temperature (the lowest air temperature at which the animal can maintain its body temperature with the metabolic rate at resting level) between 25 and 27°C [244]. In contrast, the critical temperature of the arctic Svalbard reindeer is -40°C [245]. Humans migrated from tropical areas to regions around the Arctic Circle 40,000 years ago [246]. Clearly, humans as other animals have to adapt to their environment, but are such adaptions to for example cold or heat in a specific population a result of long-term genetic changes or short-term acclimatization? In a recent review article [246] it is suggested that apparent ethnical variations in thermal tolerance represent phenotypic adaption in response to the unique lifestyle and environment of the specific population, and is not a genetic predisposition.

Research investigating adaption to season and climate has largely been concerned around studies of cold adaption. Cold adaption in humans has been described in both natives in their natural environment and in research subjects in laboratory settings. The different types of whole-body acclimatization or acclimation; hypothermic, insulative and metabolic, is related to the intensity of the cold stress and to individual factors like diet, physical fitness and body fat content [247]. However, habituation and not adaption via whole-body acclimatization seem to be the common form of cold adaption among modern humans [229, 248]. Habituation can be described as cold adaption after short local exposures to cold conditions which cause very little metabolic responses, common among populations living in regions with winter temperatures below zero and varying wind velocity [229]. These individuals are adequately clothed and often active during cold and/or wind exposure. In cold temperatures and with increasing wind speed, when being properly clothed and in light activity, the skin temperature, but not the rectal temperature, decreases [249]. When cold discomfort is experienced due to difficulties with protecting for example face or hands, the sympathetic nervous system with elevation of catecholamines give increased heart work like increased heart rate and blood pressure [229]. However, as a result of habituation, the mental disturbing effect of the cold stress is reduced and by reducing the sympathetic activity, it improves peripheral circulation and diminishes the stress on the cardiovascular system [229]. Such adaption has been found in the Inuit and in fishermen from Gaspé in Canada, among others, who have developed socio-cultural adaption strategies like proper clothing, shelters and being active in the cold [229]. Socio-cultural adaption to the local climate will be discussed further in the next section.

6.3 The culture

6.3.1 Housing

Differences in housing conditions in terms of insulation and heating is thought to be one of the main reasons for observing geographical differences in seasonal variation in mortality and morbidity from CVD [10, 13, 212, 250]. A comparison of several European countries showed clear geographical differences in housing conditions and home heating habits, where living room temperatures were lower and bedroom heating less common in regions with warm winters, and that this was highly correlated to cold-related mortality [13]. Norwegian housing conditions are of high standard, and only 3 % of the population is considered living in a cold or humid home [251]. However, even a badly insulated home may have a warm indoor climate, depending on heating habits [252]. The main energy source for heating in Norway is electricity from hydroelectric power [253] to a relatively low cost, which have contributed to high indoor temperatures throughout the year. Similarly, in Iceland there is a widespread availability of low cost geothermal energy, which has been suggested to contribute to the observed absence of seasonal variation in all-cause mortality in this country [212].

In Portugal the houses are cold and humid in winter, and a study showed that among patients with ACS 42 % considered their home to be cold [254]. Among those who experienced their symptoms indoors, only 50 % reported to have a heating device in their home, and from those, only half had used it during winter time [254]. Among patients diagnosed with acute heart failure (HF) in Spain 23 % lived in a home without heating and 73% frequently felt cold in their home, factors that also increased mortality among these patients [255]. Similarly, the lack of central heating was associated with higher excess winter CHD mortality in Great Britain [11].

Portugal, Spain, UK and Ireland are the European countries with the highest excess winter mortality [10]. Housing standards differs substantially between the Nordic countries and the Mediterranean countries, UK and Ireland. A presentation of insulation standards for the years 1985-1995 show that roof, wall and floor insulation were 2, 3 and 6 times greater in Norway compared to Ireland [250]. A study comparing homes in Dublin and Tromsø found that in Tromsø the indoor temperatures in the living room, kitchen and bathroom were 22-24°C unaffected of the seasonal changes in outdoor temperature, whereas in Dublin the indoor temperatures in the same rooms were 13-20°C and highly dependent on the outdoor temperature [252]. Another study from Ireland showed that even in centrally heated houses, the temperature in the living room and the bathroom was only 15°C respectively 13°C [256]. As a comparison, in Siberian Yakutsk, the coldest city in the world, even at outdoor temperatures down to - 48°C, living room temperatures always exceeded 19°C [257].

Interestingly, even if the indoor temperature were higher and the humidity lower in homes in Tromsø compared to those in Dublin, the individuals living in both cities reported to be equally satisfied with their respective homes both from an environmental and health symptom point of view [252]. This suggests that the impression of the indoor climate also may have a somewhat cultural aspect, as a bathroom winter temperature of less than 15°C could be normal in Dublin, whereas in Tromsø, this would be considered unacceptable.

6.3.2 Clothing

Besides housing, differences in clothing behaviour have been suggested as the other main factor for observing geographical differences in seasonal variation [13, 258]. The Russian cities Yekaterinburg [259] and Siberian Yakutsk [257] have little seasonal variation in all-cause and IHD mortality. In these cities decreasing temperature increased the number of items and number layers of clothing worn outdoors, and hats and overcoats were made of fur or other thick material and covered ears and the sides of the face [257]. However, in Yakutsk there was higher winter mortality from respiratory disease, probably because of cooling of the respiratory tract when breathing extremely cold air, which is difficult to prevent independent of clothing [257].

Studies of effect of clothing on cold-related mortality [258] and CVD risk factors [228] show that the most important items worn to reduce mortality or unfavourable levels of risk factors are hat, gloves and scarf, a clothing behaviour that vary with geographical area, even at the same given temperature [13]. At an outdoor temperature of 7°C people living in regions with warm winters are less likely to wear hat, anorak, gloves [13], socks and long underpants [258] compared to people living in colder climates. It is suggested that culture, tradition and habits play an important role for why people in warmer climates underestimate cold stress and do not protect themselves sufficiently [260].

6.3.3 Outdoor exposure

Another factor for observing differences in seasonality are the differences in patterns of outdoor exposure; during occupational activities, transportation or leisure time. Exposure time (short- or long-term) and activity level (standing still or being active) will have different effects.

As with home heating and clothing behaviour, outdoor activity has different geographical patterns. Differences in the amount of people having outdoor work in different seasons, types of transportation (walking or using a car) and seasonal leisure activities are all factors that have both a natural (dependent on environmental factors) and cultural (depending on traditions and habits) perspectives. Comparing populations in European countries, the total time spent outdoors was higher in the UK and the Mediterranean countries than in Finland [258]. In a Finnish population, the winter outdoor exposure time was only 7 hours per week (i.e. 4% of the total time), mostly due to leisure time activities (71%), commuting to work (14%) or via occupational activities (4%) [261]. The Finnish population can largely be comparable to the population of Tromsø, and we could expect similar patterns of outdoor exposure among Tromsø inhabitants. During outdoor excursions people in climates with milder winters were more likely to stand still and to shiver compared to reports from people in colder climates [13, 258]. In Yekaterinburg outdoor shivering was prevented by increased clothing and spending less time being stationary [259]. In Finland outdoor exposure during leisure time was seen in people with good health, younger age and those who did regular exercise, and choosing to walk to work was associated with urban living, being a student and doing regular exercise [261]. This suggests that winter outdoor exposure in cold climates is short and/or associated to higher activity levels and that the main cause of outdoor activity in for example the Nordic countries are voluntarily and made by preference, either as a leisure time activity or as preferred walking, biking or skiing to work instead of using a car.

Choosing to stay indoors on days with severe weather is another factor that may have a geographical pattern. In Yakutsk, at temperatures below -20°C the percentage going out steeply decreased and reduced the number of people going out to 44% at -48°C [257].

6.3.4 Living standard

The presented prevention strategies against seasonal and meteorological factors seem to vary largely with geographical area. Different geographical areas also have different living standards, both between populations and within the population. Living standards are related to both housing conditions, availability of proper clothing and to outdoor activity patterns. Socio-economic differences have shown to be related to excess winter mortality in European countries [10] and to temperature-related mortality in the USA [262]. The benefits of having a generally high living standard and socio-economic equality [204] within the population and a welfare system covering all citizens[205] probably play an important role for observing only minor seasonality in Tromsø and in the Nordic countries as a whole.

6.4 Seasonal variation – sex and age differences

Previous studies report conflicting results of which gender is the more susceptible for seasonal variation or effect weather on MI incidence [68, 162, 263] and CVD risk factors [102, 129, 134, 135], while some find no gender difference in either MI incidence [264-266] or CVD risk factors [109]. Likewise, some find no effect of age in either MI incidence [156, 266] or CVD risk factors [109, 139], while others report that the seasonal variation or weather on MI incidence [48, 49, 68, 162, 263, 265, 267] and CVD risk factors [268, 269] are greater among older than younger individuals.

Observed sex and age differences in effect of season and weather can be related to both biology and culture. Due to normal ageing processes and comorbid diseases, older individuals might be more susceptible to physiological responses to exposure to seasonal changes. Likewise, older or more fragile individuals might also take extra precautions and change their behavioural pattern. In a study comparing several populations, a stronger effect of cold on risk of MI among women than men was greater in populations living in warmer climates than those in colder climates [68]. A similar study comparing several populations with regard to age differences has not been found, but as for gender also here there might be geographical differences.

7. CONCLUSIONS AND FUTURE PERSPECTIVES

7.1 Today

7.1.1 Living in the High North

The observed small effect of season and weather on MI incidence and changes in CVD risk factors in the subarctic population of Tromsø is probably largely explained by the preventive strategies of sufficient home heating, adequate clothing, outdoor exposure behaviour and, an additional factor associated with the previously mentioned, the generally high living standard. In addition to that, habituation to for example cold exposures cannot be ruled out. Being prepared to sudden seasonal and weather changes, like large snowfalls or cold wind, may prevent cardiovascular effects. This can be seen as so-called local, traditional or indigenous knowledge [8], which is knowledge, practice and belief gained through experience and transmitted to members and further generations of the population. The high awareness of the importance of preventive strategies is probably implemented as such traditions and habits. In Tromsø, this could be seen as the extensive use of clothing suitable to the daily weather conditions, the non-acceptance of having a cold, draughty or humid home, and the choice of staying indoors on days with severe weather.

7.2 Tomorrow

Several studies suggest that most of the increase in winter excess or cold-related mortality and morbidity can be prevented by protective interventions, like proper clothing and sufficient home heating [212, 257, 259, 270], thus considering this a manmade health challenge [271]. Health promotion programs [212] and housing improvements interventions [272] have been performed. However, studies of trends in seasonality from MI mortality and morbidity show conflicting results [30, 50, 273]. Many factors are associated with the future perspective of seasonality of mortality and morbidity from disease worldwide, such as long-term changes in health and living standards or possible global climate changes. However, the three present studies of this thesis support previous research reporting geographical difference in seasonal variation, probably due to climate-adaptive protection strategies in cold climates. Such protection strategies can be adopted by other populations and thus might prevent the observed excess winter or cold-related mortality and morbidity mainly due to MI and other CVD.

8. TABLES AND FIGURES

Table 1. Seasonal variation in myocardial infarction. Description of studies published 1946–2007.

First author & publication year	Time-period	Population-based design?	N	Outcome & population	Area	Outcome source, case diagnosis & ascertainment	Exposure (season) definition	Results
Goerre 2007 [24]	1990-1994	No	6,650	MI patients	Bernese Oberland, Reuss Valley, Grisons, Basel, Jura, Swiss Plateau & Ticino Switzerland	VESKA[1] register. Hospital admissions. ECG & enzymes.	Monthly.	Peak in Jan, low in Jul.
Mbanu 2007 [25]	Jan 1994-Dec 2004	No	449	CHD mortality. Fire-fighters on-duty.	USA	"Narratives".	Monthly. W: Jan-Mar, Sp: Apr-Jun, Su: Jul-Sep, A: Oct-Dec.	Peak in winter, low in spring. Peaks in Jan-Feb & Aug-Sep.
Dilaveris 2006 [14]	Jan-Dec 2001	Yes	3,126	MI mortality	Athens Greece	The CLIMATE[2] study. Death certificates.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in winter, low in summer. Peak in Dec, low in Jun.
Gerber 2006 [156]	Jan 1979-Dec 2002	Yes	4,742	2,676 first-ever MI patients & 2,066 SCD	Olmstead Minnesota USA	Hospital admissions & death certificates; ICD-9: 410-414 & ICD-10: I20-I25. Chest pain, ECG & elevated biomarkers. Event validation.	W: Dec 21-Mar 21, Sp: Mar 22-Jun 21, Su: Jun 22-Sep 20, A: Sep 21-Dec 20.	No SV in MI (SCD: peak in winter, low in summer).

[1] Vereinigung Schweizerischer Krankenhäuser

[2] Climate impacts on myocardial infarction deaths in the Athens territory

Continued

Savopoulos 2006 [46]	1980-2000	No	2,665	SCD	Thessaloniki Greece	SCD from MI, IHD or arrhythmia. Excluded hospitalized or bedridden patients. Validation by autopsy.	Monthly. Seasons not defined.	Peak in summer, low in autumn.
Biedrzycki 2006 [26]	May 1999-May 2004	No	2,266	MI mortality	London England UK	Necropsy.	Monthly. W: Nov 1-Mar 31, Su: Apr 1-Oct 31.	Peak in winter, low in summer. Peak in Dec, low in Aug.
Manfredini 2005 [27]	Jan 1988-Dec 2004	No	4,014	MI patients	Ferrara Italy	Hospital admission. Symptoms, ECG changes (specified), elevated CK-MB or troponin & tissue necropsy.	Monthly. W: Dec 21-Mar 19, Sp: to Jun 19, Su: to Sep 21, A: to Dec 20.	Peak in winter, low in summer. Peak in Dec, low in Sep.
Azegami 2005 [47]	1992-2002	No	172	First CHD event (MI & AP) patients	Nagano Japan	Hospital admission. Symptoms, ECG & enzymes.	W: Dec-Mar, Su: Jun-Sep.	Peak in Jun-Sep, low in Dec-Mar (only among patients ≤40yrs).
Kinoshita 2005 [28]	Jan 1988-Dec 2002	No	415	MI patients	Osaka Japan	Hospital admissions. 1) symptoms or ECG changes & abnormal enzymes or 2) symptoms & abnormal enzymes or fatal event "evidence" of recent MI and/or necropsy findings. Event validation.	Monthly. Seasons not defined.	Peak in winter, low in summer. Peak in Feb, low in Jul & Nov.
Vrbova 2005 [162]	Apr 1988-Mar 2002	Yes	271,321	MI patients	Ontario Canada	Hospital discharge database. ICD-9: 410.	Monthly. Seasons not defined.	No SV.

Continued

Morabito 2005 [48]	1998-2002	No	2,683	MI patients	Florence Italy	Hospital admissions. ICD-9: 420-410.92. Non-Florentine residents excluded.	Seasons not defined.	Peak in winter & autumn, low in summer.
Ulmer 2004 [109]	1985-1999	Yes	1,266	MI mortality	Vorarlberg Austria	VHM&PP[1] register linked to cause of death register. ICD-9: 410-411.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	No SV.
González Hernández 2004 [49]	Jan 1995-Dec 1999	No	8,400	MI patients	Valencia Spain	PRIMVAC[2] register. Hospital admissions, CICU patients.	Monthly. Season not defined.	Peak in summer, low in winter. Peak in Aug-Sep, low in Nov-Jan.
Fischer 2004 [50]	Jan 1983-Dec 1999	Yes	17,989	First-ever MI patients	North Jutland Denmark	Hospital admissions. ICD-8 (1977-1993): 410-410.9 & ICD-10 (1994-1999): I21-I21.9.	Monthly.	Peak in May & Nov, low in Jul.
Straus 2004 [51]	Jan 1995-Apr 2001	No	582	Probable SCD	The Netherlands	IPCI[3] register (GPs). GPs medical records of death reviewed for cause.	Monthly.	Peak in Oct, low in Aug.
Barnett 2004 [29]	1982-1995 vary by area	Yes	128,265	66,819 MI patients & 61,446 coronary mortality men 35-64 yrs	Cities in 21 countries world-wide	WHO MONICA[4] register (35 centres).	Monthly.	Peak in Jan-Feb most common. Southern hemisphere cities peak in Jul-Aug.

[1] Vorarlberg Health Monitoring and Promotion Programme

[2] Proyecto de Registro del Infarto de Miocardio en Valencia, Alicante y Castellón

[3] Integrated Primary Care Information

[4] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Crawford 2003 [30]	1979-1998	Yes	68,683	MI mortality	Northern Ireland UK	Death certificates. ICD-9: 410.	Monthly.	Peak in Feb.
Messner 2003 [31]	1985-1999	Yes	1,139	SCD 35-64 yrs	Norrbotten & Västerbotten Sweden	WHO MONICA[1] register. Hospital admissions, GPs, death certificates, necropsy. Symptoms, ECG & cardiac enzymes.	Seasons not defined.	Peak in winter.
Yamasaki 2002 [180]	1992-1995	No	725	MI patients	Kochi Japan	Hospital admissions. 2 of 3: chest pain, ECG or enzymes.	Monthly. W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	No SV.
Figueras 2002 [157]	NIA	No	307	MI patients with recurrent MI	NIA	NIA	Monthly.	No SV for first MI (peak in Dec-Jan, low in Jun-Jul for recurrent MI).
Weereasinghe 2002 [32]	1979-1997, 1992-1998 vary by register	Yes	NIA	CA mortality	New South Wales Australia	Hospital register & death certificates (CAD): ICD-9: 410-414, 429.2, 429.7, 429.79.	Seasons not defined.	Peak in winter. Peak in Jul.
Sharovsky 2002 [33]	Jan 1996-Nov 1997	Yes	5,615	MI mortality >34 yrs	Sao Paulo Brazil	PROAIM[2] register. Death certificates. ICD-10: I21.	W: Jun-Aug, Sp: Sep-Nov, Su: Dec-Feb, A: Mar-May.	Peak in winter, low in summer.
Grech 2001 [34]	1994-1998	No	2,157	MI patients	Malta	Hospital admissions.	Monthly	Peak in Jan, low in Jun and Jul.

[1] Multinational monitoring of trends and determinants in cardiovascular disease

[2] Programa de Aprimoramento de Informações de Mortalidade

Continued

Aylin 2001 [11]	1986-1996 excl. 1989-1990	Yes	4,507,910	CHD mortality ≥65 yrs	Great Britain	ICD-9: 410-414.	W: Dec-Mar	Peak in winter.
Fujita 2000 [35]	Jan 1989-Mar 1997	No	386	Out-of-hospital CA from ACS	Yokohama Japan	≥1 of: MI symptoms before CA, ST elevation after ROSC or fresh thrombi in necropsy.	Seasons not defined.	Peak in winter peak, low in summer.
Tanaka 2000 [36]	1992-1996	Yes	NIA	IHD mortality 45-84 yrs	Okinawa & Osaka Japan	Mortality register. ICD-9: 410-414 (1992-1994) & ICD-10(1995-1996): I20-I25.	Monthly.	Peak in Jan, low in Aug (Okinawa) & Sep (Osaka).
Kloner 1999 [16]	1985-1996	Yes	222,265	CAD mortality	Los Angeles California USA	Death certificates. ICD-9: 410-414, 429.2, 429.7, 429.79.	Monthly.	Peak in Jan & Dec, low in Jun-Sep.
Chiang 1999 [186]	Jan 1992-Dec 1996	No	480	MI patients	Taiwan	Hospital admissions. 2 of 3: chest pain, CK elevation or ECG (new Q wave or ST-T changes).	Monthly.	No SV.
Sheth 1999 [37]	1980-1982, 1990-1992	Yes	159,884	MI mortality	Canada	Mortality register. ICD-9: 410.	Monthly. W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in winter, low in summer. Peak in Jan, low in Sep.
Ku 1998 [187]	Jan 1992-Dec 1996	No	540	MI patients	Southern Taiwan	Hospital admissions. CCUs. 2 of 3: chest pain, ECG (new Q wave or ST/T changes) or CK & CK-MB elevation.	Monthly.	No SV.

Continued

Seto 1998 [17]	1984-1993	Yes	11,010	CHD mortality	Hawaii USA	Death certificates. Deaths from CAD. ICD-9: 410-414. Excluded non-residents.	Monthly.	Peak in Mar, low in Aug.
Spencer 1998 [18]	Jul 1994-Jul 1996	No	259,891	MI patients	USA	NRMI-2[1] register. Symptoms, ECG findings or enzyme levels.	W: Dec 21-Mar 19, Sp: Mar 20-Jun 19, Su: Jun 20-Sep 21, A: Sep 22-Dec 20.	Peak in winter, low in summer. Peak in Jan, low in Jul. Least SV in Pacific states, largest SV in South Atlantic states.
Sayer 1997 [45]	Jan 1988-Dec 1994	No	1,225	MI patients	London England UK	Hospital admissions. CCU. 2 of 3: chest pain, ECG ST elevation or CK elevation.	Monthly. Season not defined.	Peak in winter, low in summer.
Ornato 1996 [38]	Dec 1990-Dec 1993	No	83,541	MI patients	USA	NRMI-1[2] register.	W: Dec 21-Mar 19, Sp: Mar 20-Jun 19, Su: Jun 20-Sep 21, A: Sep 22-Dec 20.	Peak in winter, low in summer.
Peters 1996 [52]	Jul 1987-Jun 1991	No	20,289	MI patients <80 yrs	USA, Canada, Sweden	CAST[3] trial register. MI patients with arrhythmia.	Seasons not defined.	Peak in winter & autumn, low in spring & summer.
Spielberg 1996 [53]	1980-1988	LIA	2,906	MI patients	Dessau Germany	MI register. Chest pain, ECG & enzymes. Out-of-hospital death: autopsy & ECG or chest pain reported by witness.	Monthly.	Peak in Mar.
Thompson 1996 [77]	1979-1988	No	2,254	MI patients	Leicester England UK	Hospital admissions. CCU. Date recordings checked with patient's partner.	Monthly.	No SV.

[1] National Registry of Myocardial Infarction 2
[2] National Registry of Myocardial Infarction 1
[3] Cardiac Arrhythmia Suppression Trial

Continued

Douglas 1995 [39]	1962-1971	No	220,000	123,000 CHD patients & 97,000 CHD mortality	Scotland UK	Hospital admissions & out-of-hospital deaths. ICD-7 (1962-1967): 420.1, ICD-8 (1968-1971): 410.	Monthly. Seasons not defined.	Peak in winter for men & women ≥ 55yrs. Peak in spring for men < 55yrs. No SV for women < 55yrs.
Enquselassie 1993 [20]	NIA	Yes	3,537	2,063 MI patients (fatal & non-fatal) & 1,474 CD <70 yrs	New South Wales Australia	WHO MONICA[1] register.	W: Jun-Aug, Sp: Sep-Nov.	Peak in winter.
Marchant 1993 [40]	Jan 1988-Dec 1991	No	633	MI patients	London England UK	2 of 3: chest pain, ECG ST elevation or CK elevation.	W: Dec-Feb.	Peak in winter.
Miric 1993 [78]	Jan 1981-Dec 1987	No	1,306	MI patients	Trogir, Makarska & middle Dalmatian islands Croatia	Hospital admissions. Chest pain, ECG changes & elevated enzymes.	Monthly. Seasons not defined.	No SV.
Cucu 1992 [54]	1971-1982	No	10,000	MI among trial participants & controls men 40-60 yrs	Bucharest Romania	Primary prevention IHD Trial (intervention not described). Followed for MI.	Monthly. Seasons not defined.	Peak in Feb, May & Oct, low in Oct, Aug, Jun & Mar (control group). Peak in Aug, Dec, Jan & Apr, low in Mar, Jun & Sep (study group). Conclusion: Intervention effect good in winter & spring, not in summer & autumn.

[1] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Ornato 1990 [19]	Jan 1980-Dec 1986	Yes	NIA	MI mortality	4 Northern & 4 Southern states USA, Australia	Mortality register. ICD-9: 410.	Monthly. Seasons not defined.	Peak in in winter, low in summer.
Hirasawa 1989 [181]	1976-1985 (W only: Nov 7-Apr 16)	No	581	MI patients	Hokkaido & Yamagata Japan	Hospital admissions. Chest pain, ECG (Q-wave, T or ST elevation) & elevated CK-MB, CK, LD or ASAT, or myocardial necrosis in necropsy.	Monthly.	No SV.
Dobson 1988 [164]	Aug 1984-Aug 1986	LIA	777	MI patients & SCD 25-69 yrs	Hunter Valley Australia	WHO MONICA[1] register. Hospital admissions & death certificates. Symptoms, ECG, cardiac enzymes, autopsy & more.	W: Jun-Aug, Su: Dec-Feb.	No SV in MI (SCD peak in winter, low in summer).
Marshall 1988 [21]	Jan 1970-Dec 1982	Yes	NIA	CHD mortality	New Zealand	Mortality register. ICD-8 (1970-1979): 410-413, ICD -9 (1979-1982): 410-414.	Monthly.	Peak in winter (mid-Jul), low in summer.
Thakur 1987 [83]	1979-1983	No	1,217	MI patients	Patna India	Hospital admissions. 1) ECG (ST changes, T inversion or Q), chest pain & ST elevation, 2) chest pain & elevated ASAT, LD or CK.	Seasons not defined.	No SV.
Al-Yusuf 1986 [55]	1979-1982	No	340	MI patients	Kuwait	Hospital admissions. All versus MI admissions. 2 of 3: chest pain, ECG changes (new Q-wave, T inversion, ST depression) & elevated CK or ASAT.	W: Dec-Mar, Su: Jun-Sep.	Peak in summer, low in winter.

[1] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Ruscone 1985 [56]	Jan 1979-Dec 1980	No	2,863	MI patients	Milan Italy	Chest pain with syncope or shock, ECG with new Q-wave, ST depression or elevation & CK elevation.	Monthly.	Low in Jul & Aug.
Beard 1982 [161]	1950-1975	No	1,054	SCD	Rochester Minnesota USA	Hospital admissions. Death within 24 hrs of symptom onset.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	No SV.
Ahlbom 1979 [182]	1973	No	4,020	MI patients	Stockholm Sweden	Hospital admissions & mortality register: ICD-?: 410.	Monthly.	No SV.
Sarna 1977 [57]	1970	LIA	1,216	MI patients & SCD <65 yrs	Helsinki Finland	IHD register. WHO MI criteria. Definite & possible MI.	Monthly. Seasons not defined.	Peak in late autumn, low in summer.
Konu 1977 [163]	Mar 1972-Apr 1973	Yes	404	MI patients ≥65 yrs	Turku Finland	Turku Heart Register. Hospital admissions, GPs records, death certificates & autopsy records. WHO criteria: chest pain, ECG & enzyme (ASAT or LD) changes, or myocardial necrosis in autopsy.	Monthly.	No SV.
Hladky 1975 [58]	1970-1972	No	495	MI patients	Brno Czech Republic	Hospital admissions to CCU. WHO criteria; chest pain, ECG & enzymes.	Monthly. W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in spring, low in winter.
Rogot 1974 [41]	1967	LIA	14,418	CHD mortality	Chicago Illinois USA	NIA	Monthly.	Peak in Jan, low in Jun.

Continued

Johansson 1972 [183]	1960-1968	No	3,819	MI patients & MI mortality	Malmö Sweden	Hospital admissions & out-of-hospital MI mortality from autopsy records.	Monthly.	No SV.
Fyfe 1972 [61] & Dunnigan 1970 [60]	1962-1966	Yes	112,772	47,281 IHD patients & 65,491 IHD mortality	Scotland UK	Mortality register & hospital admissions from IHD. ICD-?: 420.1.	Monthly. Seasons not defined.	Peak in winter & spring (non-fatal & fatal hospital events). Peak in winter, low in summer (IHD mortality).
Protos 1971 [59]	1964-1967	No	539	MI patients	New York USA	Hospital admissions. Symptoms, ECG & enzymes.	Monthly.	Peak in Apr & Dec (women only).
Anderson 1970 [42]	1958-1962	Yes	NIA	IHD mortality men only	England & Wales UK, Ontario Canada	ICD-? (1955-1968): 420-422.	Monthly.	Peak in Jan.
McWhinney 1968 [43]	Apr 1962-Apr 1967	Yes	152	MI patients & SCD	Stratford-on-Avon England UK	Death certificates & hospital admissions. Cross-checks with inhabitant register. Necropsy, ECG & chest pain. Event validation.	Monthly.	Peak in Nov & Feb, low in Aug & Sep.
Rose 1966 [15]	NIA	No	NIA	MI patients & ASHD mortality	England &Wales UK	MI trial patients (Q in ECG) & mortality statistics (ICD: 420).	Seasons not defined.	Peak in winter, low in summer.
Westlund 1965 [159]	1956-1961	LIA	2,884	First-ever MI patients & MI mortality. Women 1959-1961 only.	Oslo Norway	Hospital records, death certificates, health insurance notifications, autopsy protocols, cardiology specialist practice. Matching to avoid duplications.	Monthly.	No SV.

Continued

Fogel 1964 [274]	1952-1958	No	1,663	MI patients	Stamford Connecticut USA	Hospital admissions & death certificates. 1 of : chest pain, ECG changes, clinical/laboratory signs of tissue death and/or necropsy findings.	Monthly. W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	No SV.
DePasquale 1961 [62]	1941-1943, 1952-1955	No	1,582	MI patients	New Orleans USA	Hospital admissions. Symptoms, ECG & laboratory findings.	Monthly.	Peak in Feb (1941-1943) & Aug, low in Dec (1952-1955).
Vartio 1960 [184]	1946-1958	No	683	MI patients	Oulo Finland	Hospital admissions. Symptoms, ECG & elevated temperature, sedimentation rate, leucocytes & lowered BP. Suspected MI excluded.	Monthly.	No SV.
Adesola 1960 [94]	1953-1956	No	298	MI & coronary thrombosis patients	Belfast Ireland	Hospital admissions. Excluded recurrent events.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	No SV.
Heyer 1953 [63]	1946-1951	No	1,386	MI patients	Dallas USA	Hospital admissions. Chest pain, ECG findings, clinical/laboratory findings of tissue death from MI or autopsy. Event validation.	Monthly. W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in summer. Peak in Jul & Aug.
Weiss 1952 [64]	NIA	No	753	MI patients	Louisville & contiguous parts of Kentucky & Southern Indiana USA	Hospital admissions, home events & private practice. ECG.	W & Sp: Dec-May, Su & A: Jun-Nov.	Peak in winter & spring, low in summer & autumn. Peak in Dec, low in Nov.

Continued

Gertler 1951 [65]	1946-?	No	100	MI patients <40 yrs	Several areas in USA	Post-MI examinations.	Seasons not defined.	Peak in winter & autumn.
Jacobs 1951 [158]	1934-1947	No	88	First-ever MI patients	New York USA	Hospital admissions. ECG or autopsy.	Monthly.	No SV.
Smith 1951 [185]	1925-May 1949	No	920	MI patients	Detroit Michigan USA	Hospital admissions. Symptoms, ECG and/or autopsy.	Monthly.	No SV.
Billings 1949 [44]	1925-1946	No	240	MI patients i.e. coronary artery occlusion or coronary insufficiency	Nashville Tennessee USA	Hospital admissions. Chest pain, ECG changes or autopsy.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in winter, low in summer.
Mintz 1947 [275]	Jan 1940-Dec 1945	No	572	MI patients	Chicago Illinois USA	Hospital admissions, outpatient clinic and GPs. Symptoms, ECG or autopsy.	Monthly.	No SV.

Table 2. Weather effects on myocardial infarction. Description of studies published 1946–2007.

First author & publication year	Time-period	Population-based design?	N	Population	Area	Outcome source, case diagnosis & ascertainment	Exposure	Results
Goerre 2007 [24]	1990-1994	No	6,650	MI patients	Bernese Oberland, Reuss Valley, Grisons, Basel, Jura, Swiss Plateau & Ticino Switzerland	VESKA[1] register. Hospital admissions. ECG & enzymes.	Wind, atmospheric pressure & snowfall.	Positively associated with atmospheric pressure & wind. Snowfall associated with more events in Swiss Plateau and less in Bernese Oberland and Ticino hospitals.
Dilaveris 2006 [14]	Jan-Dec 2001	Yes	3,126	MI mortality	Athens Greece	The CLIMATE[2] study. Death certificates.	Temperature & humidity.	U-shaped association with temperature, linear association with humidity.
Gerber 2006 [156]	Jan 1979-Dec 2002	Yes	4,742	2,676 first-ever MI patients & 2,066 SCD	Olmstead Minnesota USA	Hospital admissions & death certificates; ICD-9: 410-414 & ICD-10: I20-I25. Chest pain, ECG & elevated biomarkers. Event validation.	Temperature & snowfall.	No effect of temperature on MI (SCD inversely associated with temperature). No effect of snow.
Misailidou 2006 [67]	Oct 2003-Sep 2004	No	1,608	ACS (MI & AP) patients	Karditsa, Lamia, Chalkida, Kalamata & Zakinthos Greece	Hospital admissions.	Temperature & humidity.	Inversely associated with temperature & positively associated with humidity.
Southern 2006 [97]	Apr 1996-Dec 1998	No	2,280	MI patients	Calgary Canada	Hospital admissions.	Snowfall (Jun-Sep excluded).	Positively associated with snowfall.

[1] Vereinigung Schweizerischer Krankenhaeuser

[2] Climate impacts on myocardial infarction deaths in the Athens territory

Continued

Wang 2006 [66]	1993-2002	No	3,755	MI patients	Hiroshima Japan	Ambulance records. Non-uniform criteria, ECG & enzymes if available.	Temperature & atmospheric pressure.	Inversely associated with temperature & positively associated with atmospheric pressure.
Barnett 2005 [68]	1980-1995, vary by area	Yes	87,410	Coronary event patients (non-fatal, fatal & possible MI, CD, other event) 35-64 yrs	24 populations in 21 countries world-wide	WHO MONICA[1] register.	Temperature & humidity.	Inversely associated with temperature. No effect of humidity. Populations in colder areas (Sweden, Finland) showed little change in coronary event rates with temperature changes.
Houck 2005 [96]	Jan 1993-Jan 1996	No	1,327	MI patients	Texas USA	Hospital admissions.	Atmospheric pressure.	Inversely associated with atmospheric pressure.
Morabito 2005 [48]	1998-2002	No	2,683	MI patients	Florence Italy	Hospital admissions. ICD-9: 420-410. Non-Florentine residents excluded.	Temperature.	Positively associated with temperature.
Sharovsky 2004 [69]	Jul 1996-Jun 1998	Yes	12,007	MI mortality	Sao Paulo Brazil	Mortality register. ICD-10: I21.	Temperature, atmospheric pressure & humidity.	U-shaped association with temperature & inverse association with humidity. No effect of atmospheric pressure.
Ebi 2004 [70]	1983-1997, Jan-Jun 1998	No	NIA	MI patients	San Francisco, Sacramento & Los Angeles California USA	Hospital admissions. ICD-9: 410.	Temperature.	Inversely associated with maximum temperature in San Francisco & Sacramento & minimum temperature in Los Angeles. Positively associated with minimum temperature in San Francisco & Sacramento.

[1] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Schwartz 2004 [71]	1986-1994	No	NIA	MI patients ≥65 yrs	12 cities USA	Hospital admissions ICD-9: 390-429 og ICD-9: 410.	Temperature & humidity.	Positively associated with temperature. No effect of humidity.
Panagiotakos 2004 [72]	Jan 2001-Aug 2002	No	5,458	Non-fatal ACS (MI & unstable AP) patients	Athens Greece	Hospital admissions. MI; 2 of 3: ECG changes, symptoms &/or enzyme elevations. Unstable AP; AP at rest within at last 24hrs Braunwald class III. Athens citizens only. Event validation.	Temperature, wind, atmospheric pressure & humidity.	Inversely associated with temperature & positively associated with humidity. No effect of atmospheric pressure or wind.
Chang 2004 [73]	Feb 1989-Jan 1995	No	369	MI patients women 15-49 yrs	17 countries in Africa, Asia, Europa & Latin America incl. the Caribbean	WHO Collaborative Study[1] register.	Temperature & humidity.	Inversely associated with temperature except from in Jamaica and Yugoslavia. No effect of humidity.
Messner 2002[74]	NIA	Yes	2,689	MI & AP patients 25-64 yrs	Norrbotten & Västerbotten Sweden	WHO MONICA[2] register. Records from hospitals, GPs, death certificates, necropsy. Symptoms, ECG, cardiac enzymes. Event validation.	Temperature, atmospheric pressure & humidity.	Positively associated with temperature. No effect of atmospheric pressure & humidity.
Grech 2001 [34]	1994-1998	No	2,157	MI patients	Malta	Hospital admissions.	Monthly temperature.	Inversely associated with monthly temperature.
Tanaka 2000 [36]	1992-1996	Yes	NIA	IHD mortality 45-84 yrs	Okinawa & Osaka Japan	Mortality register. ICD-9 (1992-1994): 410-414 & ICD-10 (1995-1996): I20-I25.	Monthly temperature.	Inversely associated with monthly temperature.

[1] WHO Collaborative Study of CVD and Steroid Hormone Contraception

[2] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Danet 1999 [75]	1985-1994	Yes	3,616	MI patients & coronary mortality 22-64 yrs	Lille France	WHO MONICA[1] register; hospital admissions & death certificates. Event validation.	Temperature & atmospheric pressure.	Inversely associated with temperature & V-shaped association with atmospheric pressure.
Seto 1998 [17]	1984-1993	Yes	11,010	CHD mortality	Hawaii USA	Death certificates. Deaths from CAD ICD-9: 410-414. Excluded non-residents.	Temperature.	Inversely associated with temperature.
Donaldson 1997 [76]	1976-1992	Yes	NIA	IHD mortality ≥50 yrs	Southeast England UK	ICD-?: 410-414.9.	Temperature.	Inversely associated with temperature.
Eurowinter Group 1997 [13]	1988-1992, vary by area	Yes	NIA	IHD deaths 50-59 yrs & 65-74 yrs	North & South Finland, Baden-Württemberg, The Netherlands, London England UK, North Italy, Athens Greece & Palermo Sicilia Italy	ICD-9: 410.0-414.9.	Temperature.	Inverse & U-shaped association with temperature. Effect of temperature was greater in the warmer regions than in the colder regions.
Thompson 1996 [77]	1979-1988	No	2,254	MI patients	Leicester England UK	Hospital admissions. CCU. Recordings of date checked with each patient's partner.	Temperature, atmospheric pressure & humidity.	Inversely associated with temperature, negatively & positively associated with humidity. No effect of atmospheric pressure.
Pan 1995 [99]	1981-1991	Yes	30,085	CAD deaths ≥25 yrs	Taiwan	Mortality register. ICD-8: 410-414.	Temperature.	U-shapely associated with temperature.

[1] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Enquselassie 1993 [20]	NIA	Yes	3,574	2,063 MI patients (fatal & non-fatal) & 1,474 CD <70 yrs	New South Wales Australia	WHO MONICA[1] register.	Temperature & humidity.	No effect of temperature on MI (CD inversely associated with temperature). No effect of humidity.
Persinger 1993 [276]	1983-1986	No	1,456	Cardiac emergencies (AP, MI, HF, AF, CA, arrhythmia) patients	Sudbury Canada	Hospital admissions of cardiac emergencies.	Snow in Nov-Mar.	No effect of snow.
Miric 1993 [78]	Jan 1981-Dec 1987	No	1,306	MI patients	Trogir, Makarska & middle Dalmatian islands Croatia	Hospital admissions. Chest pain, ECG changes & elevated enzymes.	Temperature, atmospheric pressure & humidity.	Positively associated with temperature & humidity. No effect of atmospheric pressure.
Marchant 1993 [40]	Jan 1988-Dec 1991	No	633	MI patients	London England UK	2 of 3: chest pain, ECG ST elevation or CK elevation	Temperature.	Inversely associated with temperature.
Frost 1992 [79]	Jan 1984-Dec 1985	Yes	NIA	MI mortality	Auckland New Zealand	Mortality register. WHO 1975: 410.	Temperature.	Inversely associated with temperature.
Auliciems 1989 [80]	Jan 1983-Dec 1984	Yes	NIA	MI mortality	Montreal Canada	Mortality statistics. WHO 1975: 410.	Temperature & snowfall.	Inversely associated with temperature & positively associated with snowfall. Mortality is lower than with similar falls in temperature in Brisbane [81].
Auliciems 1989 [81]	NIA	Yes	NIA	MI mortality	Brisbane Australia	Mortality register. WHO 1975: 410.	Temperature.	Inversely associated with temperature.

[1] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Hirasawa 1989 [181]	1976-1985 (W only: Nov 7-Apr 16)	No	581	MI patients	Hokkaido & Yamagata Japan	Hospital admissions. Chest pain, ECG with Q-wave, T or ST elevation & elevated CK-MB, CK, LD or ASAT, or necrotic myocardial areas in necropsy.	Temperature, atmospheric pressure & humidity.	No effect of temperature, atmospheric pressure or humidity.
Mannino 1989 [82]	1982-1987	No	926	MI mortality	Wisconsin USA	Death certificates. Excluded death in health care facilities & death on snowy days.	Temperature.	Inversely associated with temperature.
Thakur 1987 [83]	1979-1983	No	1,217	MI patients	Patna India	Hospital admissions. 1) ECG (ST changes, T inversion or Q), chest pain & ST elevation, 2) chest pain & elevated ASAT, LD or CK.	Temperature.	Inversely associated with temperature.
Ruhenstroth-Bauer 1985 [84]	Jan-Mar 1981	No	162	MI patients	Munich Germany	Hospital admissions.	Temperature & humidity.	Inversely associated with temperature & humidity.
Ruscone 1985 [56]	Jan 1979-Dec 1980	No	2,863	MI patients	Milan Italy	Chest pain with syncope or shock, ECG with new Q-wave, ST depression or elevation & CK elevation.	Temperature, atmospheric pressure, humidity & snowfall.	No effect of temperature, atmospheric pressure, humidity or snowfall.
Vychodil 1982 [277]	1977	No	378	MI patients	Olomouc Czechoslovakia	Hospital admissions. Symptoms, ECG, enzymes.	Atmospheric pressure.	No effect of atmospheric pressure.

Continued

Baker-Blocker 1982 [98]	1973-1977 (W only: Dec-Mar)	Yes	NIA	MI mortality	Minneapolis-St. Paul Minnesota USA	Mortality register. ICD-8: 410 & 411.	Snowfall.	Positively associated with snowfall.
Bull 1978 [85]	Jan 1965-Dec 1968 & 1970-1971 vary by area	Yes	NIA	MI mortality	England & Wales UK, New York USA	Mortality statistics. ICD-?: 420.1.	Temperature.	Inversely associated with temperature.
Sarna 1977 [57]	1970	LIA	1,216	MI patients & SCD <65 yrs	Helsinki Finland	IHD register. WHO MI criteria. Definite & possible MI.	Temperature, atmospheric pressure & humidity.	No effect of temperature or humidity. Inversely related with atmospheric pressure.
Konu 1977 [163]	Mar 1972-Apr 1973	Yes	404	MI patients ≥65 yrs	Turku Finland	Turku Heart Register. Hospital admissions, GPs records, death certificates & autopsy records. WHO: chest pain, ECG & enzyme (ASAT or LD) changes, or necrosis in autopsy.	Temperature & atmospheric pressure.	No effect with temperature or atmospheric pressure.
Bainton 1977 [86]	Jul 1970-Jul 1974	LIA	NIA	IHD mortality	London England UK	Mortality statistics. ICD-8: 410-414.	Temperature.	Inversely associated with temperature.

Continued

Rogot 1976 [87]	1962-1966	No	NIA	CHD mortality	32 metropolitan areas in USA	Mortality statistics. ICD-7: 420.	Temperature & snowfall.	Inversely associated with temperature & positively related to snowfall.
Freeman 1976 [88]	NIA	No	1,036	MI patients	Hobart Tasmania	Hospital admissions. CCU. Symptoms, ECG & enzymes.	Temperature & humidity.	Inversely associated with temperature. No effect of humidity.
West 1976 [160]	1969-1971	No	NIA	IHD mortality	England & Wales UK	ICD-8: 410-414.	Temperature.	Inversely associated with temperature.
Bull 1975 [90]	1970-1971	Yes	NIA	MI mortality >60 yrs	England & Wales UK	ICD-8: 410.	Temperature.	Inversely associated with temperature.
Rogot 1974 [41]	1967	LIA	14,418	CHD mortality	Chicago Illinois USA	NIA	Temperature, wind, humidity & snowfall.	Inversely associated with temperature & positively associated with humidity, wind & snowfall.
Bull 1973 [91]	1953-1966, 1962-1966, 1970 vary by register & area	Yes	2,348	2,348 MI patients & MI mortality (NIA on n)	Belfast, England, Wales & London UK	Mortality register. ICD-8: 410.	Temperature & wind.	Inversely associated with temperature. No effect of wind.
West 1973 [92]	1968-1970	Yes	NIA	IHD mortality	England & Wales UK	ICD-8: 410-414.	Temperature.	Inversely associated with temperature.
Fyfe 1972 [61] & Dunnigan 1970 [60]	1962-1966	Yes	112,772	47,281 IHD patients & 65,491 IHD mortality	Scotland UK	Mortality register & hospital admissions from IHD. ICD-?: 420.1.	Temperature.	Inversely associated with temperature.

Continued

Anderson 1970 [42]	1958-1962	Yes	NIA	IHD mortality men	England & Wales UK, Ontario Canada	ICD-? (1955-1968): 420-422.	Temperature.	Inversely associated with temperature. Less effect of temperature in Ontario than in England & Wales.
Sotaniemi 1970 [93]	1965-1968	No	771	MI patients	Oulu Finland	Hospital admissions. Symptoms, ECG & lab results.	Temperature.	Inversely associated with temperature.
Rose 1966 [15]	NIA	No	NIA	MI patients & ASHD mortality	England &Wales UK	MI trial patients (Q in ECG) & mortality statistics (ICD-?: 420).	Temperature.	No effect of temperature on MI (ASHD inversely associated with temperature).
Fogel 1964 [274]	1952-1958	No	1,663	MI patients	Stamford Connecticut USA	Hospital admissions & death certificates. 1 of: chest pain, ECG changes, clinical/laboratory signs of tissue death &/or necropsy findings.	Temperature & atmospheric pressure.	No effect of temperature or atmospheric pressure.
Adesola 1960 [94]	1953-1956	No	298	MI & coronary thrombosis patients	Belfast Ireland	Hospital admissions. Excluded recurrent events.	Temperature & atmospheric pressure.	Inversely associated with temperature. No effect of atmospheric pressure.
Teng 1955 [95]	1946-1951	No	1,386	MI patients	Dallas USA	Hospital admissions. Chest pain, ECG findings, clinical/laboratory findings of tissue death compatible with MI or autopsy. Event validation.	Temperature.	Positively associated with sudden onset of both warm & cold temperature.

Table 3. Seasonal variation in cardiovascular disease risk factors. Description of studies published 1946–2007.

First author & publication year	Time-period	Population-based design?	N	Population	Area	Risk factor, outcome source, & number of measurements	Exposure (season) definition	Results
Youn 2007 [101]	Sep 2002-Mar 2005	No	85	Hypertensive patients <55 yrs	Seoul Korea	SBP &DBP. Measured every 3 months over 2 yrs.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in winter, low in spring, summer & autumn.
Barnett 2007 [102]	1979-1997	Yes	115,434	35-64 yrs	25 populations in 16 countries world wide	SBP. WHO MONICA[1] register.	Seasons not defined.	Peak in winter, low in summer. Populations closer to equator show larger SV in SBP.
Rudnicka 2007 [278]	2002-2004	Yes	9,377	44-45 yrs (born in England, Scotland, Wales during week 1 Mar 1958)	England, Scotland & Wales UK	CRP & fibrinogen. National Child Development Study. Measured once.	Monthly. Seasons not defined.	No SV.
Madsen 2006 [103]	May 2000-Sep 2001	Yes	18,770		Oslo Norway	SBP & DBP. HUBRO[2] study. Measured once.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in winter, low in summer.
Perez-Lloret 2006 [104]	Dec 1988-Nov 2001	No	1,689	Hypertensive screening patients	Buenos Aires Argentina	SBP & DBP. Buenos Aires residents only. Measured once.		Peak in winter (Jul), low in summer (Dec).

[1] Multinational monitoring of trends and determinants in cardiovascular disease

[2] Oslo Health Study

Continued

Silva 2006 [166]	1996-1997	Yes	348	18-94 yrs	3 Caboclo communities in Amazon Brazil	SBP, DBP, HR & weight. 44% measured both seasons.	Wet: Dec-Jun, Dry: Jul-Nov.	No SV (subgroup comparisons).
Ma 2006 [129]	NIA	No	593	20-70 yrs	Worcester Massachusetts USA	Weight. The SEASONS[1] study. Measured 5 times in one year.	W: Dec 21-Mar 20, Sp: Mar 21-Jun 20, Su: Jun 21-Sep 20, A: Sep 21- Dec 20.	Peak in winter.
Hadaegh 2006 [134]	1999-2001	LIA	6,894	20-64 yrs	Tehran Iran	Cholesterol, HDL cholesterol & triglycerides. TLGS[2] study. Measured once.	Seasons not defined.	Cholesterol peak in winter, low in summer (men). HDL cholesterol peak in winter, low in spring (men). Triglycerides peak in summer, low in winter & spring (women).
Chen 2006 [105]	2000-2003	LIA	7,938	>40yrs	Kinmen Taiwan	SBP, DBP, cholesterol, HDL cholesterol & triglycerides. Measured during winter (Jan-Feb) or summer (Jul-Aug) vacation. Measured once.	W: Jan-Feb, Su: Jul-Aug.	SBP, DBP, cholesterol, HDL cholesterol peak in winter, low in summer. Triglycerides peak in summer, low in winter.

[1] Seasonal variation of blood cholesterol
[2] Tehran Lipid and Glucose Study

Continued

Sung 2006 [106]	Jan 2002-Dec 2003	No	18,445	Healthy volunteers for medical check-up.	Seoul & Kyunggi Korea	SBP, DBP, cholesterol, HDL cholesterol, triglycerides & CRP. Measured once.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	SBP peak in winter & spring, low in summer. DBP peak in autumn, low in spring & summer. Cholesterol peak in spring, low in summer. HDL cholesterol peak in autumn, low in spring. Triglycerides peak in winter, low in spring. CRP peak in winter & spring, low in summer.
Prikryl 2005 [107]	1980-1989	No	60	20 healthy persons, 18 hypertensive patients & 22 AP patients	NIA	SBP, DBP & HR. Measured Jan, Jun & Dec in 1980, 1984 & 1989.	(Jan, Jun & Dec).	Peak in Jun.
Wystrychowski 2005 [108]	1995-1998	No	49	Hemodialysis patients	Poland	SBP, DBP & weight. Measured weekly min 1 year.	Seasons not defined.	SBP & DBP peak in winter, low in summer. No SV in weight.
Ulmer 2004 [109]	1985-1999	Yes	149,650		Vorarlberg Austria	SBP, DBP, cholesterol & triglycerides. VHM&PP[1] register. 1-14 measurements per person.	W: Dec-Feb, Sp: Mar-May, Su: Jun-Aug, A: Sep-Nov.	Peak in winter, low in summer.
Ockene 2004 [135]	Dec 1994-Feb 1997	No	476	Healthy volunteers	Worcester Massachusetts USA	Cholesterol, HDL cholesterol & triglycerides. The SEASONS[2] study. Measured every 3 months in one year.	Monthly. W: Nov 6-Feb 4, Sp: Feb 5- May 6, Su: May 7-Aug 5, A: Aug 6-Nov 5.	Cholesterol peak in Dec (men) & Jan (women). HDL cholesterol peak in winter (women only). Triglycerides peak in fall (women only).

[1] Western Austrian Vorarlberg Health Monitoring and Promotion Programme

[2] Seasonal variation in blood lipids

Continued

Argiles 2004 [110]	Jan 1991-Sep 1998	No	99	Dialysis patients	France	SBP & DBP. Measured at each dialysis.	Monthly.	Peak in Sep-Dec, low in Jun-Jul.
Crawford 2003 [151]	1995	No	54	Healthy elderly volunteers	Belfast Northern Ireland UK	Fibrinogen. Measured monthly in one year.	Monthly.	Peak in Jun.
Hermida 2003 [152]	Jan 2000-Jul 2002	No	1,006	Hypertensive patients	Santiago de Compostela Spain	Fibrinogen. Measured once.	Monthly.	Peak in Feb, low in Sep.
Cheung 2002 [111]	Feb 1995-Mar 1999	No	1,416	Dialysis patients	USA	SBP, DBP & weight. HEMO[1] trial. Min 2 measurements per year.	Monthly.	SBP peak in Dec, DBP & weight peak in Jan.
Frölich 2002 [167]	Oct 1984-May 1985 , Oct 1987-Jun 1988 vary by register	Partly	1,547	936 men 45-64 yrs in MONICA study, 696 men in MONICA follow-up study & 15 healthy volunteers 20-41 yrs in clinical study	Augsburg Germany (MONICA study).	CRP. Measured once (WHO MONICA[2] 1 & 2) or monthly in one year (clinical study).	Monthly.	Peak in May (MONICA 2 only). No SV in the other studies.
Assanelli 2002 [153]	1993-1998	LIA	822	18-72 yrs	Brescia Italy	Fibrinogen. Measured twice in a year.	Seasons not defined.	Peak in the cold season, low in the hot season.
Prasad 2001 [112]	NIA	No	163	Renal transplant recipients	Toronto Canada	SBP, DBP & weight. Measured > once Su & W.	W: Jan-Feb, Su: Jul-Aug.	SBP & DBP peak in winter. No SV in weight.

[1] The Hemodialysis Study

[2] Multinational monitoring of trends and determinants in cardiovascular disease

Continued

Blüher 2001[136]	NIA	No	147	Four groups: vegetarians, athletes & 2 "control" groups; 20-26 & 40-48 yrs.	NIA	Cholesterol & HDL cholesterol. Measured each season.	Seasons not defined.	Peak in winter, low in summer.
Shahar 2001 [115] & Shahar 1999 [116]	NIA	No	94	Male industrial workers	NIA	SBP, DBP, cholesterol, HDL cholesterol & triglycerides. Measured twice (Jan & Jul) in one year.	W: Jan, Su: Jul	SBP, DBP, cholesterol & HDL cholesterol peak in winter. Triglycerides peak in summer.
Nakajima 2000 [113]	1994, 1996	No	95	Hypertensive patients staying indoors only	Morioka Japan	SBP & DBP. Measured once in winter & once in summer.	W: Dec 15-Mar 15, Su: Jul 15-Sep 15.	Peak in winter, low in summer.
Sposito 2000 [114]	Jan 1994-Dec 1997	No	102	Hemodialysis patients	Montevideo Uruguay	SBP & DBP. Measured 3 times per week in each patient.	Monthly.	Peak in late autumn (May), low in late spring/early summer (Dec).
Garde 2000 [137]	Jun 1995-May 1996	No	21	Healthy women 26-44 yrs	Copenhagen Denmark	Cholesterol. Measured monthly in one year.	Monthly.	Peak in Jan-Mar, low in Jul-Sep.
Crawford 2000 [148]	NIA	No	24	≥75 yrs	NIA	CRP & fibrinogen. Measured monthly.	Monthly.	Peak in Feb.
Tozawa 1999 [117]	1994	No	144	Dialysis patients	Okinawa Japan	SBP, DBP & weight. Measured 3 times per week in one year.	Monthly.	SBP & DBP peak in Dec, SBP low in Aug, DBP low in Jun. Weight peak in Feb & Mar, low in Jul & Sep.

Continued

Nazir 1999 [138]	NIA	No	22	Healthy lab workers 25-60 yrs	Hamilton Canada	Cholesterol, HDL cholesterol & triglycerides. Measured monthly in one year.	Monthly. Su: Jun-Sep.	Cholesterol & HDL cholesterol low in summer compared to non-summer. No SV in triglycerides.
Mansfield 1999 [175]	Sep 1992-May 1993	No	35	Healthy men 17-35 yrs	Montreal Canada	Cholesterol, HDL cholesterol & triglycerides. Measured in spring & autumn.	Seasons not defined.	No SV.
de Castro 1998 [128]	Jan-Dec 1992	No	16	Hemodialysis patients 24-69 yrs	Sao Paulo Brazil	DBP & weight. Measured 6 times over a year.	W: Aug 17-29, Sp: Nov 16-28, Su: Feb 17-29, A: May 18-30.	DBP peak in autumn, low in summer. No SV in weight.
Sega 1998 [118]	1989-1990 (25-64 yrs), 1990-1993 (65-74 yrs)	Yes	2,051	25-74 yrs	Monza Italy	SBP, DBP & HR. PAMELA[1] study. Measured once + 2 home measurements.	W: Dec 21-Mar 20, Sp: Mar 21-Jun 20, Su: Jun 21-Sep 20, A: Sep 21- Dec 20.	SBP & DBP peak in winter, low in summer. No SV in HR.
Argiles 1998 [119]	Nov 1988-Oct 1992	No	53	Hemodialysis patients	Montpellier France	SBP & DBP. Measured 3 times per week.	W: Dec-Feb, Su: Jul & Aug.	Peak in winter, low in summer.
Brueren 1998 [176]	1991-1994	No	47	Borderline hypertensive patients	NIA	SBP & DBP. GP case-findings (hypertension). Measured twice.	W: Dec-Feb, Su: Jun-Aug.	No SV.

[1] Pressione Arteriose Monitorate E Loro Associazioni

Continued

Kristal-Boneh 1997 [100], Kristal-Boneh 1996 [120] & Kristal-Boneh 1995 [121]	NIA	No	94-101	Industrial workers men 28-63 yrs	NIA	SBP & DBP measured twice in one year.	Seasons not defined.	Peak in winter, low in summer.
Maes 1996 [139]	NIA	No	26	Healthy volunteers 23-69 yrs	Antwerp Belgium	Cholesterol, HDL cholesterol, triglycerides. Measured monthly in one year.	W: Dec 21-Mar 20, Sp: Mar 21-Jun 20, Su: Jun 21-Sep 20, A: Sep 21- Dec 20.	Cholesterol peak in autumn, low in spring. HDL cholesterol peak in spring & autumn, low in winter. Triglycerides peak in autumn & winter, low in spring.
Otto 1996 [169]	Feb-Aug 1994	No	14	Healthy volunteers 29-49 yrs	Munich Germany	Cholesterol, HDL cholesterol, triglycerides & fibrinogen. Measured Feb, May & Aug in one year.	Cold: Feb. Warm: May & Aug.	No SV.
Stout 1996 [177]	Jan-Jul 1992	No	100	50 persons 25-30 yrs, 50 persons ≥75 yrs	Belfast Northern Ireland UK	Fibrinogen.	Cold: Jan-Feb, Warm: Jun-Jul.	No SV.
Tsuchihashi 1995 [170]	NIA	No	10	Healthy women 21-27 yrs	Kasuga Japan	SBP, DBP & HR. Measured once each season.	W: Dec-Jan, Sp: Apr, Su: Jul-Aug, A: Oct.	No SV.
Cooney 1995 [140]	May 1992-Apr 1993	No	21	Healthy volunteers 31-63 yrs	Honolulu Hawaii USA	Cholesterol & triglycerides. Measured monthly.	Bi-monthly	Cholesterol peak in Mar-Apr, low in Sep-Oct. Triglycerides peak in Jan-Feb, low in Nov-Dec.

Continued

Kanabrocki 1995 [154]	Jan 1986-Dec 1992	No	NIA	Hospitalized military veterans	Hines Illinois USA	Fibrinogen. LIA on numbers of measurements.	Monthly.	Peak in May-Jun.
Maes 1995 [155]	Dec 1991-Dec 1992	No	26	Healthy volunteers	Antwerp Belgium	Fibrinogen. Measured monthly.	W: Dec 21-Mar 20, Sp: Mar 21-Jun 20, Su: Jun 21-Sep 20, A: Sep 21- Dec 20.	Peak in spring, low in winter.
Khaw 1995 [149] & Woodhouse 1994 [150]	Jan 1991-Feb 1992	No	96	65-74 yrs	Cambridge England UK	CRP & fibrinogen. Measured every two months in one year.	Bi-monthly. W: Jan-Feb, Su: Jun-Jul.	CRP peak in Jan-Feb, low in Nov-Dec. Fibrinogen peak in Jan-Feb, low in Jul-Aug.
Manttari 1993 [130]	Jan 1981-?	No	142	Hyperlipidemic men 40-55 yrs, trial control group	Helsinki Finland	Weight, cholesterol, HDL cholesterol. HHS[1] trial. Measured 4 times one year; Feb, May, Aug & Nov.	Monthly.	Weight peak in Feb, low in Aug. Cholesterol peak in Nov, low in Aug. HDL cholesterol low in Feb.
Kristal-Boneh 1993 [279]	1985-1987	No	5,240	Industrial workers 20-64 yrs	Israel	Cholesterol. Israeli CORDIS[2] study. Measured once.	Monthly. Seasons not defined.	Peak in late winter & spring (Mar-Apr), low in summer & autumn.
Stout 1991 [142]	1989-1990	No	68	≥75 yrs	Belfast Northern Ireland UK	SBP, DBP, cholesterol, HDL cholesterol, triglycerides, CRP & fibrinogen. Measured monthly in one year.	W: Nov- Apr, Su: May-Oct.	Cholesterol, HDL cholesterol, CRP & fibrinogen peak in winter, low in summer. No SV in SBP, DBP or triglycerides.
Giaconi 1988 [122]	NIA	No	22	Mild hypertensive patients 17-54 yrs	Pisa Italy	SBP & DBP. Measured twice in one year.	W: Nov-Mar, Su: Apr-Sep	Peak in winter, low in summer.

[1] Helsinki Heart Study

[2] Israeli cardiovascular occupational risk factors determination

Continued

Abdulla 1988 [123]	1971-1977, 1978-1986	No	224	174 normotensive & 50 hypertensive patients	Mosul Iraq	SBP & DBP. Patient records. Measured twice within 3 yrs.	W: Dec 21-Mar 21, Su: Jun 21-Sep 21.	SBP peak in winter, low in summer among normotensive persons. No SV in DBP.
Kräuchi 1988 [171]	NIA	No	26	Women 24-61 yrs, control group in study of seasonality	NIA	Weight. Measured each season.	Seasons not defined.	No SV in weight.
Gordon 1988 [131] & Gordon 1987 [132]	NIA	No	1,446	Hypercholesterolemic men 35-59 yrs.	USA	Weight, cholesterol, HDL cholesterol & triglycerides. The LRCCPPT[1] trial. The placebo group (diet only), no data from first 6 months used. ≥9 measurement over 6.5 yrs.	Monthly. Seasons not defined.	Weight peak in Feb-Mar, low in Aug-Sep. Cholesterol peak in Dec-Jan, low in Jun-Jul. SV larger in southern areas. HDL cholesterol peak in mid-winter. Triglycerides peak in midsummer and late autumn.
Näyhä 1985 [124]	June 1976-Jan 1980	No	801	Men ≥50 yrs	Oulu Finland	SBP & DBP. Health screening. Measured once.	Monthly.	Peak in Apr & Nov, low in Jul.
Sato 1984 [172]	Aug 1983-Feb 1984	No	11	7 students 20-24 yrs & 4 housewives 36-43 yrs, women only	Japan	Weight. Measured twice (Aug-Sep & Jan-Feb) in one year.	W: Jan 18-Feb 2, Su: Aug 19-Sep 16.	No SV in weight.
Loutan 1984 [133]	Aug 1980-Sep 1981	No	62	Nomadic farmers >18 yrs	Niger	Weight. Measured every 3 months.	Dry: Sep-Oct, Cold: Nov-Feb, Dry hot: Mar-May, Wet: Jun-Aug.	Peak in Feb, low in May.

[1] Lipid Research Clinics Coronary Primary Prevention Trial

Continued

Chiba 1983 [143]	1978-1981	No	535	Adult farmers	44 regions in Japan	Cholesterol, HDL cholesterol & triglycerides. Measured twice in one year.	Seasons not defined.	Cholesterol peak in winter, low in summer (men only). HDL cholesterol peak in summer, low in winter. No SV in triglycerides.
Sasaki 1983 [144]	Mar 1979-May 1980	No	55	Schizophrenia inpatients & healthy physicians, 27-54 yrs, men only.	Fukuoka Japan	Cholesterol, HDL cholesterol & triglycerides. Measured monthly in one year.	Monthly.	Cholesterol peak in Jan & Mar, low in Aug (schizophrenic patients only). HDL cholesterol peak in Nov-Dec (healthy men), & in Nov-Dec, Feb & Apr (schizophrenic patients), low in Jun & Sep (healthy men) & in Jun & Jul (schizophrenic patients). No SV in triglycerides.
Nikkari 1983 [168]	Nov 1979-Apr 1980	Yes	18	Men 30-59 yrs	Tampere Finland	Triglycerides. Part of the Mini-Finland study. Measured in Nov & Apr in one year.	Apr & Nov.	No SV.
Brennan 1982 [125]	NIA	No	17,282	35-64 yrs	England, Wales & Scotland UK	SBP & DBP. Hypertension treatment trial[1] screening. Measurements from base line and first follow-up excluded (treatment start). Measured 6 times in two yrs.	Monthly.	Peak in Jan-Mar, low in Jun-Aug, dependent on age and sex.
Demacker 1982 [178]	NIA	No	53	Healthy hospital workers 21-61 yrs	NIA	Cholesterol, HDL cholesterol & triglycerides. Measured monthly.	Monthly.	No SV.

[1] Medical Research Council treatment trial for mild hypertension

Continued

Letellier 1982 [179]	Jan 1977-Dec 1980	No	NIA	Hospital workers 25-59 yrs (women) & 20-39 yrs (men)	NIA	Cholesterol, triglycerides. LIA on numbers of measurements.	W: Jan-Mar & Dec-Feb, Sp: Apr-Jun & Mar-May, Su: Jul-Sep & Jun-Aug, A: Oct-Dec & Sep-Nov.	No SV.
Mjøs 1979 [173]	1977-1978	No	28	Healthy medical students 22-29 yrs	NIA	Cholesterol, HDL cholesterol & triglycerides. Measured 5 times.	Week 6, 14, 21, 36 & 48.	No SV.
Thulin 1978 [126]	Mar 1969-Apr 1970	Yes	1,703	≥8 yrs	Dalby Sweden	SBP. Ophthalmic survey. Measured once.	Seasons not defined.	Peak in winter-half of the year.
Van Gent 1978 [147]	Feb-Jul 1976	Yes	About 1,000	40 yrs	Leiden Netherlands	HDL cholesterol. Measured once.	Monthly	HDL cholesterol peak in Jun-Jul, low in Mar.
Thelle 1976 [127]	Feb-Dec 1974	Yes	6,595	20-49 yrs men only	Tromsø Norway	SBP, DBP, cholesterol, triglycerides. The Tromsø Study. Measured once.	Monthly. Seasons not defined.	SBP & DBP peak in early spring. SBP low in Jul, DBP low in Aug. Cholesterol peak in Feb, low in Apr & Oct. Triglycerides peak in Feb, low in Aug & Dec.
Warnick 1976 [145]	Jan 1974-Jan 1975	No	11	Healthy research employees	Seattle Washington USA	Cholesterol & triglycerides. Measured monthly.	Monthly.	Cholesterol peak in Dec, low in Oct. Triglycerides peak in Jan-Feb, low in May & Dec.
Bengtsson 1974 [146]	1968-1969	Yes	1,462	38, 46, 50, 54 & 60 yrs women only	Gothenburg Sweden	Cholesterol & triglycerides. Measured once.	Monthly (none in Jul-Aug).	Triglycerides peak in Oct-Mar, low in Apr-Jun (38 yrs). No SV in cholesterol.
Samuel 1970 [174]	NIA	No	12	Out-patients in stable condition	NIA	Cholesterol & triglycerides. Measured weekly in 1-3 yrs.	Monthly.	No SV.

Table 4. Survey number, year of screening, number of and attendance rate by gender, and birth year. The Tromsø Study 1974–2008.

Survey	Year of screening	Attended n (attendance rate %)[1]		Birth year
		Men	Women	
Tromsø 1	1974	6,595 (83)		1925-1954
Tromsø 2	1979–1980	8,477 (82)	8,143 (88)	1925–1959[2]
Tromsø 3	1986–1987	10,963 (78)	10,863 (85)	1925–1966[3]
Tromsø 4	1994–1995	12,865 (74)	14,293 (79)	1897–1969
Tromsø 4 visit 2		3,397 (74)	4,568 (77)	1910–1969
Tromsø 5	2001-2002	3,511 (76)	4,619 (81)	1912–1971
Tromsø 5 visit 2		2,447 (85)	3,492 (85)	1912–1971
Tromsø 6	2007–2008	6,054 (63)	6,930 (68)	1920–1977
Tromsø 6 visit 2		3,141 (92)	4,166 (92)	1920–1969

[1] Of eligible population
[2] Women 1930-1959
[3] Women 1930-1966

Table 5. Participants by number of examinations attended. The Tromsø Study 1974–2008.

Examinations	Participants (%)
Nine	1,038 (2.6 %)
Eight	1,872 (4.7 %)
Seven	1,042 (2.6 %)
Six	1,740 (4.3 %)
Five	2,546 (6.4 %)
Four	3,334 (8.3 %)
Three	5,049 (12.6 %)
Two	7,843 (19.6 %)
One	15,587 (38.9 %)
Total	40,051 (100.0%)

Figure 1. Flowchart of study samples, papers 1–3. The Tromsø Study.

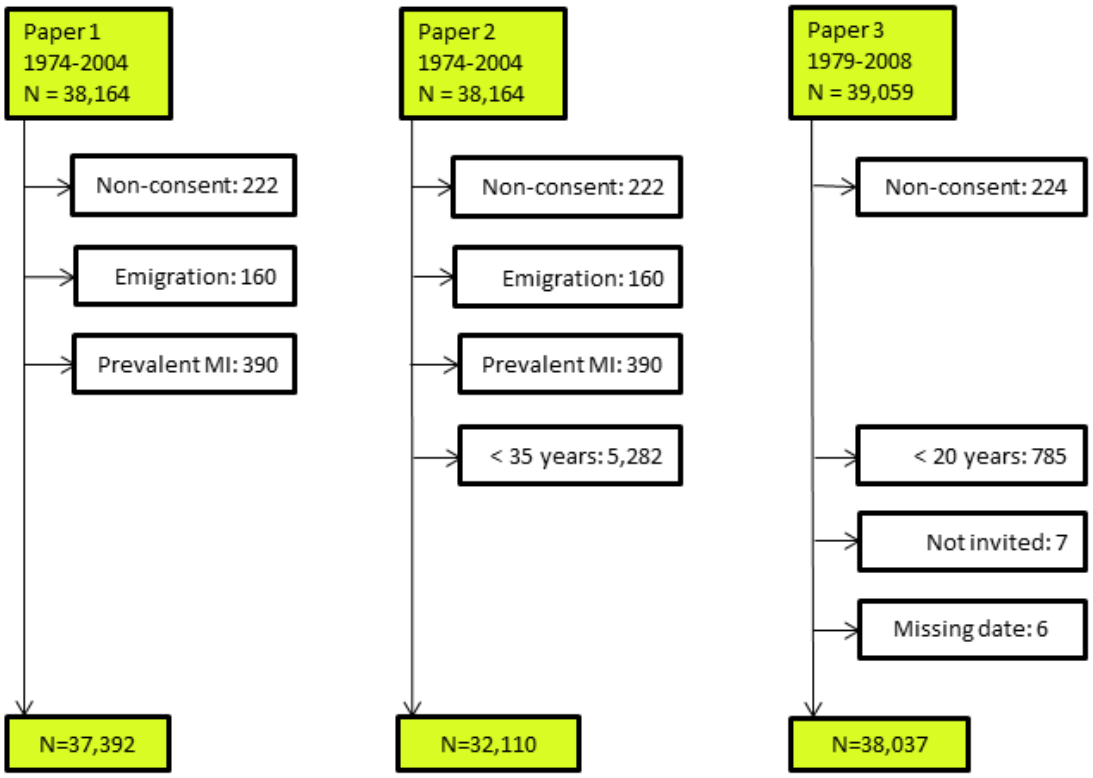
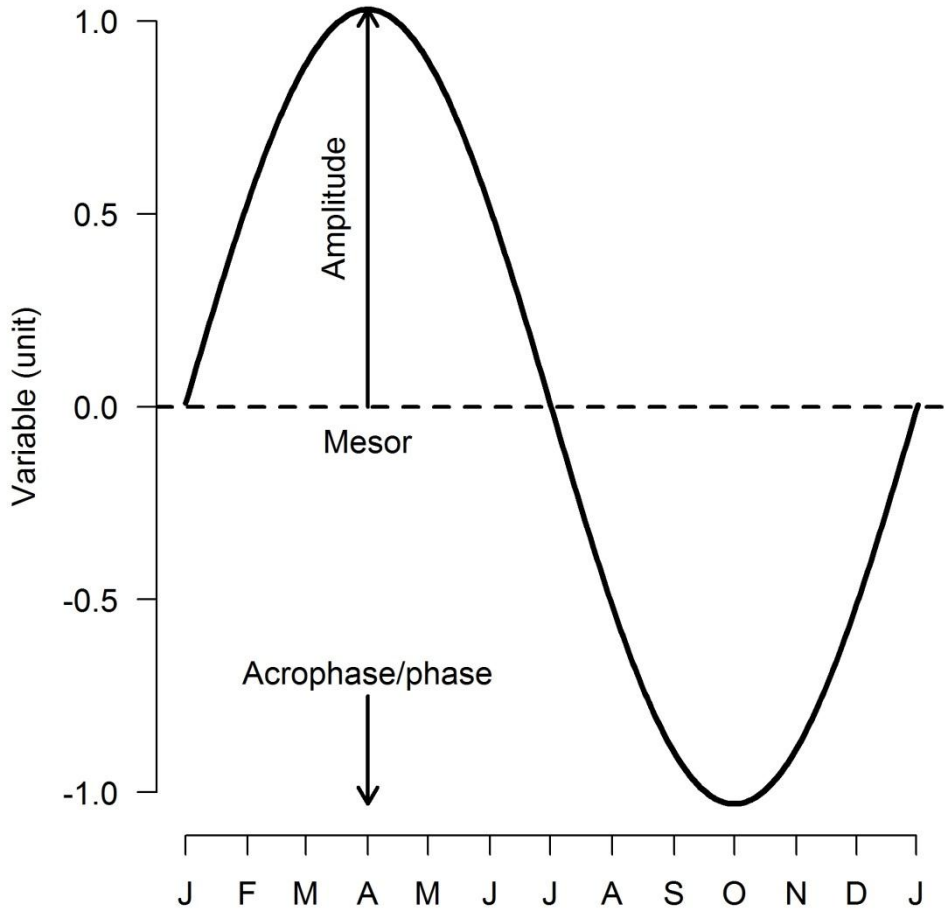


Figure 2. The Cosinor curve with parameters.



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EPILOGUE

To handle the impact of changes in season and weather, medical researchers outlined an exclusive conclusion already in the 1930ies: *"Migration out of Northern cold and storms, either temporarily or permanently, is strongly indicated for every patient of limited cardiac reserve, whose financial means permit such a course"* (Bean and Mills 1938, p. 713). Another approach is to face the challenges of the various seasons and changing weather by local knowledge and belief. The main conclusion of this thesis can be summed up in the Northern Norwegian expression "*Vi står han av",* which reflects a collective feeling of surviving the harsh environment.

Photo: Fredrik Ottosson

Appendix

The Tromsø Study 1974–2008

List of links to web pages for invitation letters, questionnaires and consent forms, all available from the Tromsø Study main web pages www.tromsoundersokelsen.no.

Tromsø 1, 1974

Invitation: http://uit.no/Content/271750/T1_Invitation.pdf

Questionnaire: http://uit.no/Content/271759/T1_Q1.pdf

Tromsø 2, 1979-80

Invitation: http://uit.no/Content/271751/T2_Invitation.pdf

Questionnaire: http://uit.no/Content/271760/T2_Q1.pdf

Tromsø 3, 1980-86

Invitation: http://uit.no/Content/271752/T3_Invitation.pdf

Questionnaire: http://uit.no/Content/271762/T3_Q1.pdf

Tromsø 4, 1994-95

Invitation: http://uit.no/Content/271754/T4_Invitation.pdf

Questionnaire: http://uit.no/Content/271764/T4_Q1.pdf

Consent form: http://uit.no/Content/70750/samtykkerklaeringer.pdf

Tromsø 4 visit 2, 1994-95

Invitation: http://uit.no/Content/271753/T4_Information_brochure_Phase2.pdf

Tromsø 5, 2001-02

Invitation: http://uit.no/Content/271757/T5_Invitation.pdf

Questionnaire: http://uit.no/Content/271768/T5_Q1_U70.pdf (< 70 yrs)

http://uit.no/Content/271767/T5_Q1_O70.pdf (≥ 70 yrs)

Consent form: http://uit.no/Content/70750/samtykkerklaeringer.pdf

Tromsø 5 visit 2, 2001-02

Invitation: http://uit.no/Content/271756/T5_Information_brochure_Phase2.pdf

Tromsø 6, 2007-08

Invitation: http://uit.no/Content/100339/Invitasjon_deltakelse_fase_1_t6.pdf

Consent form: http://uit.no/Content/111929/Samtykke%20Tr6.pdf

Tromsø 6 visit 2, 2007-08

Invitation: http://tromso6.prosjektweb.net/filarkiv/File/Invitasjon_deltakelse_fase_2.pdf

Paper 1

Paper 2

Paper 3

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