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ANNE KOUSA

The Regional Association of the Hardness in Well Waters and the Incidence of Acute Myocardial Infarction in Rural Finland

Doctoral dissertation

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ABSTRACT

Coronary heart disease (CHD), including acute myocardial infarction (AMI), is a serious public health problem in Finland and in other western countries. Geographical variation in the incidence and mortality of CHD between different countries and also within countries is well established. However, the major CHD risk factors like hypertension, smoking and serum cholesterol, gives only partial explanation to this geographical variation.

This thesis estimates the geographical variation of total water hardness, Mg, Ca, Al, Cu, F^-, Fe, Zn, Cr and NO_3^- in local ground water (well water) in relation to acute myocardial infarction (AMI) incidence among men and women aged 35-74 years in rural Finland. This work is a part of larger study “Geographical Variation of Non-Communicable Diseases and Environmental Risk Factors”.

Data of population at risk and AMI cases, from 14495 to 67755 men and 25450 women, were obtained from national registers. Pooled data from 1983, 1988 and 1993 and 1991-2003 were used in this analysis. Geochemical data were obtained from the geochemical database of Geological Survey of Finland. Bayesian spatial statistics and Geographical Information Systems (GIS) were then applied to estimate the regional patterns of AMI incidence and geochemical elements in ground water.

The spatial pattern of AMI was quite similar for men and women implying spatial risk factors seem to be same for both sexes. The results of this study showed that high water hardness and especially high Mg concentrations in local ground water was associated with lower AMI incidence whereas high Ca/Mg ratio was associated with higher incidence.

In summary, the findings of present study suggest that certain CHD risk factors tend to cluster in eastern Finland. This ecological study shows that geographical variation of AMI incidence is associated with elements from natural environment like Mg or water hardness in local ground water. A multi-country study following a single protocol with the objective to definitively clarify the association of water hardness with CHD risk is warranted. The results should then exploit for the possible detection of health based guideline values for drinking water of those elements.

National Library of Medicine Classification: WA 390, WA 686, WA 900, WG 300

Medical Subject Headings: Calcium; Finland/epidemiology; Geographic Information Systems; Hardness; Magnesium; Myocardial Infarction/epidemiology; Risk Factors; Rural Population; Small-Area Analysis; Water; Water Supply/analysis

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TIIVISTELMÄ

Sepelvaltimotauti, akuutti sydäninfarkti mukaan lukien, on merkittävä kansanterveydellinen ongelma Suomessa ja muissa läntistissä maissa. Sydäntautien ilmaantuvuuden ja kuolleisuuden maantieteellinen vaihtelu on selvästi osoitettu eri maiden välillä, mutta myös maiden sisällä. Klassiset riskitekijä, kuten verenpaine, tupakointi ja kolesteroli selittävät vain osan tästä maantieteellisestä vaihtelusta.

Tässä väitöskirjassa arvioitiin paikallisen pohjaveden kovuuden sekä Mg, Ca, Al, Cu, F^-, Fe, Zn, Cr and NO_3^- - pitoisuuksien alueellista yhteyttä akuutin sydäninfarktin (AMI) ilmaantuvuuteen Suomessa maaseutualueella asuvien 35-74 vuotiaiden joukossa. Tämä tutkimus on osa laajempaa ”Tarttumattomien tautien alueellinen vaihtelu ja ympäristön riskitekijät” – tutkimusta.

Tutkimuksen väestö- ja potilasaineisto, 14495 - 67755 miestä ja 25450 naista, on peräisin kuolinsyy-, hoitoilmoitus- ja sydäntautirekistereistä ja Tilastokeskuksesta. Tutkimuksessa on käytetty yhdistettyä aineistoa vuosilta 1983, 1988 ja 1993 sekä vuosilta 1991 - 2003. Geokemiallinen aineisto on Geologian tutkimuskeskuksen pohjavesitietokannasta. Arvioitaessa AMI ilmaantuvuuden alueellista esiintyvyyttä ja yhteyttä geokemiallisiin tekijöihin käytettiin Bayesilaisia malleja ja paikkatietotekniikkaa (GIS).

AMI ilmaantuvuus on maantieteellisesti samanlainen miehillä ja naisilla, mutta miesten sairastumisriski on huomattavasti suurempi kuin naisilla. Tämän perusteella voidaan olettaa, että ilmaantuvuuden taustalla on sama alueellinen riskitekijä. Tämän ekologisen tutkimuksen tulokset osoittavat, että paikallisen kaivoveden kovuus ja etenkin alueellisesti korkea Mg-pitoisuus ovat yhteydessä alhaisempaan AMI ilmaantuvuuteen. Korkea Ca/Mg oli puolestaan yhteydessä kohonneeseen AMI riskiin.

Sydäntautikuolleisuuden merkittävästä laskusta huolimatta viime vuosikymmenien aikana, jotkut sydäntaudin riskitekijät näyttävät edelleen kasaantuvan itäiseen Suomeen. Tämän ekologisen tutkimuksen tulokset osoittavat, että luonnon ympäristön tekijät, kuten veden kovuus ja kaivoveden Mg-pitoisuus ovat alueellisesti yhteydessä AMI-riskiin. Monikansallisia, yhtenäistä tutkimusprotokollaa noudattavia lisätutkimuksia tarvitaan vielä, jotta veden kovuuden yhteys sydäntautiriskiin voidaan lopullisesti vahvistaa. Tutkimuksen tulokset ovat tarvittaessa hyödynnettävissä juomaveden kovuuden terveysperusteisten suositusten määrittämiseen.

Yleinen suomalainen asiasanasto: alueelliset vaikutukset; epidemiologia; geokemia; kaivovesi; kalsium; kovuus; maaseutuväestö; magnesium; paikkatietojärjestelmät; pohjavesi; riskitekijät; Suomi; sydäninfarkti; vesianalyysi

To Jukka and Janne

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Kuopio, November 2008

Anne Kousa

ABBREVIATIONS

Al	aluminium
AMI	acute myocardial infarction
apo A1	apolipoprotein A1
apo B	apolipoprotein B
Ca	calcium
CAR	conditional auto-regressive
CHD	coronary heart disease
Cr	chromium
Cu	copper
CVD	cardiovascular disease
CVDR	Cardiovascular Disease Register
DBP	diastolic blood pressure
dH°	degree of hardness
F^-	fluoride
Fe	iron
FHDR	Finnish Hospital Discharge Register
GIS	geographical information systems
HDR	highest density regions
ICD	international classification of diseases
IHD	ischemic heart disease
Mg	magnesium
Ni	nickel
NO_3^-	nitrate
ppm	part per million
RDA	recommended daily allowance
SBP	systolic blood pressure
s-cholesterol	serum cholesterol
Se	Selenium
s-LDL	serum low density lipoprotein cholesterol
Zn	zinc

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original articles referred to in the text which are also appended in Appendix 1:

(I) Karvonen M, Moltchanova E, Viik-Kajander M, Moltchanov V, Rytkönen M, Kousa A, Tuomilehto J. Regional Inequality in the Risk of Acute Myocardial Infarction in Finland: A Case Study of 35- to 74-Year-Old Men. Heart Drug 2:51-60, 2002.

(II) Kousa A, Moltchanova E, Viik-Kajander M, Rytkönen M, Tuomilehto J, Tarvainen T, Karvonen M: Geochemistry of ground water and the incidence of acute myocardial infarction in Finland. Journal of Epidemiology and Community Health 58(2):136-139, 2004.

(III) Kousa A, Havulinna AS, Moltchanova E, Taskinen O, Nikkarinen M, Eriksson J, Karvonen M: Calcium to magnesium ratio in local ground water and incidence of acute myocardial infarction among males in rural Finland. Environmental Health Perspectives 114:730-734, 2006.

(IV) Kousa A, Havulinna AS, Moltchanova E, Taskinen O, Nikkarinen M, Salomaa V, Karvonen M. Magnesium in well water and the spatial variation of AMI incidence in rural Finland. Applied Geochemistry 23:632–640, 2008.

CONTENTS

1. INTRODUCTION

Medical geology is a multidisciplinary science dealing with the relationship between natural geological factors and health in humans and animals and with understanding the influence of ordinary environmental factors on the geographical distribution of such health problems (Selinus et al. 2004). Medical geology, as a sub-field of geology, is closely linked to environmental epidemiology, which comprises the study of those environmental factors that are outside the immediate control of the individual (Rothman 1993). The common characteristic feature of environmental epidemiology and also medical geology is that they focus on the environment where people live rather than on the factors of individual lifestyles or behaviour (Pekkanen and Pearce 2001) although these factors and the environment can on occasions be linked. Advances in the provision of accurate geo-referenced data over the past twenty years and recent advances in statistical methods have generated new opportunities for researches to improve on the traditional reporting of disease at national or regional scale by studying variations of disease risk at a local small-area scale (Walter 2000). Before computer-assisted mapping tools one of the limitations was the problem to handle large quantities of information. The development of Geographical Information Systems (GIS) that allows a user to input, store, retrieve, manipulate, analyze, and output spatial data has contributed to the emergence of disease mapping and medical geology (Aronoff 1989). The types of data likely to be used in medical geology fall into two broad categories: Earth science/geospatial databases and biomedical/health databases (Bunnell et al. 2005). Medical geology brings together in a coherent manner databases from these two general areas in specific applications. This approach leads to fresh perspectives enabling recognition of associations between environmental factors and human health outcomes that may have previously gone unnoticed (Bunnell et al. 2005).

Cardiovascular diseases (CVD) are the main cause of death in European Union (European cardiovascular disease statistics 2005). In Finland, CVDs were the leading causes of death in middle aged and elderly men and elderly women (Statistics Finland 2003). Mortality from coronary heart disease (CHD) has decreased over the past 30 years in Finland (Statistics Finland 2006, Salomaa et al. 2003, Pajunen et al. 2004). Despite the decreasing trend, CHD continues to be a major public health problem in Finland. Remarkable high mortality from heart disease in the eastern part of Finland has been recognized for over 60 years (Kannisto 1947). The major CHD risk factors such as serum total cholesterol, blood pressure and smoking, do not entirely explain the geographical variability of CHD risk in Finland (Jousilahti et al. 1998, Vartiainen et al. 2000). For example, in the nineteen eighties CHD risk was 40 % higher in eastern than in south-western part of Finland (Jousilahti et al.1998). Results of the recent study from 1991-2003 suggest that AMI risk was still an average 23 % greater in eastern part of the country compared to the risk in western part of the country (Havulinna et al. 2008). Geographical variation of CHD incidence depends on either genetic factors or environmental factors or both (Jousilahti et al. 1998).

The possible association of drinking water or local groundwater hardness with the risk of coronary heart disease (CHD) has been discussed since it was first suggested already 50 years ago. It has been reported that mortality from CHD has been lower in areas with hard groundwater or drinking water. Kobayashi (1957) associated first mortality from CVD with the geochemistry of river water in Japan. During the following decades, several epidemiological studies have shown the association of CHD mortality or morbidity with water hardness and/or Mg and Ca, which are the main components of water hardness (Sauvant and Pepin 2002, Monarca et al. 2006).

A good understanding of geographical variation of CHD is important to establish hypotheses on potential environmental risk factors of CHD. The most important single CVD is ischaemic heart disease, including acute myocardial infarction AMI. This work focuses on the association between geographical variation of acute myocardial infarction (AMI) incidence and the natural environment (local ground water) in rural Finland from the perspective of medical geology. In Finland, ground water accounts for around 60 % of the water distributed by waterworks around the country (Finnish Environment Institute). In sparsely populated areas most people use ground water from wells or small cooperative organization of water supplies. The urban areas with public water supplies with treated water for household consumption fall outside of the scope of this dissertation. The natural environment as a potential CHD risk factor is comparatively poorly studied in Finland. A special feature of this study is that 10 km x 10 km grid cells were used when defining the study areas instead of administrative areas. The following chapters will describe the background of medical geology, followed by the review of some pertinent epidemiological studies of spatial variation of AMI and geochemistry of ground (drinking) water, and description of the role of Mg and Ca in cardiac health.

In the future this work may lead to a better understanding of the variation in disease risk within Finland, and result in new research and more efficient preventive measures.

2. REVIEW OF THE LITERATURE

2.1 Medical Geology

2.1.1 Background

Interaction with materials from the natural environment and human health is mostly harmless, sometimes even beneficial, supplying us with essential nutrients. However, in some cases, the interaction with minerals and trace elements can cause certain health problems. These interactions are the realm of medical geology, a fast-growing field that besides geoscientists also involve medical, public health, veterinary, agricultural, environmental and biological scientists. Medical geology is the dicipline of the influence of geological materials and processes on human, animal and plant health, with both good and possibly hazardous results (Finkelman et al. 2001).

The association between geological materials, such as minerals and water, with human health has been known for centuries. Hippocrates (460-377 B.C), a Greek physician of the Classical period, noted in his treatise "On Airs, Waters, and Places" in Part 1 "*Whoever wishes to investigate medicine properly… We must also consider the qualities of the waters, for as they differ from one another in taste and weight, so also do they differ much in their qualities… These things one ought to consider most attentively, and concerning the waters which the inhabitants use, whether they be marshy and soft, or hard, and running from elevated and rocky situations, and then if saltish and unfit for cooking"* (Translated by Francis Adams 2007). More than 2000 years ago Chinese texts describe 46 different minerals that were used for medicinal purposes. Arsenic minerals, for example, were extensively featured in the materia medica (drugs) of ancient cultures (Finkelman et al. 2005).

The term geomedicine was first time introduced by Zeiss in 1931. At the time, geomedicine was considered as synonymous with geographical medicine, which was defined as a branch of medicine where geographical and cartographical methods are used to present medical research results (Davies 2005). In 1988, Meade has defined the term medical geography as follows: "Medical geography uses concepts and techniques of discipline of geography to investigate health-related topics" (Mead et al. 1988). In the 1970s, Låg (1980) redefined the term geomedicine as a science dealing with the influence of ordinary environmental factors on the geographical distribution of pathological and nutritional problems of human and animal health (Låg 1980).

Some subdivisions of geomedicine have also suggested. If the geomedical problems are related to water supply (i.e. drinking water and/or irrigation), the expression of hydrogeomedicine may be used. Some scientists have included plant diseases in geomedicine, but it falls outside the definition used by Låg. When the geomedical problems are connected to the plant disease, the expression of geophytomedicine may be used (Låg 1980). Piispanen (1990) has suggested the three subdivisions from the term geomedicine: geological geomedicine, geochemical geomedicine and geographical geomedicine. Investigations of health problems related to stone, stone dust, soil and minerals and mineral dust (e.g. asbestosis, silicosis, geophagy) are included into geological geomedicine. Geographical geomedicine contains research of area of residence, climate, humidity, topography and several other geographical factors related to human and animal health and in addition to geographical distribution of disease. The idea of geochemical medicine is to study the relationship between elements and their isotopes in air, nutrition, soil and drinking water with human and animal health (Piispanen 1990).

The discipline of environmental geochemistry in relation to health has also been stated by The Society for Environmental Geochemistry and Health SEGH: "The discipline of environmental geochemistry establishes and explains links between the chemical composition of rocks and minerals and the health of plants, animals and people. Bedrock geochemistry controls the composition of soil and hence that of water and vegetation. Pollution, arising from the extraction and use of mineral resources distorts natural geochemical systems. Geochemical surveys of soil, water and plants show how major and trace elements are distributed geographically. Associated epidemiological studies reveal the possibility of causal links between the geochemical environment and disease. Experimental research illuminates the nature or consequences of natural geochemical processes" (http://www.segh.net/journal.php).

The term "medical geology" is currently established instead of geomedicine etc. Medical geology is defined as a science dealing with the relationship between natural geological factors and health in humans and animals, and understanding the influence of ordinary environmental factors on the geographical distribution of such health problems (Selinus 2004). Medical geology is a broad and complicated subject that requires interdisciplinary contributions from different scientific fields if the problems are to be understood, mitigated and resolved. Researchers of medical geology have four principal responsibilities (Finkelman et al. 2005):

- To identify the environmental causes of known health problems and, in collaboration with biomedical/public health researches, search for solutions to prevent or minimize these problem
- To identify geochemical anomalies in soils, sediments, and water that may impact on health

- To reassure the public when there are unwarranted environmental health concerns deriving from geologic materials or processes
- To evaluate the beneficial health effects of geologic material and process

To summarise these definitions, medical geology (including geomedicine and environmental geochemistry), which focuses on the impacts of geologic materials and processes (i.e., the natural environment) on animal and human health, can be considered as complementary to environmental medicine (Finkelman et al. 2005) and environmental epidemiology. Epidemiological studies from the viewpoint of environmental geochemistry reveal potential links between the geochemical environment and disease (The Society of Environmental Geochemistry).

2.1.2 Medical Geology and Geographical Information Systems

The availability and quality of geo-referenced data relating to the health status of individuals has increased enormously during past few decades (Armstrong et al. 1999). The geographic information system (GIS) is a database and data analysis technique that is priviously used in geoscience and currently also has become familiar in public health and epidemiological studies. GIS can be used to detect abnormal disease patterns and for health policy planning and decision making (Clarke et al. 1996). The development of GIS that allows a user to readily input, store, retrieve, manipulate, analyze, and output spatial data (Aronoff 1989) has contributed to the emergence of disease mapping and medical geology. Using GIS it is possible to merge background variables related to the data of theme for research, such as socio-economic or environmental data on the population according to map coordinates. The use of high-resolution spatial data may risk the privacy of individuals (Rytkönen 2004). Although it is possible to source individual spatial data with geographical accuracy of 10 m (even 1 m in cities), data of individuals will usually be aggregated into larger grid cells for reasons of privacy protection.

Disease mapping is an important tool in medical geology. For certain groups of diseases (e.g., cancers and cardiovascular disease), the etiology is by and large unknown and challenging (Davies et al. 2005). When disease maps produced from these certain diseases, significant spatial variation has been reported that is not easily explained by genetic factors or social or dietary disparities (Davies et al. 2005). Environmental influences appear to be involved in the etiologies, and geologic role has been suggested (Davies et al. 2005, Rubenowitz et al. 1996). However, association is not necessarily evidence of causal relationship. Two conditions must be realized for disease mapping approach to be reliable

(Davies et al. 2005). First, it is essential to be able to show a clear pathway from source (e.g. soil or water) to exposure (e.g. dirt on hands) to assimilation (e.g. gastric absorption) to a target organ and physiological mechanism (e.g. enzyme system). The second, rarely satisfied, is that the hypothetical association must be predictive: If the association is positive in one area, then it should also be positive in a geologically similar area; if not, why not? This condition is well established in Finnish studies of F^- exposure and health outcomes. Naturally higher F^- in drinking water have consistently associated lower caries rates (Pärkö 1990). In contrast, the exposure to natural F^- in well water was associated with the increased risk of hip fracture among women (Kurttio et al. 1999). Another regional health problem in Finland is the association of arsenic in well water with elevated cancer risk (Kurttio et al. 1999, Backman et al. 2006).

Recent advances in the useability of GIS and statistical methodology together with the availability of high-resolution, geographically referenced health databases have generated new opportunities for researches to improve on the traditional reporting of disease at national or regional scale by studying variations of disease risk at a local small-area scale using for example 10 x 10 km grids (Walter 2000, Rytkönen et al. 2001, Elliot and Wartenberg 2004).

2.1.3 Characteristics of ecologic studies

Unlike cohort or case-control study, in ecologic analysis the individual exposure levels are not measured or if they are measured, they are not linked to the disease occurrence at the individual level (Rothman 1993). The usual unit for statistical analysis is a certain geographical area, such as an administrative area or a grid cell. It is possible to estimate at least the average exposure level and estimate overall disease rate, but we do not have measurements of both exposure level and disease status that would allow one to estimate directly the joint distribution of the two variables (Rothman 1993). Hence, ecologic studies could indicate associations between disease and potential environmental exposures at a population level.

Ecological studies can be pivotal dependent on the size of studied unit (Ranta et al. 1999). Traditional geographical health studies have been carried out within administrative areas, such as municipalities, provinces and hospital districts which may not be ideal for mapping health outcomes and that choice of boundaries may have a major influence on the results (Jarup 2004). Finland, for example, is sparsely and unevenly inhabited Nordic country. Half of the population lives in cities and 75 % of the population lives in the area that covers 5 % of the entire land area (Rusanen et al. 1993, Rusanen et al. 1995). Therefore administratively defined areas in Finland are very heterogeneous in size and number of population at risk and the interpretations of disease occurrence in the area are difficult. The associations observed at the aggregate level might not represent the association at individual level in large regions and thus can lead to the problem known as ecological fallacy. Analyses carried out using uniform boundaries such as grid cells may reduce these problems to some extent. On the other hand, if the regions are too small with few cases, the results may suggest distorted spatial patterns due the random variation (Ranta et al. 1999). Several smoothing methods, for example Bayesian smoothing technique, are used to avoid the problem of random variation (Ranta et al. 1999). However, administratively defined areas are still important from the perspective of national or regional health politics and administration (Rytkönen 2004).

An important limitation of the geographical analysis of chronic diseases is the time-lag between a potential exposure and the occurrence of the disease symptoms. People in all ages are very transient in modern world. People may have been exposed much earlier and they might have lived in a different location than where the first signs of the disease occur; thus an exposure experienced earlier in the life may become associated with an inaccurate geographical location (Jarup 2004, Löytönen 1998). This problem is predominant in studies of diseases occurring in adulthood or in old age like several non-communicable diseases.

In spite of the certain limitations of ecological studies they are useful for generating and testing hypotheses and such analysis should be used as a starting point for individual-level studies.

2.2 Epidemiological aspects of coronary heart disease

An estimated 17.5 million people around the world died from CVDs in 2005, representing 30% of all global deaths (WHO 2007). CVD is the leading cause of death in Europe. Each year CVD causes nearly half of all deaths in Europe (49 % and in the European Union 42 %). About half of all deaths from CVD in Europe were from CHD and nearly one third from stroke. CVD was the main cause of death in women in all European countries and also in men except in France and San Marino (Petersen et al. 2005). Finnish men were in the 13th and women in the 26th position in the death rates among all CVD death rates reported (American Heart Association 2005).

The mortality of CHD varies between countries and within countries but reasons for this variation are still poorly understood (Dobson et al. 1996, Tunstall-Pedoe et al. 1994). There are geographical differences between populations in nonfatal and also fatal coronary events (Tunstall-Pedoe et al. 1994). In Europe, there is a clear North-South high-to-low gradient (Thom 1989). At least a fourfold difference exists for men and an eightfold difference for women between highest and lowest CHD rates. CHD is also more common in northern and eastern countries than in the southern countries (Thom 1989, Tunstall-Pedoe et al. 1994). CHD is relatively prevailing in the western populations and quite rare in oriental populations (Tunstall-Pedoe et al. 1994, Sekikawa et al. 2001). The levels of major risk factors, such as serum cholesterol, blood pressure and smoking are, in general, higher in eastern part of Europe than in western parts. Among males major CHD risk factors explained less than 25 % of geographical variance of all CVD and IHD mortality between populations (WHO MONICA Project 1994). Classical CVD risk factors do not reflect well the geographical variation in mortality at population level (WHO MONICA Project 1994). Occurrence of CHD varies also within population. Mortality of CHD is higher in eastern and northern Finland compared to the areas in south and southwestern parts of the country (Kannisto 1947, Tunstall-Pedoe et al. 1994, Keys 1980).

2.2.1 Definitions of Acute Myocardial Infarction AMI

Acute myocardial infarction (AMI) is a serious end point of CHD. Myocardial infarction is most often caused by a sudden thrombosis (clot) that follows a rupture of an atherosclerotic plaque in the wall of the coronary artery. The clot prevents the supply of blood to the myocardium (heart muscle) in the affected area. If the circulation is not rapidly restored (e.g. by dissolving the clot), the myocardium goes into necrosis, defined as myocardial infarction. Heart muscle dies during myocardial infarction, and loss of the muscle is permanent. The most common symptoms of AMI are chest pain or pressure. Other symptoms of infarction are jaw pain, shortness of breath, nausea, vomiting, sweating, arm pain and upper back pain. Approximately 25 % of all infarctions are silent, without chest pain or new symptoms. Silent heart attacks are especially common among patients with diabetes mellitus (MedTerms™ online medical dictionary).

Besides major risk factors, such as smoking, hypertension and high cholesterol level, also type 2 diabetes, male gender, hereditary factors, old age and coagulation factors increase risk of myocardial infarction (MedTerms™ online medical dictionary).

2.2.2 Risk factors for AMI

CHD is a chronic disease with partly unknown etiology and a long period of latency (Tunstall-Pedoe 1994). The etiology of CHD is currently accepted to be multifactorial resulting from several biologic, behavioral, environmental and genetic risk factors (Tuomilehto 1989, MacCluer and Kammerer 1991, Neaton and Wentworth 1992, Vartiainen 1994, Jousilahti et al. 1995).

The major risk factors identified as hypertension, dyslipidemia, obesity, smoking, physical inactivity and diabetes are the main determinants of CHD (NIH Consens Statement 1992, Lakka et al. 1995, Haffner et al. 1998, Emberson et al. 2005).

The proportion of overweight and obese in Western populations has strongly increased in the past decades (Neter et al. 2003). The results of Swedish study (Falkstedt et al. 2006) suggest that being overweight in late adolescence was an important predictor of both CHD and stroke among men before age 55 years, independent of smoking, hypertension and early cardiovascular mortality in parents. Increased body weight is an independent risk factor for CVD. A Meta-analysis of 25 randomized, controlled trials, published between 1966 and 2002 with a total of 4874 participants, showed reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 1 mm Hg for each kilogram of weight loss. The authors stated that weight loss is important for the prevention and treatment of hypertension (Neter et al. 2003). According to the Dutch study abdominal obesity was associated with familial combined hyperlipidemia (van der Kallen et al. 2004). Hypertriglycerimia, reduced plasma high-density lipoprotein-cholesterols (HDL) and increased apolipoprotein B (apo B) concentrations, were common among overweight people. In the European population, the metabolic syndrome is associated with an approximate two-fold increased risk of cardiovascular mortality and morbidity (Dekker et al. 2005).

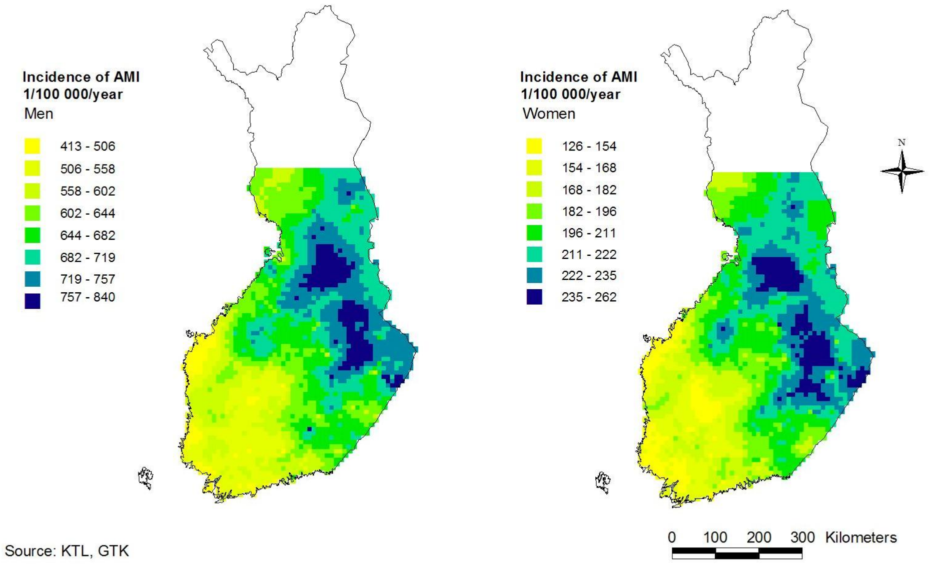
The evidence of relationship between smoking and vascular disease was first shown in the early 1950s based on the follow-up study of the male British doctor’s cohort (Doll and Hill 1954). The results have been later confirmed in numerous studies (Blanco-Cedres et al. 2002, Hozava et al. 2006). Several health effects of smoking depend on the exposure history, including the age when smoking began, the daily number of smoked cigarettes, and nicotine content and filter type (Liu et al. 1998).

Several studies have demonstrated that regular physical activity was associated with a reduced risk of CHD (Berlin and Colditz 1990, Hu et al. 2004). Studies from Finland and Japan showed that risk for hypertension decreased among men who had weekly physical activity compared to physically inactive men (Haapanen et al 1997, Hayashi et al. 1999).

2.2.3 Regional variation of CHD in Finland

The incidence of AMI in Finland has been among the highest in the world (Pajunen et al. 2004). The geographical variation in CHD within Finland has been established in several epidemiological studies (Näyhä 1989, Jousilahti et al. 1998, Viik-Kajander et al. 2003, Havulinna et al. 2008). Mortality and morbidity from CHD are higher in eastern Finland compared to western part of the country (Fig. 1) Despite declining trends (Pajunen et al.

2004) the regional differences of cardiovascular disease mortality and morbidity have remained stable over the years.



Source: KTL, GTK

Figure 1. Incidence of AMI in men and women in 1991-2003 in rural Finland.

CVD risk factor levels, such as serum cholesterol, blood pressure and smoking, have declined markedly in the past decades (Vartianen et al. 2000). According to Seven Countries follow-up study (Nissinen et al. 1993), among elderly Finnish men the total cholesterol level and both systolic and diastolic blood pressure were initially higher in the eastern part of the country, but later regional difference in cholesterol level disappeared and in blood pressure reversed. There were not significant differences in BMI between eastern and western areas.

Jousilahti et al. 1998 studied the areas which represented the highest and lowest CHD mortality areas and incidence in Finland. They found that the differences in levels of major risk factors explained about 40 % of the geographical variation between eastern and western part of Finland (Jousilahti et al. 1998).

Possible explanations of the geographical variation of the incidence CHD are genetic, socioeconomic and environmental factors. The Finnish population has been previously considered genetically relatively homogeneous (Nevanlinna 1972, Virtaranta-Knowles et al. 1991). However, a recent study suggests that there exists a sharp genetic border between male population in eastern and western parts of Finland (Lappalainen et al. 2006). Lower socioeconomic status is associated with higher mortality rates in Finland but the east-west difference is not influenced by socioeconomic status (Valkonen et al. 1992, Salomaa et al. 2000). One possible explanation for this difference is that certain environmental risk factors that are fairly stable may have a meaningful role in etiology and geographical variation of chronic illness such as CHD. There were indications that death from, or development of CHD was connected with quality of drinking water, particularly where low concentrations of certain elements such as Mg were observed (Karppanen and Neuvonen 1973, Punsar et al. 1975).

2.3 Geological and geochemical features of bedrock, soil and groundwater in Finland

2.3.1 Characteristics of the Finnish bedrock

The bedrock in Finland was mainly formed during Precambrian era (> 540 million years ago). Different processes during various geological periods have formed the bedrock that now consists of crystalline magmatic rocks and metamorphosed volcanic, sedimentary and magmatic rocks. The bedrock can be divided into several geological units (Fig. 2 and 4). The simplified map of Finnish bedrock is described in figure 2. The oldest part is the Archaean bedrock (>2500 million years) consisting of granitoids, gneisses, schists, and greenstones in northern and eastern Finland. The younger part (1930-1800 million years) of the Proterozoic bedrock in central and southern parts of the country is composed of granitoids, and schists, migmatites, amphibolites and metavolcanic rocks. Meso- to Paleoproterozoic (1650-1570 million years) rapakivi granites occur in south-east and south-west parts of the country (Vaasjoki et al. 2005).

The Archaean rocks include Ca, Mg, Na and K in practically insoluble form. Therefore, the hardness of the groundwaters in the area of Archaean rocks is low. The areas composed of younger Proterozoic rocks (Palaeoproterozoic schists and metavolcanics) release larger amounts of Ca, Mg, Na and K. However, all these crystalline rocks are much less soluble than young sedimentary rocks such as carbonates, shales, and graywackes which are almost totally lacking from Finland. A characteristic feature of the rapakivi granites is high F^- content. Other typical regional feature of the rapakivi area is high uranium and radon levels in south-eastern part of Finland (Koljonen 1992).

The average concentration of Mg in Earth's crust is 1.3 % (Koljonen 1992) and in Finnish soil (till) 0.5 % (Salminen et al. 2004). Because rocks poor in Mg dominate the Finnish bedrock this value is lower than the average in the crust (Koljonen 1992). In Finland bedrock and soil consist of a lesser degree Ca rich rocks and minerals. The average concentration of Ca in the Finnish soil (till) is 1.4 % (Salminen et al. 2004) that is markedly lower than the crustal average 3 % (Koljonen 1992). The low abundance reflects the predominance of granitoids in the Finnish bedrock.

These concentrations are however broadly similar to the median concentrations in European subsoils of 0.98 % and 1.13 % for Mg and Ca, respectively (Salminen et al. 2005).

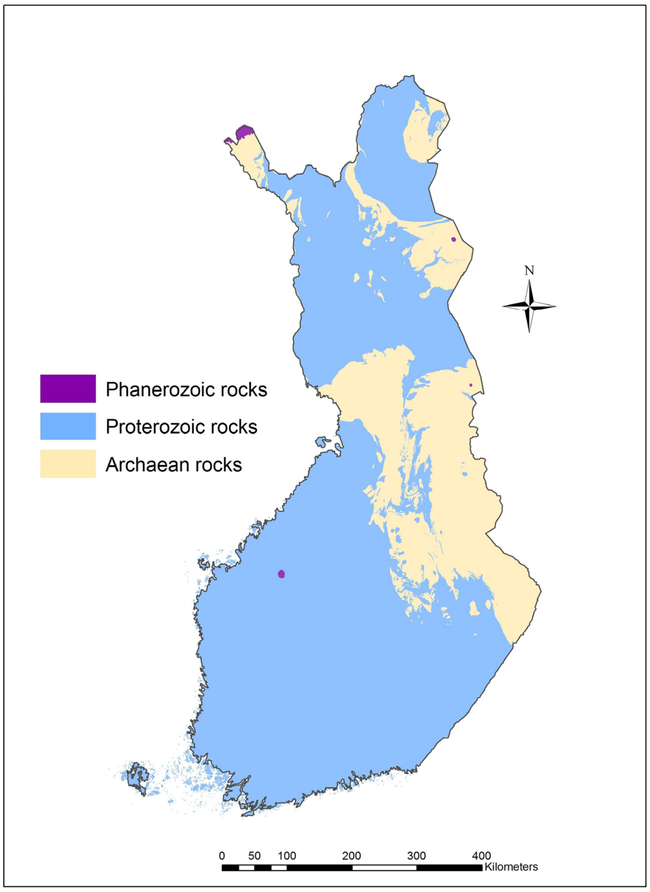


Figure 2. Main units of Finnish bedrock: Archaean > 2500 million years (soft water area), Proterozoic 2500- 540 million years (hard water area), Phanerozoic < 540 million years. (Modified after Korsman et al. 1997).

2.3.2 Characteristics of the Finnish minerogenic soil

The bedrock is covered by a glacial overburden of about seven meters average thickness (Koljonen and Tanskanen 1992). In Finland, the most widely distributed type of overburden is glacial till, while only a few percent of the total land area is covered by glaciofluvial sand and gravel deposits (Karro and Lahermo 1999). Marine silt and clay deposit occurs mainly in the southern and western coastal areas (Koljonen 1992). The composition of trace elements in glacial sediment is very heterogeneous (Salminen 1995). Till is predominantly of local origin and its geochemical composition reflects the surrounding bedrock. Abundances of nutrient are low, for example, in the areas of Archean gneisses in the northern and eastern part of the country (Koljonen 1992). Marine clays are the minerogenic sediments richest in nutrients, including Mg and Ca, owing both to the chemical composition of clay minerals and their ability to adsorb elements from soil solutions (Koljonen 1992).

Finland is a country with numerous lakes. The relatively cold climate, glacial history and prevalent Precambrian bedrock result in a relatively low rate of chemical weathering and, as a consequence the concentrations of inorganic substances in Finnish surface waters are generally low. On the other hand, the concentrations of dissolved organic substances, for example, humic acids, can be locally high, since 30 % of the area of the country is covered by bogs. The waters of Finnish lakes and rivers are mainly soft and often humic (The Finnish Environment Institute).

2.3.3 Characteristics of the Finnish groundwater

Groundwater is an integral part of the hydrologic cycle. The water in the atmosphere condenses to clouds and falls to the ground in the form of snow, rain or fog. Some part of the water evaporates directly back to the atmosphere. Another part of water used by plants may return to the atmosphere as vapor by transpiration. Some of the water flowing through the ground flows to the rivers, streams and lakes and finally back in to the oceans and becomes surface water. Whilst other water continues underground to form groundwater. Precipitation is the principal factor in the process of forming groundwater. Precipitation in Finland is approximately 500-740 mm/year. About half of the rain infiltrates deep into the ground and gravity pulls a small part of that water down through pores until it reaches the water table. The water below water table is generally called ground water. However, sometimes all water in the ground could be called groundwater. The water table closely follows the contour of the surface topography (Driscoll 1989, Korkka-Niemi and Salonen 1996).

The geological factors contributing to the chemical quality and abundance of groundwater are the texture, structure and lithologic composition of aquifer material (Lahermo et al. 1990). The most extensive groundwater reserves in Finland are in sand and gravel deposits in glaciofluvial eskers and ice-marginal formations (Salpausselkä) (Tarvainen et al. 2001). However, glacial till is the most common aquifer material for private household wells in sparsely populated rural areas in Finland. 85 % of studied private dug wells in rural areas were in till deposits (Tarvainen et al. 2001, Korkka-Niemi 2001). The groundwater quality is dependent on dissolved materials picked up by the water on its passage through soils and aquifers (Press and Siever 1978). Differences in the properties and chemical composition of groundwater vary between bedrock wells and dug wells. The abundance of substances dissolving in groundwater generally depends on residence time of water, so that mineral concentrations, water hardness and pH in drilled bedrock wells are usually higher compared in shallow aquifers. The higher pH values in drilled bedrock well water indicate more effective water-rock interaction and/or a longer residence time (Rönkä 1983, Lahermo et al. 1990, Korkka-Niemi 2001). The oxidation-reduction (Redox) conditions in the aquifer and surface water flowing to the well have also a major effect on well water quality. Elevated NO^{3-} concentarions in Finnish well water are solely of anthropogenic origin (Lahermo et al. 1990).

Tenhola and Tarvainen et al. (2008) divided Finland into four hydrogeological provinces based on the dominating topographical and Quaternary geological features and density of water courses: the southern Finland coastal belt, the western coastal belt, the central Finland lake district and the north-east Finland and Lapland (Fig. 3). The southern Finland coastal belt covers Salpausselkä esker formations, areas from south and south-west Finland and Ahvenanmaa islands. Clay deposits are characteristic in the low-lying areas and bedrock outcrops in higher areas. Glaciofluvial deposits are also characteristic for that province. In the western coastal belt, the coastal plain cutting by several rivers is dominated by clay and silt deposits and peat lands while till deposits are common in the eastern part of country. The central Finland lake district is dominated by several lakes, overburden of till and small peat lands, but to a lesser degree of clay deposits. Hills and mountains and also flat peat lands dominate north-eastern Finland and Lapland province (Tarvainen et al. 2001).

Approximately 20 % of the total Finnish population lives in rural areas and uses water for drinking, washing and irrigation from private single-household wells. This is pertaining to over one million people (Lahermo et al. 2002). Private wells generally yield water enough only for the use of a single household.

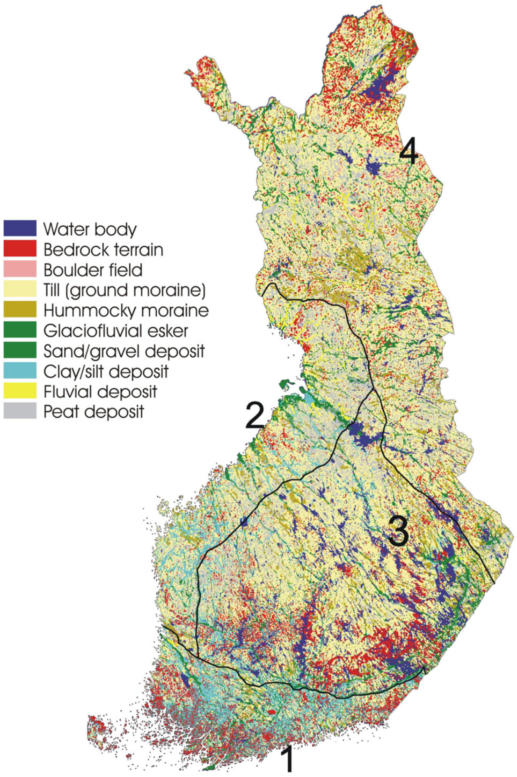


Figure 3. Hydrogeological provinces. (Tenhola and Tarvainen, 2008). 1. The southern Finland coastal belt. 2. The western coastal belt. 3. The central Finland lake district. 4. The north-east Finland and Lapland. Background: Quaternary deposits in Finland 1:1000 000 (Kujansuu and Niemelä, 1984).

2.3.4 Geochemistry of groundwater

Ca, Mg, Fe, Cu, Zn, Cr, and F^-, minerals included in present study, are nutritionally important in drinking water (WHO 2005). Al and NO_3^- are potentially (depends on dose) detrimental to health but owing to the limitations of the data a health-based guideline value for Al is not derived (WHO 2006).

Several properties or compounds of groundwater reflect the mineral composition of the bedrock or the soil derived from it (Lahermo et al. 1990). Countries with high CVD mortality in northern Europe, are generally covered by rocks of old geological age, especially

Precambrian, which are usually characterized by a low availability of essential trace elements and by soft water (Masironi 1987).

The regional distribution of F^- in groundwater is closely related to the geological environment. F^- anomalies in groundwater in the areas of rapakivi granites reflect the high bedrock F^- content (Lahermo and Backman 2000). The highest F^- concentrations in groundwater were found in south-eastern and south-western Finland, in the areas of rapakivi granite. Elevated Al concentrations were found in well water, especially in dug wells, in the rapakivi granite areas as well (Tarvianen et al. 2001).

Concentrations of Cu, Zn and Cr in Finnish groundwater were very low and did not exceed the national safe limit (2.0 mg/l, 3.0 mg/l, and 50 µg/l, respectively) (Anon 2000). Irregular distribution pattern of heavy metals in the well waters suggest that most of them originate from technical contamination (pipes and water fittings) in wells and in the water distributions and storage systems (Tarvainen et al. 2001).

Highly toxic Cr^{6+} occurs infrequently in nature and generally originates from industrial emissions (Cefalu and Hu 2004). Cr^{6+} in water will be reduced to essential Cr^{3+} by organic matter. In Finnish groundwater the average Cr concentration was 0.20 µg/l in the dug wells and < 0.20 µg/l in the drilled wells (Tarvainen et al. 2001). Areal distribution shows that dug wells in western coast contain slightly higher Cr contents than wells in central and eastern part of the country.

The highest Fe concentrations were encountered in the humus-rich shallow groundwater aquifers in the western coastal area (Tarvainen et al. 2001). Fe is not a harmful element for human but it causes aesthetic and technical problems in the practical water supply activities.

NO_3^- in groundwater is unevenly distributed in Finland. Elevated concentrations caused by anthropogenic point source contamination are occasionally encountered all over the country (Tarvainen et al. 2001).

Mg and Ca, the main conributors of water hardness, are associated with CVD in several studies (Kobayashi 1957, Schoroeder 1960, Bierenbaum et al. 1973, Masironi 1980, Pocock et al. 1980, Luoma et al. 1983, Piispanen 1993, Rubenowitz et al. 1996, 1999, and 2000, Rylander et al. 1991 and 2004, Maheswaran et al. 1999, Sauvant and Pepin 2000, Nerbrand et al 2003, Marquee et al. 2003, Ferrándiz et al. 2004). Therefore Mg and Ca were studied closely as follows.

2.3.5 Mg, Ca and water hardness in groundwater

Dug wells represent the most common well type in Finland. Formerly dug wells were lined with wood or stones, but nowadays concrete rings are mainly used. Private dug wells are generally 3-10 m deep and 80-120 cm in diameter. Wells drilled in bedrock are generally 40-80 m deep and 119 mm in diameter (Lahermo 1990). The average concentrations of Mg and Ca in ground water in different types of aquifer and wells are presented in Table 1.

Table 1.The median concentrations of Mg and Ca in ground water from dug wells and drilled wells according to aquifer material.

Well type Aquifer type	Dug well Sand and gravel* median	Dug well Till* median	Dug well Clay covered* median	Drilled well Bedrock* median	Dug well All aquifers** median
Mg mg/l	2.6	3.5	8.9	5.5	2.4
Ca mg/l	12.4	16.5	27.0	19.2	11.4

*Lahermo et al. 1990
**Tarvainen et al. 2001

The very low Ca and Mg concentrations in water were found throughout Fennoscandia compared with concentrations in Europe (De Wos et al. 2006). The median values of Ca and Mg in stream water (surface water) in Europe were 40 mg/l and 6.02 mg/l, respectively (de Vos et al. 2006). Data on the geochemistry of ground water is not available in European scale.

Initially water hardness was described as the capacity of water to get suds from soap or detergents which mean in practice the sum of concentrations of Ca, Mg, Fe, Al, Mn, Sr and Zn present in water. Hard water does not easily form lather with soap. The ions, except Ca and Mg, are playing a minor role in water hardness and nowadays it is generally accepted that definition of water hardness as a sum of the Ca and Mg abundances. Water hardness is often expressed in different terms in Europe: French, German and English degrees among others. In present study term German degrees were used to describe water hardness. Water hardness can be classified among others as follows: soft (0-8 ºdH), slightly hard (8-15 ºdH), hard (15-30 ºdH) and very hard (> 30 ºdH).

In Finland, the groundwater is slightly acidic and very soft (1-4 ºdH) or soft (4-8 ºdH). Regionally, the hardest groundwater is reported in the southern Finland coastal belt. The clay and silt sediments and occurrence of carbonate rocks in that area increases the water hardness. The softest waters are encountered in north-east Finland and Lapland (Tarvainen et al. 2001). The lowest water hardness was found in glaciofluvial sand/gravel deposits. The highest electrolyte content, pH and water hardness were suggested to be present in clay covered aquifers and caused by the long residence time of such waters (Pönkkä 1981).

2.4 Magnesium and calcium

2.4.1 Mg and Ca intake from food and water

Mg in food represents the major portion of Mg intake in the general population. Beverages contributed on average 13 % to the daily Mg intake among men and women aged between 35 to 74 years in Finland (Paturi et al. 2008). The average dietary Mg intake is about 300 mg/day. Foods rich in Mg are green vegetables, unpolished cereal grains, nuts, soy beans and chocolate. Mg is lost from processed food and refined sugar (National Research Council 1989). Fish, meat, and several fruits, with the exception of bananas, are relatively poor sources of Mg.

Recent dietary surveys have revealed that a major portion of the French population have dietary Mg intake lower than recommended (330 mg/day for women and 420 mg/day for men) (Galan et al. 1997). Increase in consumption of refined foods containing only energy without minerals have contributed to decreasing Mg intake in several western countries (Galan et al. 1997, Altura and Altura 1991-92, Ford and Mokdad 2003). In the USA, the intake of Mg has progressively declined from 475-500 mg/day in 1900-1908 to 175-248 mg/day in 1987-1992. Similar phenomen in dietary Mg intake has come up also in studies in Europe. Declined values in men were 189-262 mg/day and in women 143-283 mg/day (Altura and Altura 2006).

The recommended dietary allowance RDA for Mg is 350 mg/day in adult men and 280 mg/day in adult women in Finland (Table 2, National Nutrition Council, 1998). Mean daily intake of Mg among Finnish men and women was at recommended level being an average 405 mg and 309 mg, respectively. According to dietary assessment of Findiet 2002 the intake of Mg and Ca from food and drinks has no significant regional difference in Finland (Reinivuo et al. 2003). Consumption of bottled water is insignificant and thus intake of Mg from bottlled water is modest in Finland. It has been estimated that per capita consumption of bottled water in Finland in 2004 was only 14 l/year whereas for example in Italy it was 184 l/per capita/year (http://www.worldwater.org/data20062007/Table13.pdf). However, consumption of bottled water has lately slightly increased being 18 l/per capita in 2007 (http://www.panimoliitto.fi/panimoliitto/en/statistics).

Drinking water, especially hard water with higher concentrations of Mg, may be a major source of dietary Mg (Elin 1987, Rylander and Arnaud, 2004). Waterborne Mg has been suggested to account for about 10 % of the total daily Mg intake (Marx and Neutra 1997). Water is a variable source of Mg since the daily intake can vary widely due to considerable geographical variation of Mg content in drinking water (Institute of Medicine, 1997). Mg intake from water is usually not estimated except in controlled diet studies. This omission may lead to underestimating total intake and its variability (Institute of Medicine, 1997).

The intake of Ca is 1,187 mg/day among men in Finland (Männistö et al. 2002). It is higher than in most countries (Varo 1974). Although Ca intake on average is quite high due to high consumption of dairy products, there still are groups of people (e.g. lactose intolerants, vegetarians) whose Ca intake is below the RDA (Hirvonen et al. 2004). The recommended dietary allowances for Ca in Finland for adult men and women are 800 mg/day (table 2). About 70 % of dietary Ca is derived from dairy products, about 16 % from green vegetables and dried fruits. Drinking water, including mineral water, provides 6-7 % (Guéguen and Pointillart 2000). Grains are quite poor in Ca. However, grain products may be consumed in large quantities and thus they can account for an essential proportion of dietary Ca (Institute of Medicine 1997).

Table 2. The recommended dietary allowance (RDA)* of Mg, Ca, Fe and Zn expressed as the average daily intake per person. National Nutrition Council, Committee report 1998:7.

	Age years	Mg (mg)	Ca (mg)	Fe (mg)	Zn (mg)
Male	31-75	350	800	10	9
Female	31-75	280	800	10-18	7

*The recommended dietary allowance (RDA) is the daily dietary intake level that, based on current information, is sufficient to meet the nutrient requirements and maintain a good nutritional status of nearly all healthy individuals (97.5%) and includes the variation in the population's needs.

2.4.2 Bioavailability of Mg and Ca

Bioavailability refers to the difference between the amounts of a substance, such as a drug, herb, or chemical, to which a person is exposed and the actual dose of the substance the body receives. Bioavailability accounts for the difference between exposure and dose. If a substance is ingested, for example, its bioavailability is determined by the amount that is absorbed by the intestinal tract. (http://www.enotes.com/public-health-encyclopedia).

About 30-50 % of the ingested Mg is absorbed through the small intestine. The amount of Mg absorbed in the small intestine is inversely proportional to the amount of Mg in the diet (Elin 1987) and the fractional absorption ranges from 65 % absorption at a low intake and to

11 % absorption at a high intake (Fine et al. 1993). The presence of certain nutrients also interact with Mg in the gut (Hardwick et al. 1991). High intake of certain constituents of vegetables such as fiber, phytate, oxalate, and phosphate reduce Mg absorption (Hardwick et al. 1991, Knudsen et al. 1996, Lopez et al. 2004, Bohn et al. 2004). For example, Mg absorption from a meal served with oxalate-rich spinach was about 35 % lower than from a meal served with a kale low with oxalate content (Bohn et al. 2004).

Mg from Mg-rich mineral waters can be comparatively easily absorbed and its absorption rate is similar to that from Mg supplements (Karagülle et al. 2006). The mean bioavailability from water containing 3.9 mmol/l Mg was 59 % among men (Verhas et al. 2002). Among young healthy women, Mg absorption was 46 % and further enhanced (52 %) when the Mg-rich mineral water was consumed with a light meal (Sabatier et al. 2002). A possible explanation for the increased effect could be the slower gastrointestinal transit time due to the meal, presence of digestion products from the meal, or both (Sabatier et al. 2002). Mg concentrations were significantly lower in serum and urine among postmenopausal women when dietary Mg was lower (Klevay and Milne 2002).

Percentage Ca absorption varies inversely with dietary Ca intake (Dawson-Hughes et al. 1993). The mean Ca fractional absorption varying between 23 % and 37 %. Phytates found in cereals, oxalates in spinach and tannins in tea, can form insoluble complexes with Ca and reduce its absorbtion (Guéguen and Pointillart 2000). Fractional absorption gradually declines with age (Heaney et al. 1989).

2.4.3 Physiological role of Mg and Ca in the human body

Mg is the fourth most abundant cation after Na, K and Ca in the body and the second most abundant cation after K in intracellular fluid (Elin 1987). The adult human body contains approximately 20-24 g of Mg. About half of Mg is present in bone and the other half is intracellular in soft tissues and muscle (Elin 1994). Only less than 1 % of Mg is present in blood plasma and red cells. Mg plays an important role as a cofactor for more than 300 cellular enzymes, many of which involve energy metabolism. Transport of other ions such as K and Ca across the plasma membrane may also require the presence of Mg (Rude 1998). Mg is essential in regulating the cellular distribution of Na and K through involvement in the Na^+/K^+ -ATPase pump (Gums 2004). Mg deficiency causes dysfunction in this pump and leads to reduced intracellular ATP and increased intracellular sodium (Gums 2004). Mg has been termed “nature’s physiologic calcium channel blocker” (Iseri and French 1984, Hasebe and Kikuchi 2007).

Mg is present in three different forms in most biological systems: ionized, complexed to anions, and bound to protein (Elin 1994). Because protein-bound and complexed Mg is unavailable for biochemical processes, only ionized Mg has biologic activity (Elin 1994).

Ca is quantitatively the most abundant mineral in the human body. A body of the newborn contains an average 25-30 g Ca. An adult body contains about 1000-1500 g Ca (Heaney 2006) accounting for 1 to 2 percent of the adult human body weight (Institute of Medicine 1997). An average 99% of total body Ca is stored in the bones and teeth. The remaining 1% is found in blood, muscle, and the fluid between cells.

2.4.4 Mg and Ca and coronary heart disease

Anorexia, nauseas, vomiting, lethargy and weakness are typical early symptoms of Mg deficiency (Saris et al. 2000). There is emerging evidence that habitually low intakes of Mg are associated with etiologic factors in various metabolic diseases (Institute of Medicine, 1997). Mg deficiency is associated with several cardiovascular disorders, including hypertension, dyslipidemia, arrhythmia, and atherosclerosis (Rude 1998, Gums 2004). Serious dietary Mg deficiency is rare in wealthy societies, but dietary imbalances such as high Ca intake, can reduce Mg absorption. Under conditions of physical or emotional stress, stress hormones together with Mg deficiency can increase the risk of CVD damage (Seelig 1994). Persons, who are predisposed to Mg deficiency (for example using diuretics) and living in soft groundwater areas like residents in eastern Finland, may be at risk of CVD especially if their Mg intake from other sources is low (Klevay and Milne 2002). The common causes of Mg deficiency are presented in Table 3.

Table 3. The common causes of Mg deficiency.

- Reduced dietary intake
- Poor gastrointestinal absorption
- Increased losses from gastrointestinal tract
    - Diarrhoea
    - Vomiting
    - Laxative use
- Increased renal losses
    - Congenital or acquired tubular defects
    - Diabetes mellitus
    - Alcoholism
    - Drug induced (diuretics, angiotensin converting enzymes inhibitor)
- Others
  Increased requirements (growth, pregnancy)
  Excessive sweating

(Fawcett et al. 1999)

Potential links between Mg, Ca and cardiovascular disorders are discussed in more detail in the following sections:

Hypertension. Epidemiological evidence suggests that Mg play an important role in regulating blood pressure (Rude 1998). Mg was first recommended as therapy of malignant hypertension in 1925. Several studies have shown that Mg was associated with lowering effect of high blood pressure (Joffres et al. 1987) while some studies have not (Sacks et al. 1998). Other dietary factors may produce conflicting results.

Total intake of Mg from food and supplements was inversely associated with both systolic and diastolic blood pressure among men in the Honolulu Heart study (Joffres et al. 1987). Both systolic and diastolic blood pressure decreased significantly also among middle-aged female and male subjects after consuming 2 and 4 weeks Mg-rich water (Rylander and Arnaud, 2004). Mg deficiency is also associated with obesity and diabetes that may lead to hypertension (Resnick 1992) and several drugs, particularly diuretics, cause Mg loss into the urine (Saris et al. 2000).

Dyslipidemia. Some studies have linked Mg deficiency to metabolic syndrome (Song et al. 2005, Ford et al. 2007). Data from Mexico showed the strong relationship between low serum Mg level and dyslipidemia (Guerrero-Romero and Rodríguez-Morán 2002). Sufficient intake of Mg or a diet rich in Mg may be important for maintaining good cardiometabolic health (Ford et al. 2007). Statin drugs lower LDL-C levels more sharply than do Mg supplements, but Mg more reliably acts to improve all aspects of dyslipidemia including raising HDL-C and lowering triglycerides, and has the same pleiotropic effects as statins without their adverse effect (Rosanoff and Seelig 2004).

Arrhythmia. Low dietary Mg intake was associated with arrhythmia (Klevay and Milne 2002, Amsterdam 1999). Patients with coronary heart failure have a very high propensity for ventricular arrhythmias, which are a common cause of death in this group. Mg deficiencies may develop because of increased urinary excretion, which is a consequence of diuretic therapy among others. Intravenous Mg has been demonstrated to be beneficial in reducing the risk of arrhythmias immediately after myocardial infarction (Rasmussen et al. 1986, Saris et al. 2000). Dietary magnesium restriction to about 33% (100 mg/2000 kcal) of RDA was inadequate for healthy postmenopausal women inducing arrhytmias, impaired glucose homeostasis and decrease in serum cholesterol concentrations (Nielsen et al. 2007).

Atherosclerosis. A recent study suggested that hypomagnesemia in children and adolescent patients with type 1 diabetes were associated with early atherosclerosis (Atabek et al. 2006).

The results of the double-blind, placebo control study showed an increase in HDL and apolipoprotein A1 (apo A1) levels and decrease in LDL, apo B and triglyceride levels after Mg treatment (Rasmussen et al. 1989). The data from experimental animal studies showed that dietary Mg intake plays an important modulatory role in controlling lipid metabolism in the arterial wall (Altura et al. 1990, Saris et al. 2000). Another experimental study with mice showed a beneficial antiatherogenic effect of Mg supplementation in drinking water (Ravn et al. 2001).

The role of Ca in the etiology of CHD is controversial. More attention has been paid to the possibility that Ca is the protective "water factor" against CHD because Ca is primary constituent contributing water hardness. However, there are suggestions that Ca may increase rather than decrease the death rate from CHD (Varo 1974, Rasouli and Kiasari 2006). The association between death rates from CHD and estimated dietary Ca/Mg ratios has also been reported (Jeppesen 1987, Artaud-Wild at al. 1993, Rubenowitz et al. 1996). Authors reported that dietary Ca was associated with CHD mortality in the analysis in men aged 55 to 64 years in 40 countries (Artaud-Wild et al. 1993). Odds ratio for death from AMI was the lowest in the highest quotient of Mg/Ca ratio in Swedish case controls study (Rubenowitz et al. 1996). Imbalance in Ca/Mg ratio with high intracellular Ca has associated with hypertension (Altura et al. 1993).

In contrast, Jacqmain et al. (2003) found that a high Ca intake was associated with a plasma lipoprotein-lipid profile predicting a lower risk of CHD risk compared with a low Ca intake in men and women. Low Ca dietary intake has been linked to hypertension in several epidemiological studies (for review, see Barger-Lux and Heaney 1994). In Dutch study dietary Ca was inversely associated with systolic blood pressure in women and with diastolic blood pressure in men (van Leer et al. 1995). Birkett (1998) found in meta-analysis that differences in Ca intake of 1000 mg/day were associated with 0.5-4 mmHg changes in blood pressure. Results of another meta-analysis of 67 randomized trials showed that Ca supplementations with the total daily intake over 1000 mg/day decreased systolic blood pressure an average 1.4 mmHg and diastolic blood pressure 0.8 mmHg. The authors also concluded that the effect of supplemental Ca in the diet is at least as great as non-dietary supplementation (Griffith et al. 1999).

2.5 Elements in drinking water and CHD

The connection between geochemistry of water and human health was first described in the late 1950s. The association of cardiovascular mortality with the geochemistry of drinking water was first described in Japan by Jun Kobayashi in 1957 and later in the United States by Schroeder in 1960. After those pioneering researches, several epidemiological studies from all over the world have reported an association between mortality of CVD and geochemistry of groundwater (for review, see Monarca 2006). Masironi (1987) presented the hypothesis that a deficiency or excess in the content or availability of trace elements in rocks and soils, or in water flowing through them, may be a cause of certain chronic ailments, including cardiovascular diseases.

2.5.1 Mg and Ca concentrations and water hardness in relation to CVD – studies from different countries

Finland

Some studies of CVD in relation to geochemistry of groundwater (drinking water) have been conducted in Finland. Kaipio et al. (2004) found that in rural Finland CHD mortality declined with increasing Mg concentration in drinking water, but slightly increase with Ca content. Piispanen (1993) found that in the western part of Finland with the low CVD mortality the hardness and Mg concentration in well water was markedly higher than in the eastern part of the country. The association was not found for Ca (Piispanen 1993).

Results of the cross-section study (Luoma et al. 1973) including 300 men from 4 Finnish rural districts suggested decreasing trend in CVD with increasing Mg concentration in well water. 10 years later Luoma et al. (1983) conducted a case control study among men aged 30-64 years in 1974-1975 in Finland. They found that low Mg intake from drinking water increased the risk of AMI (Luoma et al. 1983).

Punsar and Karvonen (1979) studied mortality from cardiovascular disease and water quality in two rural areas in western and eastern Finland. All men in two rural regions born between 1900 and 1919 were included in the analysis. The study areas were divided into sub-areas, 10 in the west and 33 in the east. Association of Mg with the development of CHD and with the occurrence of sudden deaths in these two cohorts in 1959-1974 was studied. They suggest that CHD may be associated with low concentrations of Mg and Cr in the drinking water, but definite relationship between water quality and sudden death was not found (Punsar and Karvonen 1979).

Although Finnish ground water is in general soft, all studies including those with a different study design conducted in Finland have suggested the inverse association of soft ground (drinking) water, low in Mg, with an increased risk of CHD.

Sweden

In Sweden Rylander et al. (1991) studied association of drinking water hardness and cardiovascular mortality in 27 municipalities. The hardness of water samples ranged between 0.80 to 20.7 °dH. An inverse relationship between water hardness and mortality from IHD among men was observed. The relationship of the same kind, although less pronounced, was also observed among women. The study also suggested that mortality, particularly among men, could be associated with the amount of Mg in drinking water (Rylander et al. 1991).

Nerbrand et al. (1992) studied regional east-west gradient in CVD mortality in 76 communities in Sweden during 1969-1983. Water hardness and Ca concentrations of the drinking water were inversely related to ischaemic heart disease as well as stroke mortality (Nerbrand et al. 1992).

Rubenowitz et al. (1996) studied the association of mortality of acute myocardial infarction and the concentration of Mg in drinking water using mortality registers and a case-control design. The geographical variation of the water Mg concentrations occurs within a relatively small study area in southern part of Sweden. Cases were men, aged 50-69 years, who had died of acute myocardial infarction during the period 1982-1989 *(n* = 854). The controls were men of the same age in the same area, 17 municipalities, who had died from cancer during the same time period (n = 989). The odds ratio was 0.65 (0.50-0.84) for the group with Mg concentrations of 9.8 mg/l or more when age and Ca were adjusted. The authors suggest that Mg in drinking water is an important protective factor for death from acute myocardial infarction among males.

In other case-control study Rubenowitz et al. (1999) estimated concentration of Mg and Ca in drinking water and death from AMI among women in 16 municipalities in southern Sweden including 378 cases and 1368 controls. They found that ORs adjusted for age and Ca for the quartile with highest Mg concentrations, over 9.9 mg/l, was 0.70 (95% CI 0.50-0.99). The corresponding adjusted OR for the quartile with highest Ca concentration (over 70 mg/l) was 0.66 (95% CI 0.47-0.94) (Rubenowitz et al. 1999).

Rubenowitz et al. (2000) conducted a study of the importance of Mg in drinking water in relation to morbidity and mortality from AMI in 18 Swedish municipalities among men and women aged 50 to 74 years. They found reduced risk, OR 0.64 (95% CI 0.42-0.97), of death for AMI for the highest quartile of drinking water Mg concentration in men and OR 0.51 (95% CI 0.21-1.22) in women.

Nerbrand et al. (2003) evaluated the relation between Mg and Ca in drinking water and diet and major cardiovascular risk among 207 individuals aged 40-59 years living in two municipalities characterised by differences in cardiovascular mortality and water hardness in

Sweden. No correlation was found with Mg content in household water to any CHD risk factors. The Mg concentration in household water is generally low in Sweden due to geological circumstances. The results of the study instead showed a significant correlation between Ca content in water and major CHD risk factors. Negative correlations were found between Ca in water and s-cholesterol and s-LDL but, on the other hand, Ca content in water was associated with increased systolic blood pressure. Correlations were not found Ca or Mg in diet.

A Swedish population-based case-control study based on data from the Stockholm Heart Epidemiology Program was conducted in 1992-1994 (Rosenlund et al. 2005). 497 cases and 677 controls aged 45-70 were matched on age, sex, and hospital catchment area. After adjustement for matching variables and certain CHD risk factors, OR for AMI was 1.09 (95% CI 0.81-1.46) associated with tap water hardness above the median (> 4.4 ºdH) and OR 0.88 (95% CI 0.67-1.15) associated with Mg intake above the median (> 1.9 mg/d) via water. Authors conclude that low mean concentration and limited ranges in exposure, 4-6 mg/l Mg, could influence to the non-significant results.

Conflicting results of water hardness and CHD have been presented in Swedish studies. It has been argued that it is not possible to estimate for the influence of drinking water Mg on the risk factors of CHD with exposure level below 10 mg/l of Mg (Rylander 2005).

Europe - Great Britain, France and Spain

Geographical variation of CVD mortality was studied in the British Regional Heart Study during 1969-1973 among men and women in 253 urban areas in England, Wales and Scotland (Pocock et al 1980). After adjustment for the effects of climatic and socioeconomic variables, CVD mortality was 10-15% higher in areas with very soft water, around 0.25 mmol/l (corresponding 1.4. ºdH) than that in areas with medium-hard water, around 1.7 mmol/l (9.52 ºdH) , while any further increase in hardness beyond 1.7 mmol/l was not associated with additionally lower cardiovascular mortality (Pocock et al.1980).

Maheswaran et al. (1999) carried out a small area analysis and studied the relationship between Mg and Ca and mortality of AMI in north-west England among men and women aged 45 years or more. The study area was divided into 305 water supply zones, with average population of 23 000 per water zone. The apparent protective effect of Mg and Ca for IHD was found, but after incorporating the geographical trends (north-south and east-west gradient in heart disease) to the model the significant effect disappeared (Maheswaran et al. 1999).

Men aged 40-59 years from 24 British towns were followed for incident of CHD and stroke, and CHD mortality for 25 years. Participants also answered a questionnaire about their water consumption. Water hardness of tap water varied from 0.27 (1.5 ºdH) to 5.28 mmol/l (30 ºdH) between towns. The authors suggested that long-term British cohort study did not provide evidence for a protective role of water hardness, Ca or Mg against CVD. They argued that any protective effect is likely to be very small and major CVD risk factors have more public health importance. Based on study results they also argued that adding Ca or Mg to desalinated water was not justified (Morris et al. 2008).

Masironi et al. (1980) found an inverse association between drinking water hardness and the incidence of AMI in 15 European towns and cities. The population covered by the study was all persons aged 20-64 years, giving a total of 3,570,150 subjects

Sauvant and Pepin (2000) studied relationship between CVD mortality and water hardness using ecologic analysis and pooled mortality data in 1988-1992 in France. The study area was divided into 52 cantons, which were selected as geographical units for the statistical analysis and a significant inverse relationship was observed between the drinking water hardness and CVD mortality.

Marque et al. (2003) conducted an ecologic study including 14311 deaths from CVD and cerebrovascular diseases in 69 areas among population over 65 years old and drinking water quality in south-west France. The results of the study suggest a potential protective effect of Ca on CVD mortality. The authors also concluded that a U-shape effect of Mg was more pronounced for cerebrovascular mortality (Marque et al. 2003).

Ferrándiz et al. (2004) studied the relationship between CVD mortality and drinking water hardness in Spain using Rapid Inquiry Facility (RIF). They found statistical evidence of a relationship between mortality from CVD and hardness of drinking water in the data on 538 municipalities from 1991 to 1998. The authors summarized that the relationship was stronger for cerebrovascular disease than for CHD, was more pronounced in women than in men, and was more apparent with Mg than with Ca (Ferrándiz et al. 2004).

USA and Canada

In USA, Schroeder (1960) presented a study comprising the 163 largest municipalities. He found a significant negative correlation between average hardness of water supplies and death rates from cardiovascular diseases among both sexes aged 46 to 64 years (Schroeder 1960). Greathouse and Osborne (1980) studied a randomly selected sample of 4200 adults from 35 geographical areas to represent the civilian non-institutionalized population of the contiguous United States. They found that water hardness and Ca had negative association with the mortality rates for most groups of cardiovascular disease.

Bierenbaum et al. (1973) compared serum parameters in two similar populations in the hard water communities of Omaha (Nebraska) and London (England), and the soft water communities of Winston-Salem (North Carolina) and Glasgow (Scotland) among males and females aged 30-50 years. Both the serum cholesterol and the serum triglycerides were found to be elevated. However, lower CVD mortality rates were reported in hard water than soft water areas and were inversely related to serum Mg and Ca concentrations (Bierenbaum et al. 1973).

In Canada, Anderson et al. (1975) carried out the study where they compared heart-muscle concentrations of elements over a 4-month period in eight Ontario cities. They found that in 54 cases of accidental death in cities with water hardness of 60 parts per million (ppm) or less, the mean myocardial Mg concentration was 7 % lower than among 29 cases of accidental death in cities with water hardness of 300 ppm or more. There were no significant differences between the cities with soft and hard water in the mean myocardial concentrations of Ca, Zn, Cu, Cr, Pb or Cd.

Japan

Jun Kobayashi, a Japanese agricultural chemist, has been engaged in the study of the nature of irrigation water from the agricultural standpoint since 1942 and studied chemical nature of hundreds of rivers in Japan (Kobayashi 1957). The death rate from apoplexy (stroke) among middle-aged was extraordinary high compared to that in other countries. A marked difference in death rates was also noted between different parts of Japan. Kobayashi suggested for the first time the scientific basis for a role of water by demonstrating significant relationship between the ratio of sulfate to carbonate (soft) in river water and the death rate from apoplexy in Japan.

Miyake and Iki (2003) carried out an ecologic analysis of relationship between water hardness and cerebrovascular mortality in 44 municipalities in Japan. According to the results of their study, water hardness was not protective against cerebrovascular mortality. Also another ecologic study provided no evidence of protective role of water hardness against mortality of CHD in Japan (Miyake and Iki 2004). However, authors thought that lower concentrations and narrower range in water hardness might have masked the true association (Miyake and Iki 2003).

Monarca et al. (2006) concluded in their extensive review that although causality has not proven by several epidemiological studies, increased Mg intake from household water may be beneficial especially in populations with an insufficient dietary intake. The authors argued also that it would be a relatively easy way to maintain the sufficient intake of Mg via household water. Some authors have also stressed that population should be aware that using softening devices they also reduce essential minerals from drinking water (Nerbrand et al. 1992, Monarca et al. 2006). However, Morris et al. (2008) suggest that addition of Ca and Mg to desalinated water is not warranted.

2.5.2 Trace elements and CHD

Fluoride is a naturally occurring element that is essential to human health in small doses but is harmful in excess (Plant et al. 1996). Luoma et al. (1983) reported that F^- intake was inversely associated with risk of MI in men. They found that F^- concentrations of around 1 ppm in household water were not harmful; on the contrary they may even be beneficial. Finnish studies also suggest that the geographical pattern of CHD in Finland is consistent with the concentration of F^- in well water (Kousa and Nikkarinen 1997, Kaipio et al. 2004). The authors suggest that one mechanism could be that F^- prevents dental infections, which in turn reduces mortality from CHD (Kaipio et al. 2004). However, the widely used toothpaste with F^- may influence to results.

It is suggested that calcium in large amounts may reduce absorption of fluoride. The consumption of milk with a fluoride supplement and the consumption of calcium rich food with a fluoride supplement decreased fluoride bioavailability (Ekstrand and Ehrnebo, 1979). Maguire et al. (2005) found only small difference in bioavailability of fluoride between drinking waters in which fluoride was present naturally or added artificially. Only small difference was also found in bioavailability of fluoride in hard and soft waters (calcium is a major determinant of water hardness), compared with large variations within- and between-subject in fluoride absorption (Maguire et al. 2005).

Eastern Finland is a low Se area (Tarvainen et al. 2001) with high Cu content in drinking water (Punsar et al. 1975). The data of Finnish study indicate synergistic effect of high serum Cu, low serum Se content and LDL cholesterol in atherogenesis (Salonen et al. 1991). The adjusted risk of death from cardiovascular disease was on average about four times higher for subjects in the highest serum Cu quintile (greater than 1.43 mg/l) compared with those with normal concentrations (Kok et al. 1988). The Cu, Zn, and Cr concentrations were significantly lower in the atherosclerotic plaques of abdominal aorta of 40 patients who died with IHD and AMI than in the control group (Vlad et al. 1994). Simonoff (1984) reported that plasma Cr levels in patients with coronary artery disease are much lower than those in normal subjects.

Epidemiological studies have also provided evidence that the high body Fe stores increases the risk of coronary heart disease (Salonen et al. 1992, Tuomainen et al. 1998). Men with high body Fe stores have two to threefold risk to get a first AMI (Tuomainen et al. 1998). Fe status was associated with several CHD risk factors. Serum ferritin had significant correlations with blood glucose, serum triglycerides, systolic blood pressure, HDL cholesterol concentration (inversely), and serum apolipoprotein B concentration (Salonen et al.1992). Contradictory, Magnusson et al. (1994) did not find raised serum ferritin and therefore Fe stores to be a risk factor of CHD in small prospective Iceland study (Magnusson et al. 1994).

Although evidence is accumulating that Zn deficiency compromises antioxidant defences, there is no clearly defined role for low Zn status in CHD (Strain, 1994). An excess of Zn can inhibit Cu absorption, which in turn may compromise antioxidant defences (Johnson et al. 1992). No significant risk of death from cardiovascular disease was found for subjects with low or high levels of serum Zn. However, the authors suggested that high serum Zn status had a protective association with CVD risk (Kok et al. 1988). The Finnish nested case-control study showed that high serum Cu and low serum Zn were associated with increased CVD mortality among men aged 15-69 years. The Cu/Zn ratio value was 10-11 % higher among cases than among corresponding controls (Reunanen et al. 1996).

2.6 Summary of the literature review

In summary, epidemiological studies suggest that the mortality of CHD varies between countries and also within countries but reasons for this variation are ambiguous. Possible explanations for geographical variation of the mortality CHD are genetic, socioeconomic and environmental factors. Genetic and environmental factors probably explain partly this variation but there is evidence that socioeconomic factors are not associated with geographical variation in Finland. The epidemiological evidence supports the hypothesis that high water hardness, especially increased Mg concentration in drinking water, is associated with decreased risk of CHD mortality and possible morbidity. There is limited evidence of the relationship between Ca and decreased risk of CHD mortality.

Water is a variable source of Mg since the daily intake can vary widely due to considerable geographical variation of Mg content in drinking water (Institute of Medicine, 1997). The geological circumstances have a great impact in well water quality in rural areas. The Mg concentration in water especially in Sweden and Finland is lower than in most other countries due to geological circumstances (Nerbrand et al. 2003, Lahermo et al. 1991). Mg and Ca are commonly absorbed inversely with dietary intake. High intake of certain constituents of vegetables seems to reduce absorption of Mg and Ca. However, the arguments about the sufficient intake of minerals via household water were conflicting (Monarca et al. 2006, Morris et al. 2008).

The greater part of the available studies from different countries, mostly of ecological design, supports the hypothesis that soft water poor in Mg increases risk of heart diseases. The criteria for causal association were not realized in all studies. However, Monarca (2006) pointed out that it should recognize that effective public health actions may be taken even with incomplete knowledge or certainty about causality. On the other hand, risk of ecological fallacy in group-level associations and aggregations are not necessarily consistent with those measured at the individual level. Thus possible ecological bias may introduce a major source of uncertainty in ecological inference.

The ecological analysis of water factors and CHD mortality has performed in several countries based mainly areas defined administrative boundaries such as municipalities, cities, provinces etc. It is becoming clear in the field of public health that data on health information aggregated within administrative regions is inadequate to address many public health concerns (Amstrong et al. 1999). There is need for a finer geographical scale of study.

The majority of existing studies have investigated the relationship between the minerals in drinking water and mortality in CHD in Finland. As a consequence there is also need for further investigation of the incidence of heart diseases in relation to the geographical and geological environment in Finland which is the focus of this work.

3. AIMS OF THE STUDY

The general aim of the this study was to evaluate the geographical variation of acute myocardial infarction AMI incidence in relation to possible natural environmental risk factors of CHD, for example geology.

This general aim was achieved by undertaking the following research:

1. to investigate the geographical variation of the AMI incidence among Finnish men (Study I).

2. to investigate the water hardness, Al, Cu, F^-, Fe, Zn and NO_3^- concentrations in groundwater and their associations with AMI incidence among Finnish men (Study II).

3. to study relationship between Ca, Mg and Cr concentrations in local groundwater and AMI incidence among men in rural Finland (Study III).

4. to study the geographical variation in AMI incidence among men and women in rural Finland in relation to the concentrations of Mg, Ca, Al, Cu, F^-, Fe, Zn and NO_3^- in local groundwater (Study IV).

4. SUBJECTS AND METHODS

4.1 Study subjects, population at risk and study design

The geographical distribution of the incidence of AMI (Study I) and its association with the concentrations of geochemical elements in local groundwater were studied in three cross section years 1983, 1988 and 1993 among men (Studies II, III) and across a 13 years time period in 1993-2001 among men and women (Study IV). High quality geo-referenced data on health in Finland has been available since 1983. The province of Lapland in northern Finland and Ahvenanmaa and Turku islands in south-western part of the country were excluded from the analysis due to very low population density, low number of AMI cases and sparcity of geochemical samples.

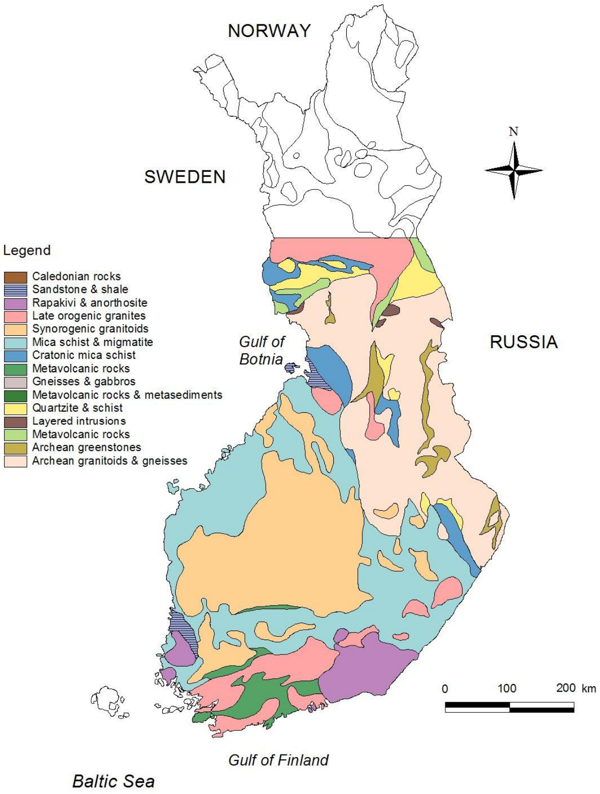


Figure 4. Study area. Background: Bedrock of Finland (modified after Korsman et al. 1997).

In total, 18,946 men aged 35-74 years diagnosed with the first AMI event were included in studies I and II, 14,495 men in study III and a total of 93,215 (67,761 men and 25,454 women) AMI cases in study IV from rural Finland.

In Finland, every resident has a unique personal identification number (ID). ID was used to perform a computerized records linkage of the register data for deaths due to coronary heart disease and hospitalization due to AMI. Each case was localized at the time of diagnosis according to the map coordinates (X,Y) of the place of residence with the geographical accuracy of 1 m. Map coordinates based on Finnish National Coordinate System (KKJ). KKJ-coordinates can be presented in geographical (latitude, longitude) or in rectangular grid-coordinates (northing, easting) (Ollikainen and Ollikainen 2004).

Data were obtained from the Population Register Centre. The data on population at risk and AMI cases from rural areas only were included in the studies III and IV. People in the rural areas mostly use well water, whereas the urban dwellers use public water supplies. The data on population at risk were obtained from the Population Register Centre. These data are updated at a national level and continuously by Statistics Finland.

The study design used in this research was based on an ecological analysis with geo-referenced data aggregated into grid cells with a resolution of 10 km x 10 km to ensure the privacy of individuals.

4.2 Assessment of AMI

The first, both fatal and non-fatal, AMI events from years 1983, 1988 and 1993 using International Classification of Diseases codes ICD 8 and ICD-9 codes 410-414 (Studies I, II, III) were included in the analysis. Data on non-fatal definite acute myocardial infarctions were obtained from the Finnish Hospital Discharge Register (FHDR) and data on AMI mortality from the statistics on causes of death produced by Statistics Finland.

Data on first AMI (Study IV) were obtained from the Finnish Cardiovascular Disease Register (CVDR) (Laatikainen et al. 2004). CVDR is a countrywide database on the occurrence of coronary heart disease (CHD) and cerebrovascular diseases in 1991-2003. In Finland, the 10th version of the ICD has been in use since January 1, 1996. Non-fatal AMI events were identified from the (FHDR) using the ICD codes I21-I22 (ICD-10) / 410 (ICD-9). Fatal AMI events were identified from the statistics on causes of death produced by Statistics using the ICD codes I20-I25, I46, R96, R98 / 410-414, 798 (not 7980A). Also the contributing cause of death was considered if it was an acute infarction (I21-I22 (ICD-10) / 410 (ICD-9). cases with no hospital discharges with ICD codes I21-I22 (ICD-10) / 410 (ICD-9) during the preceding seven years were classified as a first event of AMI.

4.3 Geochemical data

The Geological Survey of Finland (GTK) carried out the nationwide hydrogeochemical mapping programme (1 sample/50 km^2) in 1978-1982 when about 5900 water samples were collected from natural springs, dug wells and wells drilled into bedrock (Lahermo et al. 1990). Since 1982 a large number of additional groundwater samples, mainly from dug wells, were collected and analysed yearly and added to this hydrogeochemical database of GTK. In 1999, the results of separate hydrogeochemical mapping project covering the whole country and including data from 1002 groundwater samples were added to the database (Tarvainen et al. 2001). The database consists of both chemical and physical properties of groundwater samples.

Data on total water hardness, Mg, Ca, Al, Cu, F^-, Fe, Zn, Cr and NO_3^- contents were obtained from the hydrogeochemical database of GTK. Element concentrations were determined using inductively coupled plasma mass spectrometry and inductively coupled plasma atomic emission spectrometry. The total water hardness was calculated by formula 0.14 x Ca (mg/l) + 0.23 x Mg (mg/l). Water hardness was described as German degrees, °dH. The data which was used in this study consists of samples collected mainly from dug wells and drilled bedrock wells and analyzed during 1991-2004. Samples analyzed before 1991 were not comparable because the analytical methods and detection limit values are too different. The sample quality control regarding data from 1999 is described in detail by Tarvainen et al. 2001. The field part of sample quality control based on following methods: a blank sample was prepared once a week by each sampling group. Duplicate samples were collected in every 30th sampling site. The former Geolaboratory of Geological Survey of Finland (now Labtium ltd.) used their standard protocols for the internal quality control (ISO/IEC 17025) (Tarvainen et al. 2001, http://www.labtium.fi). The original data used in these studies contained from 3621 up to 12401 water samples depending on element. Sample size in Mg and Ca was 4262 in Study IV and 4300 in Study III. Regional distribution of water hardness, Mg and Ca/Mg ratio has shown in Fig. 6-8. The common way to describe geochemical concentrations in maps is a use of intensity of colours. Dark colours (i.e. red) usually describe high concentrations and light colours (i.e. blue) low concentrations. In the geochemical maps developed in this work we have purposely deviated from this approach, and have used dark colours to describe the possible presence of unfavorable concentrations of elements in relation to AMI incidence.

4.4. Classification of urban and rural areas

In Finland, municipalities vary greatly in size of population and area. A single municipality may often have both built-up areas and sparsely populated areas. The incidence of AMI was estimated separately in population living in rural and in urban areas. The binary covariate describing the urban and rural grids was included to the spatial model. The population of Finland is unevenly distributed. Half of the population lives in major cities and only quarter of the population lives in the sparsely populated area that covers 95 % of the total area of Finland (Rusanen et al. 1995). The urban–rural status of an area was defined as follows: area was considered urban if it contained only few or no sparsely populated areas, or if its population in built-up areas exceeded 15,000 inhabitants. The rest of the study area was considered rural (Keränen et al. 2000). Each 10 km x 10 km grid cell was classified according to the urban/rural status of the municipality to which it belonged in 1990 (Malinen et al. 1994). Data from only rural areas were included in studies III and IV. Only rural areas were included because people in the rural areas mostly use well water, whereas the urban dwellers use public tap water. It was not possible to determine the extent to which people were served by a public water supply even if they lived in close proximity to their own well.

4.5 Statistical methods

4.5.1 Interpolation of geochemical data

Study II. The geochemical point data were interpolated into a regular 10 km x 10 km grid using the ALKEMIA software developed at GTK. ALKEMIA was developed for storing and interpreting data from geochemical mapping programmes (Ahlsved et al. 1991). The ALKEMIA package contains software for several smoothing interpolation methods, of which the method of calculating grid values by a moving weighted median in circular window was commonly used for geochemical studies (Björklund and Lummaa 1983, Björklund and Gustavsson 1987, Gustavsson et al. 1997). In the ALKEMIA Smooth interpolation method, the value of certain element was calculated from concentrations of that element in samples within a circular window of radius R. A large radius increased the smoothing effect, while a small radius preserved the local level. Each sample within the circle receives a weight that is calculated using a 1st order Butterworth function for the distance between the sample and the center of the grid cell. The samples nearest to the grid cell received grater weight. The moving weighted median was calculated for each set of data, and the final value was then the average of these values. The same calculation procedure was repeated for each cell of the grid (Björklund and Lummaa 1983, Björklund and Gustavsson 1987)

Study III and IV. Measurements of geochemical elements were interpolated into a regular 10 km x 10 km grid using a hierarchical Bayesian Poisson conditional autoregressive (CAR) model. Number of grid cells was near 2800. Some elements had only a small fraction of samples below the detection limits while for others, nearly half of the samples were below the detection limit (Fe and NO_3^-). The observations were divided into two classes: (1) samples that were above the detection limit (valid) and (2) samples that were below the detection limit (low). The interpolation models accounted for both intra-cell (=within a grid cell) and spatial variances (=between grid cells) of the observations (see Appendix 1, study III and Appendix A, study IV).

4.5.2 Spatial statistics

The first AMI events, both fatal and nonfatal, were included to the models. AMI cases were divided into eight 5-year age groups: 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, and 70-74 years. A non-proportional hazard model described the effect of age and sex.

In each study (studies I-IV) the spatial models were applied to a contiguous regular neighborhood structure of 10 km x 10 km grid cells. The geographical distribution of AMI incidence was modelled using a full Bayesian hierarchical approach. The model used in these studies is usually referred to in the literature as the Poisson conditional autoregressive (CAR) model (Ranta and Penttinen 2000, Besag et al. 1991). In CAR models, neighborhood structure needs to be defined. In these analyses, neighbors were defined as cells adjacent to the cell through side or corner. Thus, each cell could have at most 8 neighbors.

In the case of the 10 km x10 km grid over Finland (excluding Lapland and Ahvenanmaa Islands), some grid cells were empty and have to be omitted from the analysis; thus 5% of cells would be omitted. However, once we take environmental factors into account, assuming that the disease risk is influenced by both demographic factors (that is, people who actually live within the grid cell) and environmental factors in each cell whether or not it is inhabited, the omission of unpopulated cells results in a loss of information. The covariates included in the model were the age of onset of AMI and the concentrations of geochemical elements in ground water.

Based on a through review of the available literature this work has assumed that CHD has a multifactorial etiology. As a consequence the method of spatial analysis used in this study was specifically selected because of its ability to being appropriate for testing the impact of several factors simultaneously. The validity of the method used in this study has been demonstrated elsewhere (Ranta and Penttinen 2000, Ranta 2001, Rytkönen et al. 2001, Rytkönen 2004, Moltchanova et al. 2004, Moltchanova 2005).

The posterior means in each cell were taken as the results of the interpolations. They are compromise between the observed incidence value in a grid cell and the observed values in the neighbourhood of that grid.

Study I. The geographical distribution of AMI incidence among men aged 35-74 years and the effect of the degree of urbanization of the environment on the incidence were modeled separately for three cross-section years 1983, 1988 and 1993 using a Bayesian spatial CAR model. Posterior mean incidences and posterior probabilities that the incidence exceeds the overall mean were calculated for 10 km x 10 km grid cells.

Study II. A Bayesian spatial CAR model with covariates was used to estimate the association between the geographical variation of the AMI incidence and the concentrations of geochemical elements in local groundwater. The all covariates included in the single model were age at the first AMI event and total water hardness, Fe, F^-, NO_3^-, Cu, Zn and Al. The geographical distribution of AMI incidence among men aged 35-74 years was modeled for three years 1983, 1988 and 1993 (pooled). The result of the analysis was the posterior mean incidence as well as the estimated covariate effects.

Study III. A Bayesian spatial CAR model with covariates was used to estimate the association between the geographical variation of the AMI incidence and the concentrations of Ca, Mg and Ca/Mg ratio in local groundwater. Cr was included in study because it's possible association with CHD. Data on men aged 35-74 years for separate cross section years 1983, 1988 and 1993 were pooled and only rural areas were included to the model. The result of the analysis was the posterior mean incidence with covariate effect.

Study IV. A full Bayesian CAR model with covariates was applied in this study. Both men and women aged 35-74 years in 1991-2003 from rural areas were included to the model. Because of similar spatial pattern of AMI incidence data in men and women was pooled. The observed case counts in each grid cell, age group and sex were modeled by Poisson regression. The covariates included to this analysis were Ca, Mg, F^-, NO_3^-, Cu, Fe, Zn and Al.

The models were fitted using WinBUGS (Spiegelhalter et al. 2004). The base map data used in this thesis with permission of the National Land Survey of Finland (Pohjakarttaaineisto©Maanmittauslaitos lupanumero 51/MML/08). Geospatial visualisation was undertaken in ArcView 3.2 and ArcMap 9.1 software.

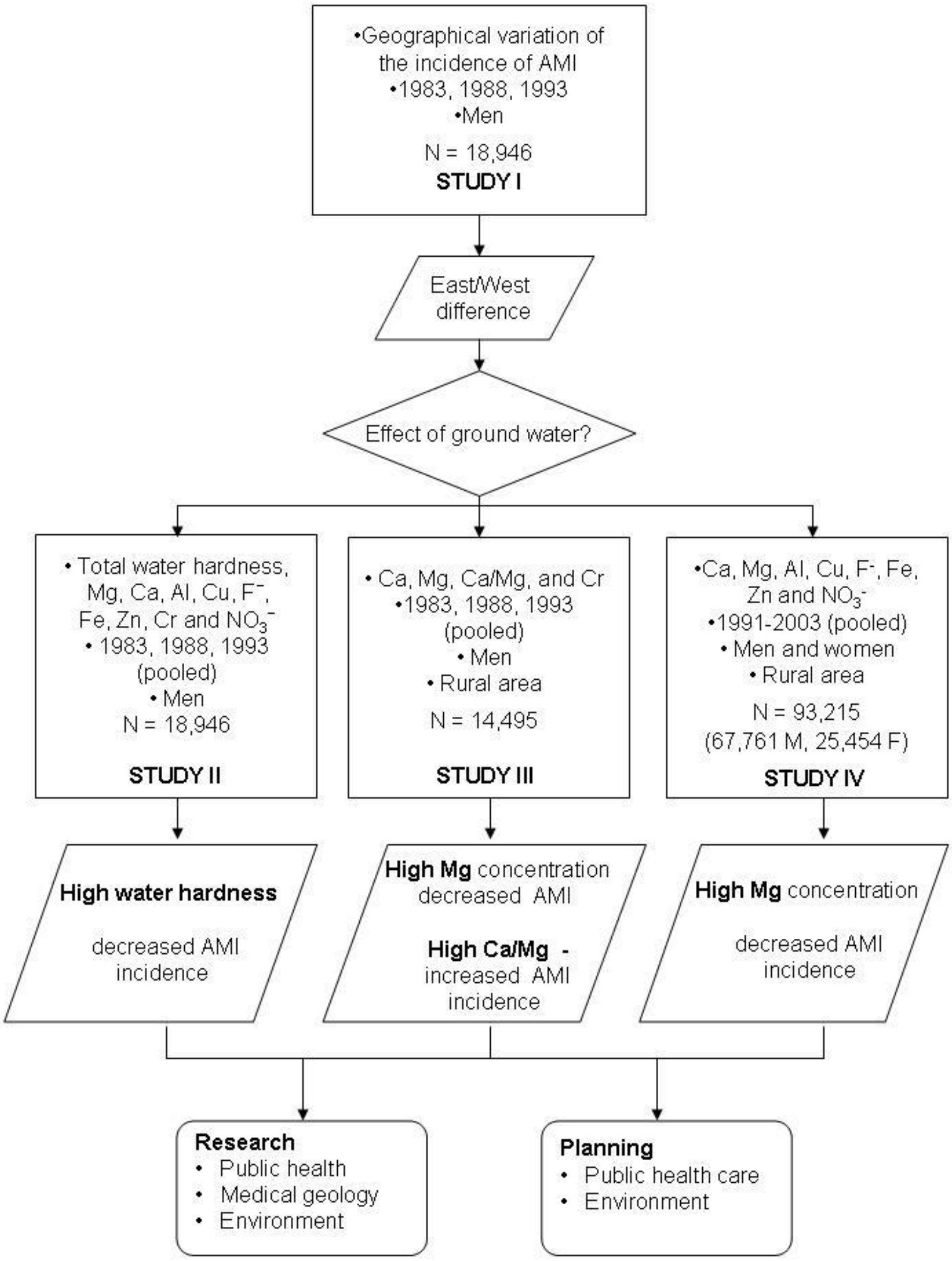


Figure 5. Description of the approach of the study.

5. RESULTS

5.1 The spatial association between the incidence of AMI and geochemical elements in local groundwater (Studies II, III, IV)

The spatial association between certain geochemical elements in local groundwater and the incidence of AMI was analysed in order to test the hypothesis of the possible association of water hardness or essential minerals of water with the incidence of AMI.

Age group and total water hardness, Ca, Mg, Ca/Mg ratio, Fe, F^-, Cu, Al, Zn, NO_3^- and Cr concentrations in local groundwater were included in the ecological analysis as covariates in Studies II, III and IV. The geochemical elements were mainly determined from water samples of dug wells or wells drilled in bedrock. The average concentrations of geochemical elements in local ground water are described in Table 4.

Table 4. Average and percentile concentrations of geochemical elements in local groundwater in rural Finland (n=2521).

Geochemical element	**Mean**	**SD**	**2.50 %**	**Median**	**97.50 %**
Hardness °dH	2.51	0.72	1.47	2.32	4.22
Ca mg/l	12.8	3.57	7.48	12.1	21.1
Mg mg/l	2.90	1.02	1.66	2.58	5.35
Al µg/l	25.6	22.5	6.0	18.5	79.3
Cu µg/l	6.01	2.66	2.70	5.26	14.0
Fe mg/l	0.06	0.03	0.03	0.05	0.16
NO_3^- mg/l	2.35	1.04	0.55	2.23	4.64
Zn µg/l	19.1	5.25	12.5	17.4	32.2
Cr µg/l	0.26	0.09	0.14	0.24	0.50
F^- mg/l	0.18	0.20	0.06	0.12	0.77
Ca/Mg	5.06	0.93	3.33	5.11	6.91

5.1.1 Total water hardness, Mg and Ca concentrations and Ca/Mg ratio

Study II

Total water hardness, Fe, F^-, Cu, Al, Zn, and NO_3^- concentrations were included in analysis as covariates. The overall age-adjusted incidence of AMI in men aged 35-74 year was 480/100 000/year (posterior 95% HDR 473, 487). The main finding was that total water hardness had an inverse association on the AMI incidence. One unit increment (in German degree °dH) in water hardness was associated with an average 1 % decrease in the AMI incidence among men other things being equal. The other geochemical elements did not have any marked effect on spatial variation in the incidence of AMI (Study II, Table 3). Regional distribution of total water hardness is described in Fig 6.

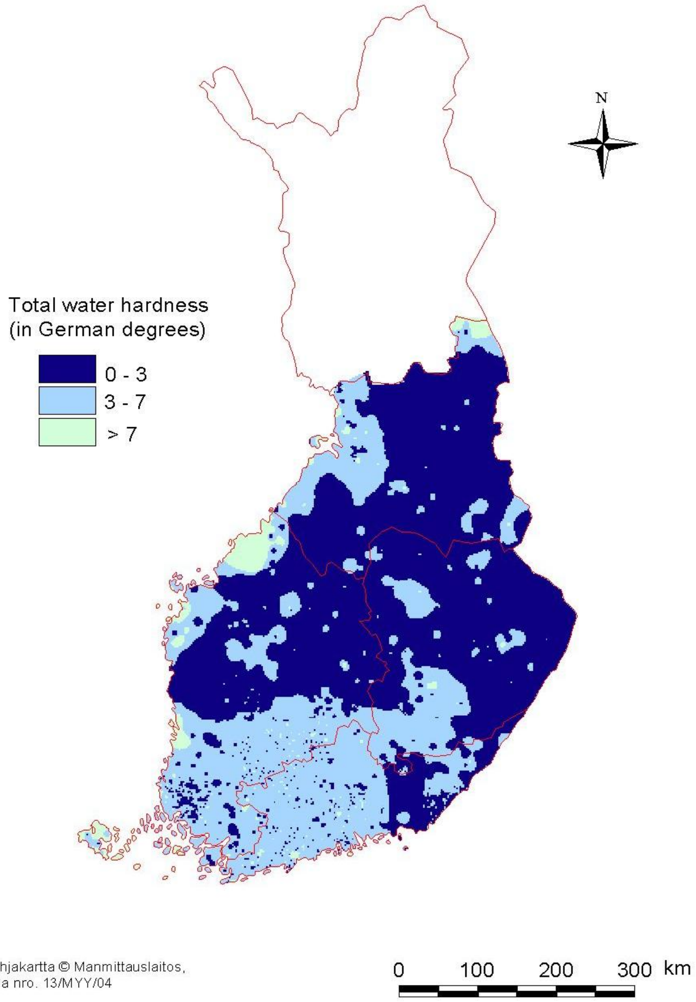


Figure 6. Water hardness in Finland (original data).

Study III

Ca, Mg and Cr concentrations and Ca/Mg ratio in ground water were included in spatial analysis. Regional distributions of Mg and Ca/Mg ratio are described in Figs. 7 and 8. The overall age standardized incidence of AMI in men aged 35-74 years in rural Finland was 503/100 000/year (posterior 95 % HDR 494, 511). 1 mg/l increment in Mg concentration in local groundwater was associated with a 4.9 % decrease in the incidence of AMI whereas a one unit increment Ca/Mg ratio was associated with a 3.1 % increase in incidence of AMI (Table 5). Ca and Cr did not have any association with spatial variation of the AMI incidence.

Table 5. The estimated regression coefficients of Mg, Ca and Ca/Mg ratio on the incidence of the first acute myocardial infarction among Finnish men in 1983, 1988 and 1993 (pooled data).

Element	Posterior mean, %	95% HDR[a]
Mg mg/l*	-4.9	-8.8, -0.9
Ca mg/l*	0.9	-0.1, 2.1
Ca/Mg**	3.1	0.5, 5.7

*single spatial model
**a separate spatial model
[a] Highest density regions

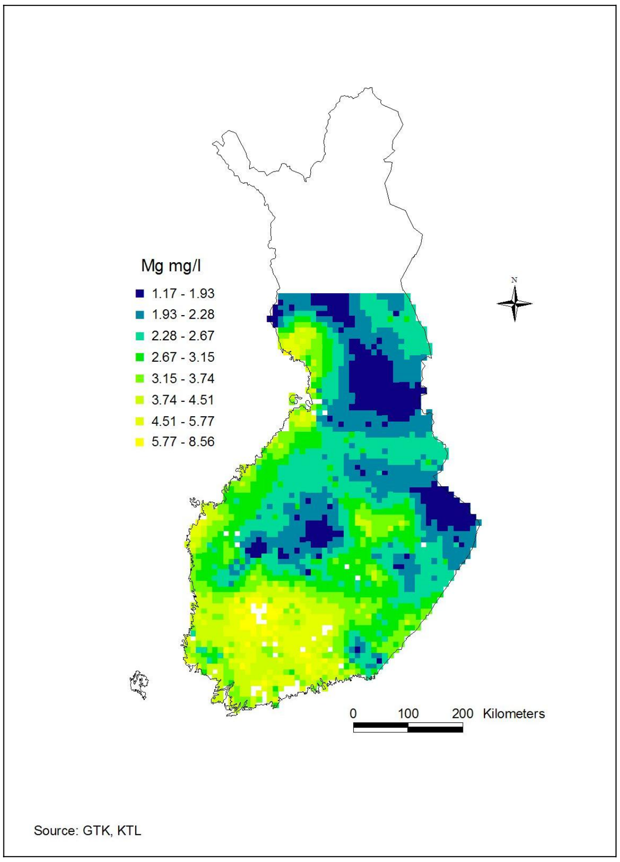
Study IV

Age group, sex, Mg, Ca, Al, Cu, F^-, Fe, Zn and NO_3^- were included as covariates in the spatial models.The age-adjusted AMI incidence in rural Finland in men and women aged 35-74 years was 589/100 000/year (95% HDR 584,593) and 177/100 000/year (95% HDR 175,179), respectively. There was no clear relationship between geochemical elements in local ground water and AMI risk in the simple model with all covariates (Study IV, Table 2). Based on the existing information of the association between water hardness and the occurrence of AMI, the associations of the main components of water hardness, Ca and Mg, were estimated in a separate model. The marked spatial association was found between Mg and the incidence of AMI (Table 6). One mg/l increment in Mg concentration in local groundwater was associated an average with 2 % decrease in the incidence of AMI. However, Ca concentration in groundwater did not have any marked spatial association with the incidence of AMI.

Table 6. The estimated regression coefficients of Ca and Mg on the incidence of the first acute myocardial infarction in men and women (pooled) in1991-2003 in rural Finland.

Element	Posterior mean*, %	95% HDR	
Ca mg/l	-0.1	-0.6	0.4
Mg mg/l	-2.2	-3.9	-0.3

The regression coefficients were estimated in a single spatial model.
*Adjusted for age and sex.



Source: GTK, KTL

Figure 7. Regional distribution of Mg (mg/l) concentration in local groundwater in rural Finland.

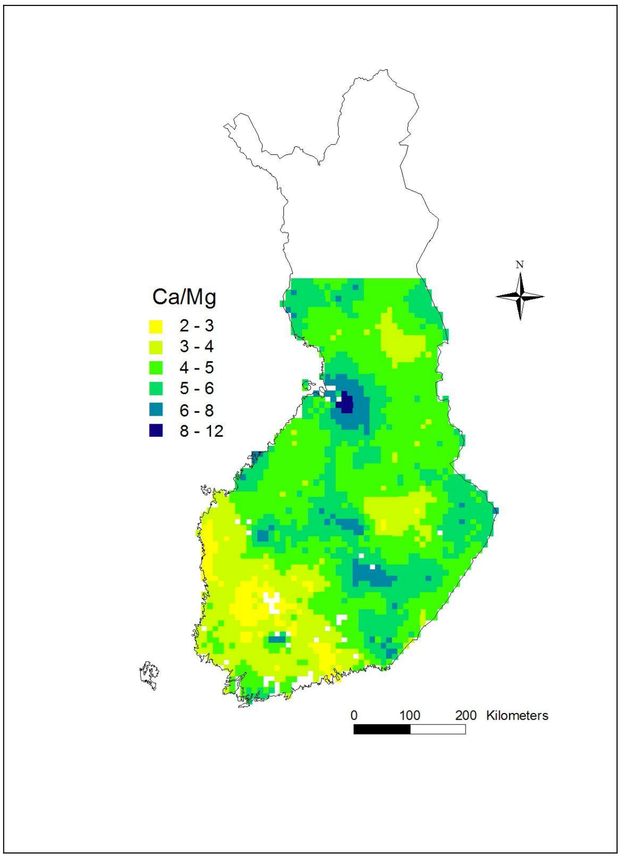


Figure 8. Ca/Mg ratio in local groundwater in rural Finland

5.2 Geographical distribution in the incidence of AMI in Finland (Study I, Study IV)

5.2.1 The incidence of AMI in men aged 35-74 years in cross-section years 1983, 1988 and 1993 (Study I)

The spatial distribution and temporal trends in first acute myocardial infarction (N=18 946) were studied in three separate calendar years in 1983, 1988 and 1993. The overall AMI incidence was 524/100 000/year (95 % HDR 503, 529) in 1983, 490/100 000/year (95% HDR 465,490) in 1988 and 428/100 000/year (95% HDR 408, 430) in 1993. The marked decline was found in observed incidences during both periods. The decrease of ten years period in AMI incidence was approximately 18%. However, the maps of age-adjusted observed AMI incidence did not represent a clear spatial change in incidence. Despite the almost 20% decrease in the incidence of AMI over that period, the spatial pattern has remained relatively stable (Study I; Fig. 1a, 2a, 3a). The maps of the posterior mean incidence of AMI showed an increasing risk from south-west to the north-east (Study I; Fig. 1b, 2b, 3b). This spatial pattern of the AMI incidence remained constant from year to year.

5.2.2 The incidence of AMI in rural population aged 35-74 in 1991-2003 (Study IV)

Incidences in rural areas were 589/100 000/year (95% HDR 584,593) for men and 177/100 000/year (95% HDR 175,179) for women. The overall incidence of AMI in women was only one third of that in men but there was no difference in the spatial pattern of the incidence (Fig. 1). The spatial pattern of AMI incidence consistently proved that the risk increases over and again from south-west to north-east Finland (Fig. 9 a and b).

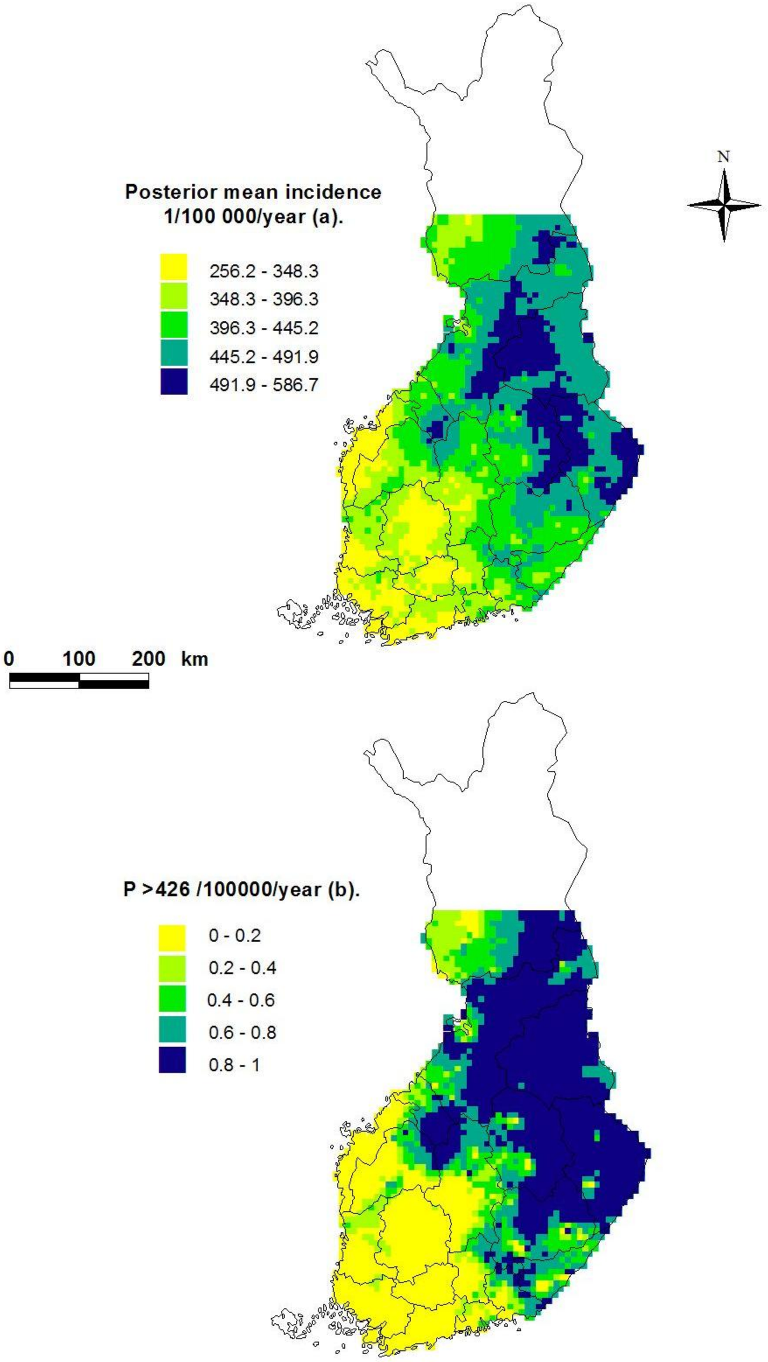


Figure 9 a and b. Posterior mean age standardized AMI incidence (a) and posterior probability of the risk exceeding overall country risk 426/100 000/year (b) among men and women (pooled) in 1991-2003 in rural Finland.

5.2.3 The difference in the incidence of AMI between rural and urban areas (Study I, Study IV)

In years 1983, 1988 and 1993 incidence among men living in rural areas was an average 7 % -12 % higher than in men living in urban areas. Although the difference in incidence of AMI between rural and urban areas was decreased during the period 1991-2003, the incidence was still 3% higher in rural areas compared to urban areas among men. Also among women living in rural areas the incidence of AMI was 2% higher than among those living in urban areas.

6. DISCUSSION

The studies described in this thesis showed that despite of decreasing trend in the incidence during last decades the highest AMI risk still locate in the eastern part of Finland as it has been at least 60 years. The present study is consistent with the results of earlier studies that water hardness and especially Mg in local groundwater were geographically associated with the incidence of AMI.

6.1 Methodological issues

Geographical health studies have been traditionally carried out using administrative boundaries when defining study areas. It is obvious that health information aggregated by administrative areas is inadequate to address several public health concerns (Armstrong et al. 1999). Diseases do not recognize areas or borders defined for administrative or political purposes, and finer geographical scale is often more appropriate for epidemiological studies (Rytkönen 2004).

In the present study, Bayesian disease-mapping methods were used to demonstrate different risk areas of AMI in Finland. A Bayesian ecological modelling approach was applied to study the association of the AMI incidence with covariates as well. In present ecological study geo-referenced data were aggregated into 10 km x 10 km cells to protect the privacy of individuals. The observed incidence rates calculated in the grid cells varied largely but approach used in present study reduced the random variation. As a result of Bayesian smoothing method, the posterior mean incidences represent a compromise between the observed incidence value in a grid cell and the observed values in the neighbourhood of the grid cell. One disadvantage often cited when considering the use of high resolution spatial data is that it may endanger the privacy of individuals if used incautiously. However, the use of a Bayesian smoothing technique as used in this work is beneficial in this respect as the smoothing tends to ensure the privacy of individuals (Ranta et al. 1999, Rytkönen 2004).

One of the methodological limitations in spatial analysis is the use of aggregated data. Ecological or group-level associations and aggregations are not necessarily consistent with those measured at the individual level and possible ecological bias introduces a major source of uncertainty in ecological inference (Greenland 2001). Thus the inference or conclusion from group level is not transferable to the individual level.

Furthermore, one additional problem in spatial study is how to address the lag-time between an exposure and the onset of the disease symptoms. Populations in modern countries are very mobile and it is not uncommon for people to move from region to region within municipality or country, or from one country to another. Therefore, subjects with a chronic disease could have been exposed to the potential risk factors much earlier in their lives and in a different area where the first signs of the disease occurred (Löytönen 1998). Thus an exposure experienced earlier in the life may associate with an inaccurate geographical location in the map (Ranta et al. 1999).

Ecological studies have certain limitations, but they also have several undoubted advantages over individual-level studies. Ecological data are often cheaply and readily available (Haneuse and Wakefield 2008). Use of the Internet, large data bases, disease registers and census data are relatively easily accessed. Such databases are often the only recourse for a researcher where ethical or logistical considerations may impact the availability of high quality individual level data, and the ecological analysis have been performed at the geographical level (Haneuse and Wakefield 2008). Development of GIS allows a researcher to link data from various databases. Another attractive feature is that ecological studies have the advantage to cover larger areas of the population than studies in individual-level design.

In this study, the availability of the health data with additional geographical attributes (i.e. x,y coordinates) enabled a link to be established to the georeferenced geochemical data via GIS. GIS is the essential link between epidemiology, geography and geology. Due to ecological study design together with Bayesian spatial analysis it was possible to investigate simultaneously the association of geochemical elements in well water with the incidence of AMI in finer scale in almost whole country (excluding Lapland and Ahvenanmaa Islands) instead of provinces or communes or other administrative boundary defined areas used in other ecological studies in this area.

6.1.1 Possible confounding factors

Major CHD risk factors may confound the results of any study. Data of major CHD risk factors, such as blood pressure, serum cholesterol and smoking, were not available in present study. Major CHD risk factors may confound the association of AMI incidence and water hardness only if they are associated with soft groundwater. However, it is unlikely that major CHD risk factors are basically associated with soft drinking water poor with Mg (Monarca et al. 2005).

Previous studies in Finland and elsewhere have shown that the lower socioeconomic status is related to higher CHD mortality and morbidity rates (Hallqvist et al. 1998). However, the east-west difference in AMI incidence and coronary mortality rates is not affected by socioeconomic status (Salomaa et al. 2000).

Consumer habits within the country may affect the intake of Mg in different part of Finland. People living in eastern Finland eat more Mg-rich cerealis products, especially rye bred, than those living in southwestern Finland. Vegetables are commonly used in southern Finland (Similä et al. 2005). Mg poor fish is most commonly consumed in northern Finland and least commonly in southwestern part of Finland, except some areas on the west coast. Consumption of fruits is most common in southern Finland (Similä et al. 2005). Milk is on average commonly used in central and northern part of Finland and meat is slightly commonly used in northern Finland (Männistö et al. 2002).

6.1.2 Geochemical data

In Finland about 4.7 million people derive their drinking water from the public water supply system. Such water is derived relatively locally from surface and/or groundwater reserves and distributed to individual consumers by pipe. However, about half million people living in rural areas use ground water derived from their own local wells (Finnish Environment Institute SYKE). The number of well water users increases also in summer time when wells of almost half million (Statistics Finland 2007) free-time residence are in use.

A part of the AMI cases were diagnosed in 1983 and 1988 and the water data from those years were not available. However, this is not major factor because the variation in general quality of groundwater was quite insignificant from year to year (Lahermo et al. 1990, Korkka-Niemi 2001, Tarvainen et al. 2001). Generally seasonal variation of element concentrations were quite stable (Rosborg et al. 2006). The medians of water hardness in in autumn, spring and summer were 3.4 ºdH, 3.3 ºdH and 3.8 ºdH, respectively (Korkka-Niemi 2001).

6.2 Geographical difference in the incidence of AMI

The present study showed that incidence of AMI declined considerably during time periods 1983-1993 and 1993-2001 in Finland. Despite of this declining trend the high-risk areas in CHD in eastern and north-eastern part of Finland have remained persistently unchanged over years. During these years, the levels of the major risk factors have decreased, socio-economic situation has improved and the lifestyle has become uniformly healthier in the Finnish population. Therefore the stability in the geographical variation in the incidence of AMI supports the hypothesis that some factors in physical environment might play a role in developing AMI in the susceptible population, because it has been clearly shown earlier that the major CHD risk factors do not totally explain the regional variation in mortality and morbidity (Jousilahti et al. 1998).

The genetic problem of the east-west difference is not conclusively solved (Norio 2003). The results of recent study suggest that there is east-west difference in the genetic structure of the Finnish male population (Lappalainen et al. 2006). Genetic factors may explain partly east-west difference in disease. However, the spatial pattern of AMI incidence is quite similar among the male and female population. This is consistent with other common risk factors associated with this disease.

6.3 The difference in the incidence of AMI between rural and urban areas

In each cross-section year, 1983, 1988 and 1993, the estimated AMI incidence was higher in rural areas than in urban areas. The AMI incidence was higher in rural areas in whole country, not only in eastern Finland. A greater part of high risk areas in eastern Finland are sparsely populated remote rural areas with a low socio-economic status of population. The geographic distribution of high risk areas suggest that presence or absence of socio-cultural or physical environments that promote or inhibit the given risk factor or preventive behavior. Although the difference in AMI incidence between rural and urban areas decreased in 1991-2003, the incidence was still slightly higher among rural men and women. The effect of urban/rural-status was eliminated in studies III and IV and study areas were limited only to rural areas.

6.4 Total water hardness, Mg and Ca concentrations and Ca/Mg ratio and the incidence of AMI

Study II showed an inverse association of total water hardness with the incidence of AMI. The results were in line with other epidemiological studies from different countries (Masironi et al. 1980, Rylander et al 1991, Piispanen 1993). The main components of water hardness, Ca and Mg, were also analysed separately in studies III and IV. Mg concentration in local groundwater was associated with lower incidence of AMI. Ca concentration did not have any clear association with the incidence.

The results of study III showed the increased Ca/Mg ratio in local groundwater was associated with the higher incidence of AMI. The estimated Ca/Mg ratio was in current study around 5. The association between CHD and Ca/Mg ratio has reported in Finland already 30 year ago (Karppanen et al. 1978). It has been proposed that the optimum Ca/Mg total intake ratio should be close to 2 (Durlach 1989). It has been also suggested that Ca/Mg ratio greater than 5 may increase a risk for Mg inadequacy (Seelig 1994). In Finland the intake of

Ca is high due to the consuming of dairy products (Männistö et al. 2002). On the other hand, CHD mortality and morbidity are unusually high as well and thus protective effect of Ca is unlikely true in Finnish situation.

Mortality from CHD has declined since the 1970 both in eastern part (area with soft groundwater) and in western part (hard water) in Finland. However, relative excess in eastern part of the country has remained the same in males but has even increased in females (Kaipio et al. 2004).

The distributed water by waterworks was soft, an average 4 ºdH and 3.3 ºdH in 2006 in Kuopio and Helsinki, respectively. Drinking water was slightly harder in urban areas than in rural areas in this study.

Some criticism of the Mg theory has been presented. Studies with very low concentration of Mg (< 10 mg/l) in drinking water do not have the power to estimate the CHD risk in relation of Mg (Rylander 2005). It is also argued that only a small proportion, less than 5-10 % of the daily intake of Mg, comes from drinking water (Marx and Neutra 1997). On the other hand, it has been also suggested that Mg in water is more bioavailable (Anderson et al. 1975). However, Sabatier et al. (2002) reported that bioavailability from mineral rich water is enhanced when water was consumed with a meal.

7. SUMMARY AND CONCLUSIONS

In summary, the results of this study showed that despite of favourable trend in CHD mortality and morbidity the high CHD risk areas are still in eastern part of Finland where they been observed for over 60 years. This study is consistent with the results of earlier studies that total water hardness and especially Mg in local groundwater were associated with the lower incidence of AMI among middle-aged and older men and women in rural Finland. Although Mg deficiency is not common in Finland, it can be assumed on the basis of this that populations living in geographical areas with low total water hardness but high Ca/Mg ratio in local groundwater may have an increased risk of CHD. Several researchers and nutritionists have suggested that the current RDA for Mg, 350 mg/day, is too low and it should be 450 to 400 mg/day (Altura and Altura 2006). Other geochemical elements in local groundwater analysed in this study did not show any marked relationship to CHD risk. The results of this work showed that difference in the incidence of AMI between urban and rural areas has decreased but is still slightly higher in rural areas.

In this study, the geographical association of AMI incidence with geochemical elements of ground water was for the first time studied using flexible geographical scale without administrative boundaries at a whole country level (excluding Lapland and Ahvenanmaa Islands). Unique identification numbers assigned at birth enabled the location of individuals according to map coordinates of the place of residence at the time of diagnosis. The special advantage in Finland for spatial analysis is that the data from national death and disease registers are accurate and the diagnostic classification has been shown to be high quality (Pajunen et al. 2005).

Ecological studies have certain limitations which have been discussed earlier. However, there are no reasons to believe that carefully planned and performed ecological studies should not produce robust and reliable results. Although ecological studies are not able to establish causal relationship between exposure and disease they are useful for generating hypotheses and starting point for studies carried out individual level. Because case-controls or cohort follow-up studies are expensive and time consuming the ecological studies are valuable tools as the first line tests of hypothesis.

The results of studies undertaken during the development of this thesis and other work fully support and warrant the forthcoming new multi-country water hardness, Mg and Ca, and health outcome study to eventually prove – or disprove - if the low water hardness poor in Mg is an important contributor to the risk of, and spatial distribution of CHD. If positive the weight of evidence from such studies would be expected to identify the need for, and underpin the development of, health based quideline values for hardness, Mg and Ca in drinking water and associated community public health strategies further minimising the occurence of CHD.

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APPENDIX 1: ORIGINAL PUBLICATIONS I-IV

Kuopio University Publications D. Medical Sciences

D 423. Karinen, Hannele. Genetics and family aspects of coeliac disease.
2008. 110 p. Acad. Diss.

D 424. Sutinen, Päivi. Pathophysiological effects of vibration with inner ear as a model organ.
2008. 94 p. Acad. Diss.

D 425. Koskela, Tuomas-Heikki. Terveyspalveluiden pitkäaikaisen suurkäyttäjän ennustekijät.
2008. 253 p. Acad. Diss.

D 426. Sutela, Anna. Add-on stereotactic core needle breast biopsy: diagnosis of non-palpable breast lesions detected on mammography or galactography.
2008. 127 p. Acad. Diss.

D 427. Saarelainen, Soili. Immune Response to Lipocalin Allergens: IgE and T-cell Cross-Reactivity.
2008. 127 p. Acad. Diss.

D 428. Mager, Ursula. The role of ghrelin in obesity and insulin resistance.
2008. 123 p. Acad. Diss.

D 429. Loisa, Pekka. Anti-inflammatory response in severe sepsis and septic shock.
2008. 108 p. Acad. Diss.

D 430. Joukainen, Antti. New bioabsorbable implants for the fixation of metaphyseal bone : an experimental and clinical study.
2008. 98 p. Acad. Diss.

D 431. Nykänen, Irma. Sepelvaltimotaudin prevention kehitys Suomessa vuosina 1996-2005.
2008. 158 p. Acad. Diss.

D 432. Savonen, Kai. Heart rate response to exercise in the prediction of mortality and myocardial infatction: a prospective population study in men.
2008. 165 p. Acad. Diss.

D 433. Komulainen, Pirjo. The association of vascular and neuroprotective status indicators with cognitive functioning: population-based studies.
2008. Acad. Diss.

D 434. Hassinen, Maija. Predictors and consequences of the metabolic syndrome: population-based studies in aging men and women.
2008. Acad. Diss.

D 435. Saltevo, Juha. Low-grade inflammation and adiponectin in the metabolic syndrome.
2008. 109 p. Acad. Diss.

D 436. Ervasti, Mari. Evaluation of Iron Status Using Methods Based on the Features of Red Blood Cells and Reticulocytes.
2008. 104 p. Acad. Diss.

D 437. Muukka, Eija. Luomun tie päiväkotiin: luomuruokailun toteutettavuus ja ravitsemuksellinen merkitys päiväkotilapsille.
2008. 168 p. Acad. Diss.

D 438. Sörensen, Lars. Work ability and health-related quality of life in middle-aged men: the role of physical activity and fitness.
2008. 83 p. Acad. Diss.