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Doctoral Thesis

NTNU
Norwegian University of
Science and Technology
Thesis for the degree of
Philosophiae Doctor
Faculty of Medicine
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Validitet og relevans av internasjonale retningslinjer for forebygging av hjerte- og karsykdom i allmennpraksis

De siste tiårene har forebygging av hjerte- og karsykdom (HKS) blitt et svært sentralt tema i klinisk praksis, helsepolitikk og offentlig debatt. I vår del av verden er det først og fremst allmennlegene som arbeider med forebygging av HKS på individuelt nivå. For dette formålet er det utformet kliniske retningslinjer som skal gjøre det mulig for legene å gjøre en best mulig forebyggende jobb. Retningslinjene er ment å formidle nødvendig og oppdatert kunnskap til legene og slik fungere som et instrument for klinisk kvalitetsforbedring. Retningslinjer legger føringer for hva som regnes som forsvarlig klinisk praksis og kan bli styringsverktøy for helsemyndighetene med mulighet for økonomiske sanksjoner om de ikke følges. Flere studier har imidlertid vist at allmennleger i beskjeden grad følger retningslinjer for forebygging av HKS, og at anbefalte behandlingsmål ofte ikke oppnås. Enkelte vil forklare dette med at allmennlegene gjør en dårlig jobb, mens andre har pekt på svakheter ved grunnlaget for og utformingen av retningslinjene.

Målet med prosjektet var å analysere validitet og relevans av autoritative, internasjonale retningslinjer for forebygging av hjerte- og karsykdom i allmennpraksis.
Mer spesifikt:

- Å dokumentere HKS- risikoprofilen til en generell befolkning hvis risikodefinisjonene som retningslinjene anvender appliseres som anbefalt.
- Å estimere arbeidsbyrden for allmennlegene om retningslinjene ble tatt i bruk i en gitt populasjon.
- Å identifisere mulige årsaker til at retningslinjene synes å overestimere risiko, med utgangspunkt i analyse av isolerte risikofaktorer: total-kolesterol og kroppsmasseindeks.

Avhandlingen bygger på analyser av data fra Helse-undersøkelsen i Nord-Trøndelag (HUNT 2) som er en befolkningsstudie med over 65 000 deltakere. Hovedfunn: Majoriteten av befolkningen hadde risiko for HKS med behov for regelmessig oppfølging i helsetjenesten ut fra retningslinjenes definisjoner av risiko. Om retningslinjene ble implementert i norsk allmennpraksis ville det destabilisere fastlegetjenesten.

To delstudier ble gjennomført for å finne ut om det overraskende høye antallet av personer med medisinsk risiko ('risikanter') som retningslinjene definerer evt. kan forklares av hvordan to isolerte risikofaktorer, nemlig kolesterol og fedme, behandles av retningslinjene.

Total-kolesterol viste seg å ikke være en så entydig prediktiv markør for dødelighet som generelt antatt. Måten kolesterol betraktes på ble dermed identifisert som en mulig svakhet ved retningslinjene. Dersom våre resultater kan reproduseres og er generaliserbare, må anbefalinger knyttet til kolesterol revideres, både for klinisk bruk og i folkehelsekampanjer.

Kroppsmasseindeks (KMI) / body mass index (BMI) har til nå vært den mest anvendte og anbefalte metoden for å måle kroppssammensetning og definere fedme. KMI viste seg i vår analyse å være en dårligere prediktor for dødelighet enn følgende tre mål var: forholdet mellom liv- og hoftevidde (waist-to-hip ratio; WHR), forholdet mellom livvidde og høyde (waist-to-height ratio; WHtR), eller kun livvidden. WHR og WHtR predikerte dødelighet best. På bakgrunn av dagens kunnskap virker det rimelig å anbefale WHR for å måle kroppssammensetning med tanke på sykdomsforebygging.

I avhandlingen identifiseres og diskuteres også andre faktorer som potensielt kan begrense retningslinjenes validitet og relevans.

Samlet dokumenterer avhandlingens fire delstudier problemer med retningslinjene som har vesentlig betydning, både for klinisk praksis, ressursbruk og planlegging av helsetjeneste. I praksis overestimerer retningslinjene hjerte-kar risiko og de hjelper dermed ikke allmennlegene til å gjøre en god og målrettet jobb. En strategi som i utgangspunktet skulle bidra til å gjøre det enklere for legene å identifisere og prioritere pasienter med høy risiko, ender i praksis opp som en dårlig planlagt massestrategi som ikke synes bærekraftig og heller ikke ansvarlig å implementere.

Resultatene som presenteres i avhandlingen har en rekke implikasjoner. Det vil trolig kreve mye nytenkning og ytterligere forskning å utarbeide forebyggende retningslinjer som fungerer godt i klinisk praksis. Avhandlingen inneholder noen forslag til hvordan man kan starte arbeidet med å forbedre retningslinjene.

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ABBREVIATIONS

4S	The Scandinavian Simvastatin Survival Study
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CHD	Coronary heart disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EBM	Evidence-based medicine
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation working group
HDL	High density lipoprotein
HPA	Hypothalamo-pituitary-adrenal axis
hs-CRP	High-sensitivity C-reactive protein
HUNT	The Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)
IDI	Integrated discrimination index
IHD	Ischaemic heart disease
ISH	International Society of Hypertension
JNC	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL	Low density lipoprotein
MI	Myocardial infarction
NCD	Non-communicable diseases
NRI	Net reclassification index
RCT	Randomised controlled trial
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socio-economic status
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

ABSTRACT

Background
Cardiovascular diseases (CVD) are currently the leading cause of death worldwide, and a major cause of disability. CVD, including supervision of risk factors with respect to prevention, have in recent decades become an increasingly important topic for general practice. These issues have also become prominent in public debate and health care policy. Specific strategies of individual prevention are to a large extent, at least in the Western world, in the hands of the general practitioners (GPs). In recent years, there has been much emphasis on clinical practice guidelines to aid GPs in their preventive work and guide them to the most cost-effective management. This refers both to recommendations on therapeutic options as well as methods to identify those who would benefit the most from preventive treatment. These guidelines can provide important and updated information for clinicians and function as an instrument for quality improvement and potentially also performance assessment in clinical practice. However, various studies have shown that GPs only follow the guidelines to a certain extent, and that recommended treatment goals are often not reached. Some authors have explained this in terms of physicians' inadequacy, whilst others have pointed out that at least part of the explanation is likely to lie in the nature of the guidelines as such. The quality and usefulness of clinical guidelines for prevention of CVD are of great importance to many, both on the level of individual health care and from the perspective of resource allocation.

Aims
The objective of this project was to study and discuss the validity and relevance of international CVD prevention guidelines for general practice. More specifically:

- To document the CVD risk profile of a general population as defined by selected, authoritative preventive clinical guidelines, by means of modelling studies.
- To estimate the workload associated with following the recommendations of the selected guidelines for a well-defined general population in whole.
- To identify potential causes of guidelines' overestimation of risk, focusing on individual risk factors.

Material and methods
This dissertation is based on analyses of data from the Norwegian HUNT 2 population survey, including roughly 65 000 participants. Two studies were conducted to document the CVD risk profile of this general population and to model the implications of implementing current clinical guidelines, regarding the proportion of the population identified at “increased risk”, and the clinical workload associated with following the guideline recommendations. Subsequently, two studies were conducted to analyse whether potential causes of guidelines' overestimation of CVD risk might stem from the way two individual risk factors, cholesterol and obesity, are handled in the guidelines. The dissertation further includes analysis and identification of additional factors potentially limiting the validity and relevance of preventive CVD guidelines.

Results

If authoritative guideline recommendations for CVD prevention are literally applied, a vast majority of adults in Norway would exhibit "unfavourable" CVD risk profiles and thus be considered in need of individual, clinical attention and follow-up. The potential workload associated with implementing current European clinical guidelines could destabilise the healthcare system in Norway, one of the world's most long- and healthy-living nations, by international comparison.

Total cholesterol was not found to be as predictive of mortality as generally assumed. Thus, possible errors regarding the role of total cholesterol in the CVD risk algorithms of many clinical guidelines were identified. If our findings are generalisable, clinical and public health recommendations regarding the "dangers" of cholesterol should be revised.

Body mass index, the most widely recommended measure of obesity in preventive CVD guidelines, was found to be inferior to waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and waist circumference in relation to predicting mortality. WHR and WHtR exhibited the best predictive properties. It appears reasonable to recommend WHR as the primary clinical measure of body composition and obesity for preventive purposes.

Conclusion

There currently appears to be a range of factors limiting the validity and relevance of clinical practice guidelines on prevention of CVD, at least in Norway. Such limitations may have important effects on clinical practice and resource allocation, as well as population health. The guidelines appear to overestimate CVD risk and fail to correctly identify a manageable proportion of the population as "high-risk individuals", for whom individual preventive strategies would be effective and beneficial. The strategy of targeting individuals at risk ends up being recommended at the level of mass strategy, which can hardly be regarded as sustainable or responsible. A number of factors potentially limiting the validity and relevance of current guidelines were identified. The dissertation includes a proposal of ways to improve the guidelines.

ACKNOWLEDGEMENTS

The work presented in this dissertation was done in Iceland and in Trondheim, Norway. The project has received financial support from the Norwegian Medical Association's Funds for Research in General Practice; the Research Fund of the Icelandic College of Family Physicians; and the Research Unit of General Practice, Department of Public Health and General Practice, NTNU. My supervisors have been Linn Getz, Jóhann Ágúst Sigurðsson, and Irene Hetlevik.

I want to thank the HUNT Research Centre for contributing HUNT 2 data, and I am grateful to the Department of Public Health and General Practice, NTNU, for enabling me to conduct this study and giving me a place to work. Luckily, the financial catastrophe in Iceland did not teach Norwegians that Icelanders should not be trusted with money and I am grateful for the financial support. Of course, moving to Norway and the financial custody of NTNU was mandatory for receiving the grant – you can never be to careful when it comes to citizens of a nation in a financial and moral crisis. Bearing the damaged reputation of Icelanders in mind, I am grateful to the Norwegian people for the positive regard I have received.

I am extremely grateful to Jóhann and Linn for everything they have done for me. They literally took me into their home and gave me good, thorough, flexible, practical, inspiring, and warm guidance throughout this project. I am thankful for the magical combination of Linn's inspiring and mind-blowing flight of ideas and discoveries and Jóhann's relaxed and practical approach supported by his extensive experience. I am thankful for their combined critical thinking and the innumerous hours of agonising frustration after receiving drafts of manuscripts, all painted red, after their critical reading. I am grateful to them for opening the doors to academy and research for me and opening my eyes for research. I was never keen on going into research and had no plans of doing so. The main reason for me accepting their proposal (or challenge) of a PhD project was the unique chance of working with the two of them and getting acquainted to a part of their vast academic social-network.

I am grateful to Irene Hetlevik for being a reliable anchor on the churning seas of administrative formalities and academic debate. I am thankful for her guidance and her vast experience, for her calm, determined yet warm, and steady steering of the AFE-Trondheim vessel, and I am grateful to her for recruiting me to her crew.

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I am thankful for being included in the fruitful and inspiring work of the Nordic Risk Group through my supervisors – a research collaboration whose vision is:

> To promote general practice which is salutogenic, empowering and sustainable, by - careful balancing of biomedical and humanistic approaches to health, illness and disease [and] - systematically aiming to minimise medicalization and risk labelling and avoid interventions of disputable benefit (Nordic Risk 2011)

I got the opportunity to participate in workshops held by this productive group at three international conferences, including hosting one workshop with Professor Steinar Westin and Iona Heath, President of the Royal College of General Practitioners. Working with the Nordic Risk Group has influenced me in many ways during the research period. Especially I would like to thank my dear friend, John Brodersen, who has inspired me with his critical thinking and extensive methodological competence.

In May 2011, I participated in the 12th Nordic workshop in evidence based health care, "Forskning ved Fjæra", in Holmsbu, Norway. The workshop was held by the Norwegian Knowledge Centre for the Health Services. This workshop was extremely useful and had great effect on me. I was lucky enough to have Gordon Guyatt, one of the fathers of *evidence-based medicine*, as the tutor of my group. Our discussion in the workshop had invaluable influence on this dissertation. I am very grateful to Gordon Guyatt and the Norwegian Knowledge Centre.

I am very grateful for the support of my friends and family – three persons in particular: My dear brother, Pétur Pétursson, whose assistance and advice through the years has made a great impression, and although his oppinion (as a cardiologist) has not been in favour of my research, his personal and academic support has been of importance. Though his words are often few in number, they tend to be golden. My father, Pétur Pétursson, has been by far my most important mentor as a medical doctor – as a practitioner and as an academic. He taught me, among other things, the importance of critical thinking and not bending for unjust authorities, and he opened my eyes for the importance of social, psychological, and mental determinants of health. Our hot tub discussions have included some enlightening moments of major importance for this project. I hope our hot tub sessions will be many to come.

Finally, my dear Lilja. Thank you for everything. I hope you forgive me for placing you second to my work all this time – through your pregnancy and the first weeks of our little daughter's life. Unfortunately, you will still have to accept the second place – the first place belongs to our daughter, Ísafold Dóra.

LIST OF PAPERS

This thesis is based on the following original research papers:

I. Can individuals with a significant risk for cardiovascular disease be adequately identified by combination of several risk factors? Modelling study based on the Norwegian HUNT 2 population. Petursson H, Getz L, Sigurdsson JA, Hetlevik I. *J Eval Clin Pract* 2009;15:103-9.

II. Current European guidelines for management of arterial hypertension: Are they adequate for use in primary care? Modelling study based on the Norwegian HUNT 2 population. Petursson H, Getz L, Sigurdsson JA, Hetlevik I. *BMC Fam Pract* 2009;10:70.

III. Is the use of cholesterol in mortality risk algorithms in clinical guidelines valid? Ten years prospective data from the Norwegian HUNT 2 study. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TIL, Getz L. *J Eval Clin Pract* 2011;18:159-68.

IV. Body configuration as a predictor of mortality: Comparison of five different anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TIL, Getz L. *PLoS ONE* 2011;6:e26621.

1. INTRODUCTION

Cardiovascular diseases (CVD, see definition in the next paragraph), including supervision of risk factors with respect to prevention, have in recent decades become an increasingly important topic for general practice. These issues have also become prominent in public debate and health care policy. Recently a global campaign against non-communicable diseases (NCD) was initiated, aimed at CVD, diabetes, cancer, and chronic respiratory diseases. This campaign is led by the NCD Alliance (see: www.ncdalliance.org) and supported by numerous organisations, such as the United Nations and the World Health Organization (WHO) (NCD Alliance 2011). The aim of the alliance and the campaign is to reduce the burden of NCDs (including CVD) worldwide through various means. It is, perhaps, not strange that CVD receives enormous attention, since it is the number one cause of death worldwide, and a major cause of disability (NCD Alliance 2011). But besides being important to patients, populations at risk, health care systems, and governments, treatment and prevention of CVD are of huge interest to the pharmaceutical industry and various other commercial actors, for whom CVD prevention is a tremendously lucrative field. Thus, it is obvious that CVD prevention is a very important theme from many perspectives.

In this thesis the term *CVD* refers to atherosclerotic disease, where coronary heart disease (CHD) and cerebral stroke are the major components. Strategies to prevent CVD can be directed at either populations as a whole, such as restrictions of tobacco sales, or individuals, such as blood pressure (BP) lowering treatment (Rose 1985). Specific strategies of individual prevention are to a large extent, at least in the Western world, in the hands of the general practitioners (GPs). In recent years, there has been much emphasis on clinical practice guidelines to aid GPs in their preventive work and guide them to the most cost-effective management. This refers both to recommendations on therapeutic options as well as methods to identify those who would benefit the most from preventive treatment. These guidelines have the potential to provide important and updated information for clinicians and function as an instrument for quality improvement in clinical practice. However, various studies have

shown that GPs only follow the guidelines to a certain extent, and that recommended treatment goals are often not reached (Fretheim et al. 2006; Hetlevik et al. 1997 i and ii). Some authors have explained this in terms of physicians' inadequacy (Philips et al. 2001), whilst others have pointed out that at least part of the explanation is likely to lie in the nature of the guidelines as such (Getz et al. 2004 and 2005; Getz 2006; Hartz et al. 2005; Hetlevik 1999; Hetlevik et al. 2008; Lindman et al. 2007).

The quality and usefulness of clinical guidelines for prevention of CVD are of great importance to many, both on the level of individual health care and from the perspective of resource allocation. This thesis investigates the validity and relevance of guidelines for prevention of CVD, with a focus on primary prevention. The thesis' aim is **not** to study the epidemiological impact of individual risk factors on the development of CVD or the effect of specific therapeutic options. The focus is on how the guidelines function as working tools for GPs.

To fully comprehend the current guidelines and their recommendations (i.e., the current status of mainstream preventive medicine) it is crucial to appreciate the context in which they are developed. I will therefore begin with a short overview of the secular trends in CVD mortality, followed by a discussion of some of the major CVD risk factors in a historical perspective. Then before introducing the present study, I will focus on *evidence-based medicine* (EBM) and the guideline development processes. In the background section I will focus on the risk factors BP, cholesterol, and obesity because they are specifically addressed empirically in the present study. I will also discuss some important CVD risk factors that have received far less attention in the guidelines than the above-mentioned ones. After introducing the present study, I will discuss limitations to the guidelines' validity and relevance and reflect on potential ways forward, with the aim of improving future guidelines.

2. BACKGROUND

2.1. Secular trends in cardiovascular disease mortality

In the first half of the 20th century an "epidemic" of CVD was on the rise in the Western world. The incidence and mortality from CHD and stroke rose sharply in many Western countries, primarily among men (Lawlor et al. 2001). The age-standardised death rate from CHD among 35- to 74-year-old men in England and Wales increased from 150 per 100 000 persons in the 1920s to 500 in the 1960s when the incidence peak was reached (Lawlor et al. 2001; Mirzaei et al. 2009 and 2011). For both sexes combined, these numbers reached 700 per 100 000 in Finland; 600 in the US, Australia, and Scotland; and 350-400 in Norway, Sweden, and Denmark (Mirzaei et al. 2009). Quite understandably, a strong interest in CVD awoke, leading to, among other things, the establishment of major scientific projects.

A number of epidemiological studies were set up in the mid-20th century to identify causal and prognostic factors of CVD. The Framingham Heart Study (see: www.framinghamheartstudy.org), which was established in 1948, is the most renowned among these. Although the original study population included only 5 209 individuals in the town of Framingham, Massachusetts, it has become an important source of innovative knowledge in the field of CVD, including a series of highly influential publications (see: www.framinghamheartstudy.org/biblio/index.html). Surveys such as the Framingham Study led to the identification of various risk factors of CVD and marked the beginning of an era of primary preventive medicine. The focus on risk and prevention would further increase in the upcoming decades, with the introduction of a range of drugs for lowering risk factor levels, starting with antihypertensives and later followed by cholesterol-lowering drugs.

In the 1970s the CHD mortality rates began to fall in most Western countries (Lawlor et al. 2001; Mirzaei et al. 2009). The mortality from stroke, in fact, began to decrease even earlier (Mirzaei et al. 2011). This decrease has continued into the 21st century

(Scarborough et al. 2010; Scholte op Reimer et al. 2006). It is intriguing to note that the mortality from CVD began to fall before the introduction of effective medical interventions, and also that the decrease has subsequently been more dramatic than can be explained by progress in preventive and therapeutic medical treatment alone. The scale of the "epidemic" (or rather, pandemic) also varied tremendously across countries. The Mediterranean countries, for instance, maintained relatively low CVD mortality rates throughout the 20th century, while the mortality increased in the latter half of the century in many of the Eastern European countries, until the 1990s (Lawlor et al. 2001; Mirzaei et al. 2009 and 2011).

At the dawn of the 21st century, treatment of risk factors for CVD had become an established part of clinical practice, and a wide range of therapeutic agents (constantly increasing in number) was available for that purpose. With the introduction of *EBM* in the 1990s (Guyatt et al. 2008), an increasing emphasis was put on the development of *clinical practice guidelines* as decision aids for clinicians in their everyday practice of preventive medicine. These clinical guidelines are the main theme of this thesis. To gain a deeper understanding of the complexity of the guidelines, both their theoretical foundation and practical usefulness, one has to be familiar, with both the risk factors they incorporate and the process of guideline development.

2.2. Risk factors of cardiovascular disease

2.2.1. Blood pressure

When Stephen Hales, in 1733, became the first person to document BP measurement (Booth 1977) it must have been impossible to imagine the future consequences of his finding. For example, roughly two centuries later hardly anyone could be admitted to a hospital without having their BP measured – luckily, by means of dramatically different measurement methods. But advances have not only been made in the method of measuring BP. The understanding of this phenomenon has changed drastically; associations with diseases have been discovered as well as methods to control BP. High BP has gone from being an interesting physiological phenomenon to being a

complication of diseases and a risk factor, to being regarded as a disease – even a "silent killer" (Seedat 1981). This chapter offers a short overview of BP as a medical phenomenon in a historical perspective, leading to the recommendations of the current clinical guidelines.

Measuring blood pressure

In 1733 Stephen Hales inserted a brass pipe into the crural artery of a lying horse, attached it to a vertical glass tube, and watched the blood rise inside the tube to about 2.5 meters (Booth 1977). No significant improvement was made in the field until a century later when scientists, such as Poiseuille, developed easier methods for intra-arterial BP measurements. Though it was von Basch that invented the non-invasive *sphygmomanometer* in 1881, it was Scipione Riva-Rocci who made the first really practical version of it in 1896. The utility of the instrument was then increased in 1905 when Korotkoff introduced a way to identify both diastolic (DBP) and systolic blood pressure (SBP) by auscultation of the brachial artery distal to the arm-cuff (Booth 1977). Riva-Rocci's mercury sphygmomanometer, without any fundamental alterations, still holds its status as the gold standard for BP measurements, although the use of aneroid manometers and automatic oscillometers has become widespread (Moe et al. 2010).

Hazards of hypertension begin to reveal

Fundamental research in the field of BP was done late in the 19th century and at the dawn of the 20th century. Theories that high blood pressure was secondary only to arteriosclerosis, heart and kidney diseases were proposed. But with the efforts of scientists, such as Allbutt, Mahomed and Janeway, hypertension was identified in patients with no organ damage, and the term *essential hypertension* (hypertension without a [known] primary cause) was introduced (Esunge 1991; Sinclair 1969; Ventura et al. 2001). In 1914 Volhard and Fahr described and classified glomerular diseases in more detail than had previously been done. They identified hypertension associated with kidney diseases to have poor prognosis, while hypertensive patients without nephritis did better (Ventura et al. 2001). In 1928 Keith et al. proposed the term *malignant hypertension* for the clinical entity of very elevated BP with retinal damage,

papilloedema, hypertrophy of the heart, and affected kidneys (Keith et al. 1928; Ventura et al. 2001). The term was found to be appropriate because of the extremely high fatality – with life expectancy of less than one year if untreated (McMichael 1952).

Anti-hypertensive treatment

Salt restriction was first recommended for hypertensive patients in 1904 but induced very mixed response (not to mention the patients' adherence) in the following decades. Salt restriction gained some support in Europe in the 1920s and in USA in the 1940s (Esunge 1991; Moser 1997 and 2006; Piepho and Beal 2000; Ventura et al. 2001). In recent years it has achieved a fundamental status in BP-lowering treatment and individual CVD prevention, and has been discussed as a public health issue (mass strategy of CVD prevention) (Graham et al. 2007; Institute of Medicine 2010; Norheim et al. 2009; WHO 2007).

During the first half of the 20th century, no really effective and harmless BP-lowering treatments existed. Conservative treatment was recommended for "mild benign hypertension" with salt restriction, weight reduction, sedatives (such as phenobarbital and bromides), bed rest and avoidance of stress (Moser 2006; Piepho and Beal 2000). Further drug treatment was only recommended for malignant hypertension and BP above 200/100 mmHg. And the list of drugs used was not appealing, including, e.g., veratrum alkaloids, rauwolfia derivatives, thiocyanates, and ganglion blocking agents like hexamethonium (McMichael 1952; Moser 1997 and 2006; Piepho and Beal 2000; Ventura et al 2001). Few of the drugs were very effective, and they all had unacceptable side-effects' profiles. Even intravenous bacterial pyrogens were used to lower BP in the 1940s and 1950s (Ventura et al. 2001; McMichael 1952). Because of the lack of good drugs and because of the poor prognosis, surgical sympathectomy, introduced in the 1920s, became a much used treatment for malignant hypertension (Esunge 1991; Moser 1997 and 2006; Piepho and Beal 2000; Ventura et al. 2001).

The major breakthrough came in 1958 with the introduction of the diuretic chlorothiazide (Freis et al. 1958). For the first time, BP could be lowered considerably by means of a well-tolerated oral agent. With the addition of β-blockers in 1962 (Black

and Stephenson 1962; Prichard 1964; Prichard and Gillam 1964), the anti-hypertensive armamentarium again improved significantly.

Decades of dramatic changes

The 1960s and 1970s were times of turmoil, some great events and even paradigm shifts in the history of mankind – also in the field of BP. The thiazides and β-blockers changed BP-lowering treatment significantly, and treatment goals and indications were also about to change. In 1959 WHO defined BP below 140/90 mmHg as normal range and BP ≥160/95 mmHg as "abnormal (hypertensive) range" (WHO 1959:10). This seems to have been the first international definition on the matter, but no recommendations regarding treatment were given: "The values given are for statistical application to population studies and no significance for the individual person is implied" (WHO 1959:10). In the WHO report in 1962 on preventive aspects of hypertension and ischaemic heart disease (WHO 1962), the cut-off points remained unchanged but BP-lowering drug treatment was recommended if signs of organ damage (such as left ventricular hypertrophy) were identified. About hypertension without complications the report stated that inadequate evidence existed at the time to support that early treatment delayed the disease progress. Interestingly, it further states:

> The Committee feels [sic] that different factors may contribute to the hypertension at this stage. Thus in some patients nervous or emotional stress appears to be of major importance. (...) that what may be described as "common-sense psychotherapy" is the most effective treatment (...) Apart from sedation, treatment with drugs is usually unnecessary and ineffective (WHO 1962:11).

In 1961 data from the Framingham Heart Study for the first time identified hypertension as a strong risk factor for CHD (Kannel et al. 1961). This was one of the first papers from Framingham, a study which would in the following decades have huge impact on the field of cardiology. But other influential studies were on the horizon. In 1964 Hamilton et al. (Hamilton et al. 1964) published results from a placebo-controlled trial of BP-lowering treatment (including a thiazide) in symptomless patients with severe hypertension (DBP ≥110 mmHg) without signs of atherosclerosis or organ damage. The

treatment proved to have considerable effect reducing the incidence of stroke and other BP-related complications.

> The idea of recommending potentially life-long medical intervention to individuals who were free from both subjective symptoms and objective signs of organs damage when therapy is instituted, motivated by the presence of what could be considered *a disease risk factor only*, represents something completely new in medicine (Getz 2006:278).

Decades later this idea became the norm. Similar results from the "Veterans Study" were published in 1967-72 (Veterans Administration 1967, 1970 and 1972), showing the effect of BP-lowering treatment for symptomless patients with DBP ≥105 mmHg and less effect if DBP was in the range of 90-105 mmHg. As a result DBP became the focus of treatment. The American Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC), in their first report (JNC 1977) in 1977, as well as WHO in 1978 (WHO 1978), recommended drug treatment of DBP ≥105 mmHg. The definition of hypertension remained unchanged, but *borderline hypertension* was defined as BP in the range of 140/90-160/95 mmHg. Because of little evidence of effect, more conservative treatment was recommended for patients above 65 years of age, and SBP levels of 100 + age were regarded as "normal" (JNC 1977; Moser 1997 and 2006; WHO 1978).

Both JNC (JNC 1977) and WHO (WHO 1978) advocated opportunistic BP screenings in the general population, identification and follow-up of patients with diagnosed hypertension. However, WHO emphasised that "unless the existing health care system is able to cope with the identified hypertensive patients a programme of detection and follow-up should not be initiated" (WHO 1978:43). This statement is of interest in a larger context in this thesis. This consideration of practical applicability became less prevalent in later guidelines and recommendations on the matter.

Interestingly, the *feelings* of the consulting experts towards "common sense psychotherapy" seemed to have changed since 1962 (WHO 1962), as the report in 1978 stated:

> There is no definite evidence that behavioural procedures such as biofeedback, relaxation, psychotherapy, yoga, and transcendental meditation can lead to sustained lowering of blood pressure. (...) Prolonged adverse psychological and social factors have not been proved to contribute to blood pressure elevation (WHO 1978:41).

New drugs and new definitions

The last quarter of the 20th century brought many new drugs. Most notably were the angiotensin converting enzyme (ACE) inhibitors in the late 1970s (Ondetti et al. 1977), the calcium channel blockers in the 1980s (Moser 1997; Rosenthal 2004), and the angiotensin receptor blockers (ARB) in the 1990s (Goldberg et al. 1995). And many trials were conducted, that had implications for the standard treatment of BP, such as the SHEP study (SHEP Cooperative 1991) and the STOP-Hypertension trial (Dahlöf et al. 1991), which proved BP-lowering treatment to be beneficial in older patients.

In 1993 the definition of hypertension was lowered to 140/90 mmHg and, if persistent, regarded as an sufficient indication for drug treatment at all ages, both in the fifth JNC report (Moser 1997; Schillaci et al. 2009) and in the guidelines by a joint committee of the WHO and the International Society of Hypertension (ISH) (WHO 1993). However, WHO/ISH recommended conservative treatment and observation if BP was in the range of 140/90-160/95 mmHg if no other CVD risk factors were present. The upper cut-off was lowered to 150/95 mmHg in the 1999 WHO/ISH guidelines (WHO 1999) and the BP range 130/85-139/89 mmHg defined as *high normal*, <130/85 as *normal*, and <120/80 as *optimal*, as in the JNC 6 report in 1997 (JNC 1997).

In 2002, a meta-analysis (Prospective Studies 2002) of 61 studies, including almost one million participants in total, indicated that a continuous and graded association existed between blood pressure and mortality (in total as well as from CVD specifically) without a threshold level, at least down to BP of 115/75 mmHg. As a response the JNC in their seventh report (JNC 2003) defined a new concept - *prehypertension*. Prehypertension was defined as BP in the range of 120/80-139/89 mmHg and regarded a strong risk factor for hypertension – i.e., a risk factor of a risk factor of CVD. At that

time the recommended levels for initiating of BP-lowering drug treatment for patients with diabetes or signs of target organ damage were down to 130/85 mmHg (De Backer 2003; JNC 2003).

Risk stratification

As early as the 1970s algorithms for estimating CVD risk were designed on the basis of data from the Framingham study (Anderson et al. 1991). The idea, brilliant in nature, was to identify those at highest risk of CVD, who would benefit the most from preventive medical intervention. Instead of focusing on individual risk factors, estimating the combined effects of multiple factors was proposed to be more informative. This combined risk approach was in 1994 recommended by a joint European task force on prevention of CHD (Pyörala et al. 1994) and the simple four-level risk stratification chart in the 1999 WHO/ISH guidelines (WHO 1999) was based on the Framingham risk score. The combined risk approach has since become the standard for recommendations on managing CVD risk factors. European risk estimation charts were introduced with the SCORE Project (Conroy et al. 2003) in 2003, which have been recommended in the European guidelines (De Backer 2003; Graham et al. 2007; Mancia et al. 2007), while many national guidelines base their recommendations on risk calculators derived from local data (Hippisley-Cox et al. 2010; Norheim et al. 2009). In recent years most guidelines on management of hypertension and prevention of CVD have based the treatment recommendations on combined risk estimates, and the BP cut-offs have become less clear. Some guidelines recommend medical intervention at BP 140/90 mmHg and lower for high-risk individuals (Graham et al. 2007; JNC 2003; Mancia et al. 2007), while others are more conservative, recommending a cut-off of 160/100 mmHg in general and 140/90 mmHg for high-risk individuals (Norheim et al. 2009; WHO 2007). For further discussion of risk stratification algorithms see chapter 2.3.2.

Blood pressure, an important risk factor

When all debate on specific cut-off points is set aside, agreement is unanimous that high BP is an important risk factor for mortality and CVD. Persistently high arterial BP can accelerate atherogenesis (development of atherosclerosis) and cause excessive strain on

the cardiovascular system, leading to complications, such as left ventricular hypertrophy, nephrosclerosis, retinal haemorrhages, and strokes (Kaplan and Domino 2011). BP is associated with CVD and mortality in a log-linear fashion, with an increase in SBP of 20 mmHg roughly doubling the estimated relative risk of a fatal CVD event among 40-69 year olds (Prospective Studies 2002), and BP-lowering treatment has been shown to be effective in reducing morbidity and mortality (Kaplan and Domino 2011). However, the appropriateness of BP-lowering interventions, on the population level as well as the individual level, has to be evaluated in the context of the distribution of BP levels in the population.

Danaei and co-workers (Danaei et al. 2011) estimated the change in mean age-standardised SBP from 1980-2008 globally, combining data on 5.4 million study participants from 199 countries. In men this estimated global average decreased from 131 to 128 mmHg, and in women from 127 to 124 mmHg. In Western Europe the change in mean age-standardised SBP was estimated from ca. 138 to 132 mmHg in men and from ca. 134 to 123 mmHg in women (according to figures, detailed numbers not given) (Danaei et al. 2011). WHO estimated the world mean SBP (not age-standardised) in 2004 at 127 mmHg in men and 126 mmHg in women, and the prevalence of hypertension (SBP ≥140 mmHg) was estimated at 23% (WHO 2009). In Europe the estimated mean was 134 mmHg and the prevalence of hypertension 36%. In 2008 the estimated prevalence of hypertension (BP ≥140/90 mmHg) in Norway was 50% among men and 43% among women (WHO 2011 i). In the Norwegian HUNT studies the prevalence of hypertension decreased among men from 48% in 1995-97 (HUNT 2) to 34% in 2006-08 (HUNT 3), and among women from 38% to 26%, the same years (Krokstad og Knudtsen 2011). Thus, mean BP levels have been decreasing worldwide (although not in all regions) in recent decades, and the greatest decrease has been seen in high-income countries (Danaei et al. 2011).

2.2.2. Cholesterol

Anitschkow and the early works

The work of Nikolai Anitschkow in 1913 (Anitschkow and Chalatow 1983) might be considered the first major step towards identifying serum cholesterol as a risk factor for CVD. He fed rabbits with purified cholesterol and found that this diet induced vascular lesions comparable to human atherosclerosis. His research was most notably inspired by the works of Alexander Ignatowski (Ignatowski 1908), who suspected animal-derived proteins of being the harmful agent. Others (Windaus 1908) had previously identified cholesterol within human atherosclerotic plaques. Among them was Rudolf Virchow, who was the first to write a detailed review on atherosclerosis (Virchow 1856 and 1858).

The Norwegian professor of internal medicine, Carl Müller, published a paper in 1939, reviewing the literature on associations of hereditary xanthomatosis (familial hypercholesterolemia) with hypercholesterolemia and heart disease, adding his own observations from Norwegian cases (Müller 1939). His conclusion was that this hereditary disease caused xanthomatous deposits in the coronary arteries (i.e., atherosclerosis), as well as other parts of the body, resulting in myocardial ischemia, often at a young age. Since then studies involving patients with familial hypercholesterolemia have been important in the field of cholesterol research (Brown and Goldstein 1974 and 1976; Goldstein and Brown 1973 and 1977).

Epidemiology, eating habits, and an evolving theory

Cholesterol gained its status as a major risk factor for CVD in the 1960s with publications of several epidemiological studies (Dawber et al. 1957; Doyle et al. 1957; Kannel et al. 1961; Keys et al. 1963). The Framingham Heart Study is without a doubt the most renowned of these. A strong, continuous, and graded association was found between cholesterol and CHD events (Dawber et al. 1957; Doyle et al. 1957; Kannel et al. 1961). Since then, this relationship has been found in various studies, both regarding CHD events and CHD mortality (Anderson et al. 1987; Asia Pacific 2003; Chen et al. 1991; Clarke et al. 2009; Iso et al. 1994; Klag et al. 1993; Law et al. 1994; Neaton and

Wentworth 1992; Neaton et al. 1992; Njølstad et al. 1996; Prospective Studies 2007; Rose and Shipley 1986; Smith et al. 1992; Stamler et al. 1986 and 2000; Verschuren et al. 1995; Wannamethee et al. 1995; Wilson et al. 1998).

One of the early major epidemiological studies linking high cholesterol levels to CHD was The Seven Countries Study (1958-1970) (Keys 1980; Keys et al. 1984), led by Ancel Keys. One of the primary findings was that populations with high levels of serum cholesterol tend to have high mortality rates from CHD, compared to populations with lower cholesterol levels (Keys 1980; Keys et al. 1984). A second important finding of Keys and his colleagues was that serum cholesterol levels were proportional to the dietary saturated fat intake (Keys 1980), which, in fact, had been shown earlier (Keys et al. 1955; Keys 1957; Keys and Grande 1957; de Langen 1916 and 1922). Although Keys' results suggested a strong association of cholesterol with CHD, the study populations were heterogenous and the association was likely to be confounded by selection bias and other factors (Ravnskog 2000).

Many later (and earlier) observational studies, as well as clinical trials, have shown association of "Mediterranean diet" (low in saturated fats) with low levels of cholesterol and other biological risk factors and supported Keys' conclusions (Ehnholm et al. 1982; Giugliano et al. 2006; Hjermann et al. 1981; Kastorini et al. 2011; Leren 1968 and 1970; Mensink and Katan 1992; Rahilly-Tierney et al. 2011; Tortosa et al. 2007). The association of "Mediterranean diet" with lower mortality rates has also been confirmed in observational studies (Fung et al. 2009; Knoops et al. 2004; Martínez-González et al. 2011; Trichopoulou et al. 2003). Some trials involving secondary prevention of CVD have shown lifestyle changes, such as adopting "Mediterranean diet", to be associated with decreased mortality and coronary events rate compared to standard treatment (Ketola et al. 2000; King et al. 2007; Leren 1968 and 1970; de Lorgeril et al. 1999). The same has not been shown decisively to apply in primary prevention even though one Norwegian study indicated so (Hjermann et al. 1981). The most famous trial involving lifestyle intervention in primary prevention was the Multiple Risk Factor Intervention Trial (MRFIT) (Multiple Risk 1982), conducted in 1972-1978 in the USA. This was a study of primary prevention where over 350 000 men, aged 35-57 years, were screened

and 12 866 high-risk individuals were randomly assigned to either a control group, receiving the usual care in their community, or an intervention group, receiving thorough, protocol-based treatment for high blood pressure, counselling for smoking cessation, and dietary advice for cholesterol lowering (Multiple Risk 1982). Although a significant reduction in risk factors was achieved in the intervention group, compared to the controls in the six years of follow-up, only a small, non-significant reduction of CHD mortality was observed (17.9 deaths per 1 000 compared to 19.3 in the control group), and the difference was even smaller in all-cause mortality (Multiple Risk 1982). As a more recent example, an even bigger intervention trial, the Women's Health Initiative Randomized Controlled Dietary Modification Trial (Howard et al. 2006), also failed to show any benefit, regarding mortality, from dietary intervention. So, even though lifestyle interventions have been shown to affect serum cholesterol levels (Kastorini et al. 2011; Kelley et al. 2004 and 2011; Ketola et al. 2000), there are still limited or no data showing clinical benefit, regarding mortality or CVD events, from lifestyle interventions in primary prevention, as a recent Cochrane report shows (Ebrahim et al. 2011).

Sub-fractions of certain interest

The interest in sub-fractions of cholesterol came later. Low density lipoprotein (LDL) was found to have even stronger association with CHD and mortality than total cholesterol (Besterman 1957; Pekkanen et al. 1990; Williams and Feldman 2011; Wilson et al. 1980 and 1998). Today, LDL is most often regarded as the primary target of lipid lowering treatment (Graham et al. 2007; Mancia et al. 2007; National Cholesterol 2002; WHO 2007). On the other hand, high density lipoprotein (HDL) was found to have an inverse association with CHD (Asia Pacific 2005; Assmann et al. 1996; Barr et al. 1951; Castelli et al. 1986; Després et al. 2000; Emerging Risk 2009; Goldbourt et al. 1985; Gordon et al. 1989; Miller and Miller 1975; Pekkanen et al. 1990; Williams and Feldman 2011; Wilson et al. 1980 and 1998). Both LDL and HDL are today much used in the estimation of CVD risk on the individual level as well as in monitoring lipid lowering treatment (Graham et al. 2007; Mancia et al. 2007; National Cholesterol 2002; Norheim et al. 2009; WHO 2007). Much of the knowledge about these lipoproteins stems from the works of John Gofman (Gofman et al. 1949 and 1950;

Gofman 1956; Lindgren et al. 1951; Lyon et al. 1956). His work was followed by Goldstein and Brown, who were awarded with the Nobel Prize in Medicine in the year 1985 for their research on LDL and the pathogenesis of atherosclerosis (Brown and Goldstein and 1976; Goldstein and Brown 1973 and 1977), where data from patients with familial hypercholesterolemia played a crucial role.

The drugs

Further evidence to support the "cholesterol hypothesis" appeared in the 1970s and 1980s with some clinical drug studies (Carlson and Rosenhamer 1988; Dewar and Oliver 1971; Committee of Principal 1978; Frick et al. 1987; Manninen et al. 1988; Oliver 1984; WHO 1984). At that time, primarily three main groups of lipid-lowering drugs were shown to be effective and are currently still in use for CVD prevention. These are fibrates (e.g., clofibrate, gemfibrozil) (Abourbih et al. 2009; BIP Study 2000; Carlson and Rosenhamer 1988; Dewar and Oliver 1971; Committee of Principal 1978; Frick et al. 1987; Jun et al. 2010; Lalloyer and Staels 2010; Lee et al. 2011; Loomba and Arora 2010; Manninen et al. 1988; Rubins et al. 1999; Tenkanen et al. 2006; WHO 1984), nicotinic acid (niacin) (Altschul and Hoffer 1958; Birjmohun et al. 2005; Bruckert et al. 2010; Canner et al. 1986; O´Reilly et al. 1959; Parsons 1963), and bile acid sequestrants (also called resins, e.g., cholestyramine, cholestipol) (Lipid Research 1984 i and ii; Oliver 1984; Thompson 1971). All of these drugs can lower LDL. The resins are, however, less effective than fibrates and nicotinic acid in increasing HDL and can increase triglycerides, whereas fibrates and nicotinic acid lower them (National Cholesterol 2002). Drugs from all of these three groups have been shown to beneficially affect lipid-profile and reduce CHD events but decisive evidence of reduction in mortality is lacking (Abourbih et al. 2009; Altschul and Hoffer 1958; BIP Study 2000; Birjmohun et al. 2005; Bruckert et al. 2010; Canner et al. 1986; Carlson and Rosenhamer 1988; Costa et al. 2006; Frick et al. 1987; Jun et al. 2010; Lee et al. 2011; Loomba and Arora 2010; Manninen et al. 1988; Muldoon et al. 1990; O´Reilly et al. 1959; Parsons 1963; Rubins et al. 1999; Tenkanen et al. 2006; Thompson 1971; WHO 1984). Today, the primary use of these drugs in CVD prevention is in addition to statin drugs or instead of statins when they cannot be used.

The statin era

The "statin era" began in 1987 when lovastatin was the first statin drug to be marketed (Endo 2010). By then, the "lipid hypothesis" was generally accepted, but disagreement remained regarding treatment, since none of the available lipid-lowering drugs had shown clear reduction in mortality. The Scandinavian Simvastatin Survival Study (4S) (Scandinavian 1994) was a major breakthrough, both regarding further acceptance of the "lipid theory", and for lipid-lowering treatment. It showed not only considerably more reduction in total cholesterol and LDL than trials of earlier drugs but also reduction in coronary events, and, most importantly, significant reduction in all-cause mortality was demonstrated for the first time. The 4S study was a trial of secondary prevention in patients with clinical CHD and high cholesterol levels (5.5 – 8.0 mmol/L) (Scandinavian 1994). In 1995, a year later than publication of the 4S paper, Shepherd and co-workers (Shepherd et al. 1995) published their results from the West of Scotland Coronary Prevention Study (WOSCOPS). This was a trial of pravastatin in hypercholesterolemic (total cholesterol ≥ 6.5 mmol/L and LDL ≥ 4.5 mmol/L) men (supposedly) without evident CHD (5% had angina pectoris and 3% intermittent claudication); it also showed an impressive reduction in cholesterol and CHD outcomes as well as all-cause mortality (statistically non-significant) (Shepherd et al. 1995). These important results warranted the use of statins for primary prevention in "high-risk" patients.

In the years to come, results from a number of statin trials were published, steadily increasing their popularity as well as widening the criteria of eligibility for statin treatment. In 1996 Sacks and co-workers (Sacks et al. 1996) published the next important paper on statins, results from the Cholesterol and Recurrent Events (CARE) trial. They demonstrated the beneficial role of statin treatment in secondary prevention for patients with low or average levels of cholesterol (total cholesterol <6.2 mmol/L and LDL 3.0-4.5), as did the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (Long-term Intervention 1998) in 1998 (total cholesterol 4.0-7.0 mmol/L), and the Heart Protection Study (HPS) (Heart Protection 2000) in 2000 (total cholesterol >3.5 mmol/L). The HPS study is the largest statin trial conducted, with over 20 000 participants. The Air Force/Texas Coronary Atherosclerosis Prevention Study

(AFCAPS/TexCAPS) (Downs et al. 1998) demonstrated reduction of CVD events and mortality in primary prevention in individuals with average cholesterol levels but did not show reduction in all-cause mortality (Downs et al. 2001).

Further publications during the next decade further supported what was already evident, that statins were well tolerated and powerful lipid-lowering agents that reduced mortality significantly. Recent meta-analyses showed a relative risk reduction of about 20% in CVD mortality and about 10% risk reduction in all-cause mortality (Cholesterol Treatment 2010; Mills et al. 2011 ii), even in primary prevention (Mills et al. 2008; Taylor et al. 2011), although this has been a subject of debate (de Lorgeril et al. 2010; Ray et al. 2010; Therapeutics Initiative 2010). Trials have also indicated that higher doses give better clinical results (Mills et al. 2011 i), and supported the hypothesis that the lower the cholesterol, the better (Verschuren et al. 1995). Hence, the possible market for the product is gigantic, and it is no wonder that the pharmaceutical companies have made a fortune from selling statins. For instance, atorvastatin (brand name Lipitor) has been generating annual revenues of more than $10 billion each year since 2004, making it the best selling drug in history, and the only drug ever to achieve such sales (Jack 2009; Pfizer 2011).

The impressive results and good sales inspired pharmaceutical companies and their associates to conquer new markets. The study aims kept getting more aggressive with trials like the Atorvastatin Versus Revascularisation Treatments (AVERT) study (Pitt et al. 1999), which compared treatment with atorvastatin with angioplasty in stable CHD, and the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study (Schwartz et al. 2001), a trial of statin treatment in acute coronary syndrome. One study deserves special mention in this context, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (Ridker et al. 2008). The study included 17 802 healthy men (aged 50 or older) and women (aged 60 or older) with LDL levels below 3.4 mmol/L and high-sensitivity C-reactive protein (hs-CRP) levels of 2.0 mg/L or more. The participants were randomly assigned to being administered either rosuvastatin or a placebo; the planned length of follow-up was five years. There was a statistically significant reduction in CVD events

(HR: 0.53) and all-cause mortality (HR: 0.80) and the number needed to treat (NNT) for one year to avoid a clinical endpoint was 190. This study raised a number of serious concerns regarding ethical and methodological issues (de Lorgeril et al. 2010), a few of which will be mentioned. First, the name of the study clearly indicates an intention to justify the use of a drug in certain circumstances, rather than reducing the burden of CVD for individuals and society. Second, there are conflicts of interest. As with most pharmaceutical intervention trials, this one was supported by a drug company, AstraZeneca, the manufacturer of the drug (rosuvastatin). Additionally, 11 of the 14 authors reported having received fees from pharmaceutical companies, 10 of them from AstraZeneca. Third, the first author, Paul Ridker, is listed as a coinventor on patents licensed to AstraZeneca that relate to the use of hs-CRP in the evaluation of patients' risk of CVD. Fourth, the study was terminated early, with a median follow-up of 1.9 years (Ridker et al. 2008).

The financial ties and the early termination severely damage the credibility of the study (de Lorgeril et al. 2010). The question arises whether concern for patients and good research ethics took second place to eagerness to expand possible markets (including registered indications) of the drug and increase the use of hs-CRP in CVD risk estimation, even if neither would be cost-effective. Because of the early termination, valuable information was lost, and it cannot be taken as given that the results would have been the same if the five-year follow-up had been carried out. This was an especially poor decision since the standard care for the participants in the placebo group did not include statin treatment, since these were individuals at low CVD risk without raised cholesterol levels, and hence, they were not being denied life-saving treatment. Their alternative would have been no treatment at all (Graham et al. 2007; National Cholesterol 2002). In spite of its shortcomings the JUPITER study has greatly impacted the debate regarding CVD prevention (Fricker 2009; Hirschler 2008; Hlatky 2008; Kolata 2009; de Lorgeril et al. 2010; O'Keefe et al. 2009; Shishehbor and Hazen 2009) and has succeded in expanding the registered indications of rosuvastatin (U.S. Food and Drug 2010). The JUPITER study group has continued its work to justify statin use in primary prevention and published further sub-analyses, such as regarding the older participants (Glynn et al. 2010).

Even though some have touted statins as miracle drugs and compared their importance to that of penicillin (Roberts 1996), they have their drawbacks, and important adverse effects have emerged. The most common side-effects are myopathy and myalgia, and the most important one, although rare, is a more serious form of the same problem, rhabdomyolysis (Ballantyne et al. 2003; Pasternak et al. 2002; Silva et al. 2006). These adverse events have been shown to increase with larger statin doses (Silva et al. 2007), and in combination with certain other drugs (Gruer et al. 1999; Pasternak et al. 2002), most notably fibrates (Pierce et al. 1990, Ballantyne et al. 2003). In fact, in 2001 cerivastatin had to be withdrawn from the market because of this (Pasternak et al. 2002). An increase in the incidence of diabetes has also been shown to be associated with statin use (Preiss et al. 2011; Sattar et al. 2010).

Statins currently hold the position of the first-line lipid-lowering agents and are recommended for secondary CVD prevention as well as for primary prevention in individuals at high risk of CVD and elevated levels of cholesterol (Cooper et al. 2008; Graham et al. 2007; National Cholesterol 2002; Norheim et al. 2009; WHO 2007). However, they have not gained acceptance in primary prevention for individuals with low cholesterol levels or low combined CVD risk because of debatable effect (de Lorgeril et al. 2010; Peretta et al. 2010; Ray et al. 2010; Therapeutics Initiative 2010) and issues of cost-effectiveness (Taylor et al. 2011).

The end of the cholesterol controversy?

Although many have regarded the statins' effective mortality reduction as the ultimate proof of the “cholesterol hypothesis” (Steinberg 2004 v; Thompson 2009), opposing arguments have also been raised (see, for instance: www.THINCS.org). The classic belief that total cholesterol has a strong, graded association with CVD (Dawber et al. 1957; Doyle et al. 1957; Kannel et al. 1961) and mortality (Clarke et al. 2009; Stamler et al. 2000; Verschuren et al. 1995) without a threshold has been challenged. This association has primarily been shown regarding IHD, whereas many studies have reported no association of cholesterol with all-cause mortality (Chen et al. 1991; Jonsson et al. 1997; Krumholz et al. 1994; Neaton and Wentworth 1992; Neaton et al. 1992; Weverling-Rijnsburger et al. 1997), a “U-shaped association” (Harris et al. 1992;

Higgins and Keller 1992; Onder et al. 2003), or even an inverse one (Beaglehole et al. 1980; Forette et al. 1989; Iso et al. 1994; Kozarevic et al. 1981; Petersen et al. 2010; Schatz et al. 2001; Tuikkala et al. 2010). This has been explained by the inverse or U-shaped association often found between cholesterol and non-CVD death, such as from cancer (Ibarren et al. 1995; Jacobs et al. 1992; Ravnskog 2003; Rossouw and Gotto 1993). The phrase "U-shaped association" (or alternatively "J-shaped" (Forette et al. 1989)) means that higher mortality (or incidence) is seen in individuals with both low levels and high levels of cholesterol, compared to those in between. This phrase does not necessarily indicate that both arms of the 'U' are equal in terms of mortality rates or the proportion of the population belonging to each arm. An inverse or U-shaped association has also been described between cholesterol and CVD mortality, as well as a lack of association (Anderson et al. 1987; Forette et al. 1982; Lindquist et al. 2002; Nissinen et al. 1989; Petersen et al. 2010; Tsuji 2011; Weverling-Rijnsburger et al. 1997). This has been explained by the association with death from stroke. Positive association has been found with ischaemic stroke, but inverse or no association with haemorrhagic stroke (Asia Pacific 2003; Cui et al. 2007; Eastern Stroke 1998; Iso et al. 1989; Li et al. 2008; O´Donnell et al. 2010; Prospective Studies 1995 and 2007; Tsuji 2011). Interestingly, some studies have also found a U-shaped (Okamura et al. 2007; Petersen et al. 2010; Shestov et al. 1993; Simons et al. 2001; Weijenberg et al. 1994 and 1996) or an inverse (Krumholz et al. 1994; Räihä et al. 1997; Tsuji 2011) association with IHD incidence and mortality, primarily among individuals over 60.

The fact that statins are the only lipid-lowering treatment shown to reduce mortality (Bruckert et al. 2010; Cholesterol Treatment 2010; Ebrahim et al. 2011; Lee et al. 2011; Mills et al. 2008 and 2011 ii; Muldoon et al. 1990; Taylor et al. 2011) is another counterargument to the "lipid hypothesis". The most recent example is the drug ezetimibe, which is an effective lipid-lowering agent without proven mortality reduction (Tenenbaum and Fishman 2010). Also, statins have been shown to reduce mortality more than the lipid effects would suggest (Gould et al. 1998), compared to observational data (Verschuren et al. 1995). A range of non lipid-related, pleiotropic effects of statins has been documented (Meng 2005; Vaughan et al. 1996). Statins have anti-inflammatory effects (Meng 2005; Vaughan et al. 1996) and reduce blood

concentrations of inflammatory markers such as CRP (Libby et al. 2002; Ridker et al. 1999). They inhibit smooth muscle cell proliferation (Rodríguez-Vita et al. 2008; Vaughan et al. 1996), affect platelet function (Schrör et al. 1989; Tsai et al. 2011; Vaughan et al. 1996), and reduce the adhesion of monocytes to endothelial cells (Meng 2005; Teupser et al. 2001; Vaughan et al. 1996). All of these mechanisms are important in the pathogenesis of atherosclerosis (Meng 2005; Ross 1999; Vaughan et al. 1996).

Alternative lipid measures have been suggested to be better markers of risk than total cholesterol, which might indicate different atherogenic properties of different particles (Miller et al. 2011; Packard 2003; Triglyceride Coronary 2010; Welin et al. 1992). As mentioned above, LDL is the lipid measure most often recommended, along with total cholesterol, to be used for CVD risk estimation and for defining treatment goals (Graham et al. 2007; National Cholesterol 2002; Norheim et al. 2009; WHO 2007). HDL and the total cholesterol/HDL ratio are often recommended for estimation of risk but rarely as treatment goals (Graham et al. 2007; National Cholesterol 2002; Norheim et al. 2009; WHO 2007). The value of triglycerides as a risk factor has been debated for more than half a century (Kannel and Vasan 2009), and it has been associated with increased risk of CHD (Asia Pacific 2004; Harchaoui et al. 2009; Mora et al. 2008; Sarwar et al. 2007) and all-cause mortality (Langsted et al. 2011). Guidelines often recommend triglycerides be included in CVD risk estimation but recommendation of treatment goals are often lacking (Graham et al. 2007; National Cholesterol 2002; Norheim et al. 2009; WHO 2007). More recently the apolipoproteins A1 (ApoA1) (O'Brien et al. 1995) and B (ApoB) (Sniderman et al. 2003), as well as the ApoB/ApoA1 ratio, have been recommended to replace the conventional measures of total cholesterol, LDL, and HDL (Ip et al. 2009; McQueen et al. 2008; Sniderman et al. 2011; Walldius et al. 2001; Yusuf et al. 2004). ApoA1 is a sub-fraction of HDL, whereas ApoB is primarily a sub-fraction of LDL (Walldius et al. 2001). These markers have, however, not been found to yield enough additional information to the conventional markers to justify the additional cost (Brunzell et al. 2008; Ingelsson et al. 2007; Mora 2009; van der Steeg et al. 2007), and guideline authors (Graham et al. 2007; National Cholesterol 2002; Norheim et al. 2009; WHO 2007) have been reluctant to

include them in their recommendations. Thus, it is apparent that the field of cholesterol is still a much debated theme of constantly progressing evidence.

For decades there has been an ongoing debate on cholesterol and its importance in CVD, and this discussion between scholars has not always been civilised (Steinberg 2004 i-v). The current mainstream view is that cholesterol is an important risk factor for CVD with a strong and graded association and should be lowered in high-risk individuals. Because of research led by the pharmaceutical industry (Long-term Intervention 1998; Ridker et al. 2008; Scandinavian 1994; Sacks et al. 1996; Shepherd et al. 1995), there has been a trend toward widening the definition of "high-risk". Fortunately, those striving to point out flaws in the mainstream opinion are still to be found (see, for instance: www.THINCS.org). The current focus of the debate is in whom cholesterol should be lowered by drug treatment, by how much, and at what cost.

Despite all "Cholesterol controversy" (Steinberg 2004 i; Unknown 1962) it cannot be denied that it plays a crucial role in the pathogenesis of atherosclerosis. Russell Ross wrote an excellent paper on the matter (Ross 1999), reviewing the evidence for the currently most widely accepted hypothesis of the pathogenesis of atherosclerosis. In short, it is believed that the process starts with injury of some sort to the endothelium (caused, e.g., by hyperglycaemia, high blood pressure, infection, etc.), causing endothelial dysfunction or denudation leading to an inflammatory response. Endothelial adhesiveness to leukocytes and platelets increases, as well as permeability of the endothelium. LDL undergoes oxidative modification and stimulates further inflammatory response as it gets trapped in the arterial wall. Macrophages gather the LDL and become "foam cells", and smooth muscle cells undergo proliferation and migration in response to inflammatory cytokines. A soup of hydrolytic enzymes, cytokines, chemokines, and further influx of LDL and mononuclear cells gradually becomes a necrotic lipid core of the atherosclerotic lesion, surrounded by a "fibrous cap" of smooth muscle cells and fibrous tissue. This process also makes the endothelium pro-thrombotic. This can lead to arterial stenosis and atherothrombosis. This is a very simplified explanation of this hypothesis (Ross 1999).

Whether unmodified LDL can cause the initial endothelial injury (making it a primary causal factor of atherosclerosis) or not (making it dependent on other causal factors of endothelial injury), it is clear that LDL is an important factor in the process of atherosclerosis. This association, however, is complex and needs further clarification. At least it is plausible that the view and the emphasis on cholesterol as a risk factor for CVD will change in the coming decades.

2.2.3. Obesity and body configuration

Obesity is an established risk factor for a range of diseases, such as CVD, type-2 diabetes, and osteoarthritis (Kulie et al. 2011; WHO 2000). This is thoroughly documented in the medical literature as well as regarded as common lay knowledge (American Heart 2011; International Association 2011; WHO 2000). The harmfulness of obesity has been increasingly emphasised in the past few decades alongside the rise of the "obesity epidemic" (James 2004). But in the mind of today's general public, fatness has not only been associated with detrimental effects on health but also unaesthetic qualities (Kwan 2009), and even poor personality properties (Rosengren and Lissner 2008). However, it has not always been thus, as the famous Venus von Willendorf (Naturhistorisches museum 2011; Witcombe 2011) and various paintings from the Renaissance (Woodhouse 2008) bear witness. Throughout history corpulence has, in various cultures, been associated with wealth, fertility, and general prosperity (Woodhouse 2008), especially in times of shortage. This view has changed in current period of bounty in many parts of the world.

This chapter will discuss obesity and body configuration in relation to CVD. It will focus on the definition and measurement of obesity, and the importance of the distribution of body fat.

The obesity epidemic

In the twentieth century, and especially after the Second World War, general living conditions improved dramatically throughout the Western world. A more sedentary lifestyle, combined with the abundance of affordable food available to the general

public, led to the rise of a health problem, previously of low prevalence – "the obesity epidemic" (James 2004). Of course, this happened gradually, with the support of the fast-food culture, television, video games, and carbonated beverages, to name a few aggravating factors, and it was not until 1997 that the WHO defined obesity as a global epidemic (i.e., pandemic) (Caballero 2007; WHO 2000).

The worldwide prevalence of adult obesity (body mass index [BMI] ≥30 kg/m^2) has almost doubled in the last three decades, with an estimated number of 500 million obese individuals in 2008 (WHO 2011 ii). Finucane et al. (Finucane et al. 2011) estimated that the age-standardised prevalence of obesity increased among men from 4.8% in 1980 to 9.8% in 2008, with an age-standardised global average increase in BMI of 0.4 kg/m^2 per decade. Among women the estimated average BMI increase was 0.5 kg/m^2 per decade, with an age-standardised worldwide increase in prevalence of obesity from 7.9% in 1980 to 13.8% in 2008. The global age-standardised mean BMI in 2008 was estimated to be 23.8 kg/m^2 for men and 24.1 kg/m^2 for women. The largest rise in BMI was seen in Oceania for both sexes, and the highest age-standardised average BMI (>28 kg/m^2) was seen in North America among men, and among women in North America, north Africa and Middle East, and southern Africa (Finucane et al. 2011). In the Norwegian HUNT studies (1985-2008) the average BMI (not age-standardised) has increased among men from 25.3 kg/m^2 (HUNT 1) to 27.5 kg/m^2 (HUNT 3), and among women from 25.1 kg/m^2 to 26.9 kg/m^2 (Krokstad and Knudtsen 2011). In 2008 the prevalence of obesity (not age-standardised) was estimated 23% in men and 20% in women in Norway (WHO 2011 i).

The Quetelet Index

The currently most common measure of obesity, the Quetelet index, better known as the BMI, was first described in 1832, by the Belgian statistician Adolphe Quételet (Eknoyan 2008). In his search for a measure to describe the weight of the "average person" in a population adjusted for the height, he found the ratio of weight (kg) divided by the height (m) squared (kg/m^2) to be the most appropriate. He did not, however, show any special interest in identifying those who were over- or underweight, and his

index did not achieve status in clinical practice until more than a hundred years later (Eknoyan 2008).

Although the association of obesity with some of its complications had already been documented in the 18th and 19th century (Bray 2009), the increased mortality risk was first acknowledged early in the 20th century by insurance companies, which derived the "ideal weight" for a given height from their actuarial tables (Association of Life 1912). It was not until the 1970s that the use of the Quetelet index became widespread. In 1972, Ancel Keys and coworkers showed the Quetelet index to be better correlated with body fat (defined by skinfold thickness) than the various other widely used anthropometric measures derived from height and weight, such as the simple weight to height ratio and the ponderal index (cube root of weight divided by height) (Keys et al. 1972). Keys et al. suggested the Quetelet index be called *body mass index*. And that it be used as the primary anthropometric measure of body configuration and obesity.

In 1985, the US National Institutes of Health (NIH) defined obesity by the 85th percentile of BMI for each sex (derived from a study population, aged 20-29), 27.8 kg/m^2 for men and 27.3 for women (National Institutes 1985). Doctors were urged to use these cut-offs as warning signals for patients at high risk for obesity-related complications. The following decade various organisations published similar recommendations, some including age-specific cut-offs since body weight tends to increase with age (Committee on Diet 1989; Kuczmarski and Flegal 2000). After a WHO consultation meeting in 1997, the WHO published (in 2000) revised cut-offs and recommendations made by the International Obesity Task Force (WHO 2000). These were the cut-offs currently in use. For both sexes underweight was defined as BMI <18.5 kg/m^2, normal weight as 18.5-24.9, overweight as 25.0-29.9, and obesity as ≥ 30.0 (WHO 2000). Although the new recommendations offered some simplicity, compared to earlier methods, with the same cut-offs for both sexes at all ages and easier to remember numbers, it might be seen as problematic that this consensus increased dramatically the number of individuals defined as being overweight. It is also known that the International Obesity Task Force received generous financial support from the pharmaceutical industry (Moynihan 2006).

The BMI is currently the most frequently used marker of body composition and obesity worldwide. This is true in research as well as clinical practice, and use of the index has also become widespread among the general public, fitness trainers, and dietitians. The index is easy to obtain and use, and rather simple to understand, although most people will require a calculator to divide by the squared height. Generally thought to be a good marker of adiposity, BMI has been found to be more strongly correlated with body fat percentage than most other anthropometric measures (Shiwaku et al. 2005), although some studies have not found it to be superior to waist circumference (Flegal et al. 2009). But the index has its drawbacks. One limitation to the official WHO cut-offs is ethnic difference. For a given BMI value, the fat percentage has been shown to vary with ethnicity (Chang et al. 2003; Deurenberg et al. 1998 and 2002; Deurenberg-Yap 2002; Gurrici et al. 1998 and 1999; Ko et al. 2001; Misra et al. 2005), as well as the association with patient-important outcomes (Deurenberg-Yap 2002; Misra et al. 2005). Another limitation to the use of BMI is that it can wrongly define lean, muscular individuals as being overweight. The BMI does not take body configuration and fat distribution into account. Perhaps the most important limitation to the use of BMI is related to this fact. The BMI is more weakly associated with mortality, both overall (Lindqvist et al. 2006; Pischon et al. 2008; Price et al. 2006; Schneider et al. 2010; Taylor et al. 2010) and regarding CVD specifically (Price et al. 2006; Yusuf et al. 2005; Schneider et al. 2010), than the anthropometric measures of obesity discussed below: waist circumference (Pischon et al. 2008; Schneider et al. 2010; Taylor et al. 2010; Yusuf et al. 2005), waist-to-hip ratio (WHR) (Lindqvist et al. 2006; Pischon et al. 2008; Price et al. 2006; Schneider et al. 2010; Taylor et al. 2010; Yusuf et al. 2005), and waist-to-height ratio (WHtR) (Schneider et al. 2010; Yusuf et al. 2005; Taylor et al. 2010). Partly, this is because the BMI has a J-shaped association with mortality (Flegal et al. 2007; Waaler 1988), and the lowest mortality rates are usually found in the range of 23.5-25 kg/m^2 (Berrington de Gonzalez et al. 2010; Canoy et al. 2007; Lindqvist et al. 2006; Orpana et al. 2009; Pischon et al. 2008). In addition, a meta-analysis from 2008 found BMI to have weaker associations with diabetes, hypertension, and dyslipidaemia than the other measures although the difference was small (Lee et al. 2008).

Android and gynoid obesity

In the 1940s Frenchman Jean Vague began writing about what he called "android and gynoid obesity" (Vague 1947 and 1956). From his studies and those of others he concluded that central or abdominal accumulation of fat (android obesity) was associated with atherosclerosis, diabetes mellitus, gout, and urolithiasis, while fat located on the lower part of the body, the hips and thighs (gynoid fat distribution), was not (Vague 1956). He attributed this to a complex (not fully understood) interaction of neural, hormonal, and metabolic factors, including hypothalamo-pituitary-adrenal (HPA) axis activity and difference in metabolic activity of fat depending on its anatomical location (Vague 1956). Decades later, this complex interaction and its complications became known as "the metabolic syndrome" (Reaven 1988).

Waist circumference has by many been regarded as superior to BMI because of better correlation with the metabolically unfavourable android fat distribution (Huxley et al. 2010). Numerous studies have also shown this simple measure to have stronger association with mortality (Pischon et al. 2008; Schneider et al. 2010; Taylor et al. 2010) and CVD than BMI (Asia Pacific 2006; Gelber et al. 2008; Oliveira et al. 2010; Page et al. 2009; Schneider et al. 2010; Taylor et al. 2010; Yusuf et al. 2005). Although BMI still holds its place as the primary marker of obesity, guidelines often recommend waist circumference to be used in addition to BMI, with the cut-off points for obesity at 102 cm for men and 88 cm for women (Graham et al. 2007; JNC 2003; Mancia et al. 2007; Norheim et al. 2009; WHO 2000) – European derived cut-offs.

Hip, hip, hurrah!

WHR (waist circumference divided by hip circumference) was first reported in 1984 in the Swedish Gothenburg population studies (Lapidus et al. 1984; Larsson et al. 1984). Numerous studies have since shown WHR to have stronger association with mortality than both BMI (Bengtsson et al. 2009; Canoy et al. 2007; Lindqvist et al. 2006; Pischon et al. 2008; Price et al. 2006; Schneider et al. 2010; Taylor et al. 2010; Yusuf et al. 2005) and waist circumference (Canoy et al. 2007; Price et al. 2006; Yusuf et al. 2005). This has been shown for mortality in total (Lapidus et al. 1984; Larsson et al. 1984; Lindqvist et al. 2006; Pischon et al. 2008; Price et al. 2006; Schneider et al. 2010;

Taylor et al. 2010) as well as from CVD in particular (Canoy et al. 2007; Price et al. 2006; Schneider et al. 2010; Yusuf et al. 2005). For the followers of Vague's hypotheses (Vague 1956), this comes as no surprise since WHR is better suited to identifying android and gynoid obesity than waist circumference alone, not to mention BMI. In fact, when adjusting for the waist circumference, increasing hip or thigh circumference has even been found to be inversely associated with mortality – i.e., to be protective (Bigaard et al. 2004; Canoy et al. 2007; Heitmann et al. 2004; Heitmann and Frederiksen 2009; Lissner et al. 2001; Yusuf et al. 2005; Zhang et al. 2008)! Despite this, WHR has gained far less popularity than BMI and waist circumference, and its use is rarely recommended in clinical guidelines. The usual WHR cut-offs defining obesity are ≥0.90 (or ≥0.95) for men and ≥0.80 for women (Misra et al. 2005; WHO 2011 ii).

Another ratio useful for identifying obesity was reported in 1995, the WHtR (waist circumference divided by height) (Hsieh and Yoshinaga 1995). Various studies indicated WHtR to be a superior predictor of mortality and CVD than both BMI (Ashwell and Hsieh 2005; Page et al. 2009) and waist circumference, and similar (Gelber et al. 2008; Taylor et al. 2010; Yusuf et al. 2005) or superior (Schneider et al. 2010) to WHR. WHtR offers the benefit of taking height into account but does not discriminate android from gynoid obesity as well as WHR. No consensus on how to define obesity with WHtR has been reached, but the cut-off point of 0.50 has been suggested (Ashwell and Hsieh 2005). To my knowledge, no guidelines have recommended the use of this measure.

Other methods available

In addition to the anthropometric measures mentioned above, there is a range of available methods to estimate adiposity that will not be discussed in detail. Some of these measures are used practically only for research, such as magnetic resonance imaging (MRI) (Heymsfeld 2008), while others have been applied in clinical practice to some degree, such as measuring skinfold thickness (Oliveira et al. 2010). Although some of these methods yield more precise estimates of fat percentage or total body fat volume than the measures mentioned above, they rarely offer better predictive abilities

regarding patient-important outcomes (Menke et al. 2007; Simpson et al. 2007; Stevens et al. 2008; Sun et al. 2010).

The apple and the pear

The difference between apples and pears is not confined to the taste alone. Likewise, the difference between apple (android) and pear (gynoid) body shapes lies not only in their aesthetic qualities. The apple shape refers to abdominal subcutaneous and visceral fat accumulation while subcutaneous fat on the hips, thighs, and buttocks result in the pear form. It has become clear that metabolic activity of adipose tissue differs depending on its localisation (Després et al. 1990; Manolopoulos et al. 2010; Perrini et al. 2008; Shively et al. 2009; Snijder et al. 2006), and where it accumulates, again, is dependent on a number of hormonal and metabolic factors (Björntorp 1990; Després et al. 1990; Epel et al. 2000; Jayo et al. 1993; Kyrou and Tsigos 2009; Manolopoulos et al. 2010; Moyer et al. 1994; Müssig et al. 2010; Shively et al. 2009; Snijder et al. 2006).

Compared with subcutaneous fat, visceral adipose tissue is more sensitive to lipolytic stimuli and less sensitive to anti-lipolytic stimuli, such as insulin (Björntorp 1990; Després et al. 1990; Krotkiewski et al. 1983; Manolopoulos et al. 2010; Perrini et al. 2008; Snijder et al. 2006). Visceral fat is, therefore, more likely to cause increased levels of free fatty acids in the circulation (Björntorp 1990; Després et al. 1990; Krotkiewski et al. 1983; Manolopoulos et al. 2010). In particular visceral fat affects the liver because of increased fatty acids in portal circulation, which, e.g., inhibits hepatic insulin uptake, leading to hyperinsulinaemia (Björntorp 1990). Removal of visceral fat has also been shown to have more beneficial effect on insulin resistance and glucose intolerance than removal of subcutaneous fat, both in experimental animals (Barzilai et al. 1999; Gabriely et al. 2002) and (less documented) in humans (Thörne et al. 2002). A difference has also been suggested between deep and superficial abdominal subcutaneous adipose tissue (divided by *fascia Camper*) – the deep adipocytes being more lipolytic and more strongly associated with insulin resistance (Kelley et al. 2000; Monzon et al. 2002). Likewise, gluteofemoral adipose tissue is less lipolytic than subcutaneous abdominal fat, and better suited for lipid storage without increasing levels of free fatty acids (Björntorp 1990; Manolopoulos et al. 2010). Regional differences

also exist in the secretion of cytokines involved in, e.g., inflammation and development of insulin resistance (Manolopoulos 2010; Perrini et al. 2008).

Glucocorticoids, glucocorticoid receptor concentration, and HPA activity play a crucial role in insulin resistance as well as explaining some of the regional difference in adipose tissue metabolic activity (Björntorp 1997; Després et al. 1990; Manolopoulos et al. 2010). Insulin resistance and high levels of circulating free fatty acids increase ectopic fat storage (*lipotoxicity*), i.e., accumulation of fat in the liver, muscles and other organs, which in turn promotes further insulin resistance (McGarry 2002; Snijder et al. 2006).

Various factors affect the localisation of fat accumulation. These factors include hormones (glucocorticoids, sex hormones, growth hormone) (Després et al. 1990; Jayo et al. 1993; Kyrou and Tsigos 2009; Manolopoulos et al. 2010; Moyer et al. 1994; Müssig et al. 2010; Shively et al. 2009), behaviour (smoking, diet, physical activity) (Björntorp 1990 and 1997; Jayo et al. 1993), demographic factors (sex, age, ethnicity) (Cozier et al. 2009; Gurrici et al. 1998; Krotkiewski et al. 1983; Misra et al. 2005), and autonomic nervous system function (and dysfunction) (Cozieret al. 2009; Kyrou and Tsigos 2009; Müssig et al. 2010). The details will not be discussed here. Many of these factors affect metabolism and disease risk through other mechanisms. In these ways obesity and body configuration become surrogate markers for a range of risk factors.

Defining obesity

Defining obesity is a multifactorial challenge. First, the phenomenon itself has to be defined clearly, and then the most appropriate measure has to be identified. The Merriam-Webster dictionary defines obesity as "a condition characterized by the excessive accumulation and storage of fat in the body" (Obesity 2011), and WHO states: "Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health" (WHO 2011 ii). However, WHO has a second definition of obesity as BMI $\geq$30 kg/m^2 (WHO 2000 and 2011 ii). Relying on these definitions, the BMI seems to be a suitable and easily applicable measure, arguably a better measure of body fat percentage than the other anthropometric measures mentioned above.

Alternatively, the definition of obesity could emphasise the hazardous effects on health instead of merely suggesting the possibility, as the WHO definition does (WHO 2011ii). This kind of a definition would emphasise patient-important outcomes, such as mortality and obesity-related metabolic disorder. Measures of central adiposity and body configuration (waist circumference, WHR, and WHtR) would be better suited than BMI in that case.

A third option would be to define body configuration as a more important risk factor than "obesity" (meaning body-fat percentage). In any case, considering the physiology of different types of adiposity as well as data on mortality associations, it seems reasonable to recommend measures of body configuration (WHR and WHtR) to be used in clinical practice instead of BMI, at least when evaluating mortality and CVD risk. However, because of its strong status and widespread use, the BMI will not be easily abandoned. The limitations to the "new" anthropometric measures also have to be taken into account and compared to the advantage of adopting them. Some people might find it uncomfortable and stigmatising to have the measuring tape wrapped around their belly and buttocks. It might be seen as more intrusive than measuring height and stepping on a weighing scale – having to undress further adds to the vulnerability. It has also been pointed out that waist and hip circumferences are subject to more measurement error than BMI (Sebo et al. 2008). This problem can be addressed by adhereing to standardised measurement procedures (WHO 2011 ii) and adequate training (Sebo et al. 2008).

When defining cut-offs, gender and ethnic difference has to be taken into account. Such differences exist for all of the anthropometric measures discussed above, whether the reference point is fat percentage or mortality (Chang et al. 2003; Deurenberg et al. 1998 and 2002; Deurenberg-Yap et al. 2002; Gurrici et al. 1998 and 1999; Jackson et al. 2002; Ko et al. 2001; Misra et al. 2005; Yusuf et al. 2005). In part, this difference can be explained by ethnic variance in muscularity and skeletal structure (Deurenberg et al. 1998 and 2002; Gurrici et al. 1999; Jackson et al. 2002). Recommended threshold levels are primarily based on data from people of European origin but some suggestions for

ethnic-specific cut-off points have been made (Chang et al. 2003; Deurenberg-Yap et al. 2002; Gurrici et al. 1998; Ko et al. 2001; Misra et al. 2005).

2.2.4. Other physical and psychosocial risk factors

A whole range of risk factors have been associated with CVD, and their number is constantly growing. Age is by far the strongest known risk factor of CVD, and very few other factors add any substantial information to a prediction model already including age (Wald and Law 2003). Male sex (Lawlor et al. 2001), smoking (Dawber et al. 1959; Huxley 2011; Yusuf et al. 2004), diabetes mellitus (Wilson 2011; Yusuf et al. 2004), and a family history of CVD at a young age (Andresdottir et al. 2002; Wilson 2011) are the risk factors generally considered the most important, in addition to those mentioned in sections 2.2.1-2.2.3. Physical inactivity (Yusuf et al. 2004), diet (Dauchet et al. 2005; Yusuf et al. 2004), ethnicity (Cooper 2001), some infectious agents (Anderson 2011), various genes (Lovely et al. 2011; Rosenson and de Ferranti 2011), and (systemic) inflammation (Koenig et al. 1999; Libby and Crea 2010; Ridker et al. 1998) are also among the factors associated with increased risk of CVD. Guidelines mention these factors to various degrees. Detailed discussion of them is outside the scope of this thesis, but it is worth bearing in mind that the identified risk factors are numerous, and the importance of each of them is understood only to a certain extent. The development of atherosclerosis and CVD is a complex phenomenon that can only be predicted to a small degree, even with information on all of these factors.

The common denominator of the risk factors already mentioned is that they can be *measured* in some way without any *personal subjective interpretation*. They therefore fit well into the Cartesian tradition of biomedicine. There are, however, other risk factors that may not be as easily quantified and have been included in the CVD guidelines to a much less extent. These include psychosocial factors, such as adverse childhood experiences, harsh working conditions, experiences of trauma, and detrimental social relations (Getz et al. 2011; Kirkengen et al. 2008).

The social gradient

In 1967 the Whitehall Study was established. In the study, led by Donald Reid and Geoffrey Rose, 17 530 civil servants in London, all male, were classified according to their employment grade, and their mortality was recorded prospectively over 10 years (Marmot et al. 1984). The main findings of the study were that mortality from CHD increased with lower employment status, in a gradient manner. Numerous studies have subsequently confirmed these results, finding a graded association between low socio-economic status (SES) and high CVD mortality (Alboni et al. 2003; Jeemon and Reddy 2010; Marmot et al. 2008). This can be partly explained by the relations between unhealthy lifestyle (smoking, fast food diet, etc.) and lower SES (Marmot et al. 1984 and 2008), which, in turn, affects physiological risk factors, such as BP. But even after adjusting for other risk factors, these socio-economic inequalities cannot be fully accounted for (Jeemon and Reddy 2010; Marmot et al. 1984 and 2008). In the Whitehall Study, for instance, the CHD mortality in the group with the lowest employment status was twice as high as in the group with the highest status after adjusting for other risk factors (Marmot et al. 1984).

In 1985 a second study of London civil servants was initiated, the Whitehall II Study (see: www.ucl.ac.uk/whitehallII), including roughly 10 000 men and women (Marmot and Brunner 2004). The study was led by Michael Marmot. The main findings were that high job strain and low perceived control at work increased the risk of CHD, as did demand-reward imbalance, poor support and weak social network (Ferrie 2004). Multiple studies have since then confirmed the importance of mental stress (in a wide sense), both acute (Guðjónsdóttir et al. 2011; Wilbert-Lampen et al. 2010) and chronic (Proietti et al. 2011; Rosengren et al. 2004; Tofler 2011), unpredictability (De Vogli et al. 2007; Surtees et al. 2007), and social relations (Holt-Lunstad et al. 2010), in the risk of CVD.

Allostasis and allostatic load

To fully appreciate how stress and other psychosocial factors influence the development of CVD, one has to seek explanations within the field of stress research and *psycho-neuro-immunology*. *Allostasis* and *allostatic load* are useful terms in this regard (Epel

2009; McEwen 1998 i and ii; Sterling and Eyer 1988). Allostasis, coming from Greek, meaning "stability through change" (McEwen 1998 i and ii), is "defined as a dynamic regulatory process wherein homeostatic control is maintained by an active process of adaptation during exposure to physical and behavioural stressors" (McEwen and Gianaros 2010:191). Thus, homeostasis refers to stability in vital parameters that must be kept within narrow ranges, such as blood oxygen concentration, pH, etc., while allostasis refers to the active process maintaining this stability through changes in heart rate, BP, etc. It is regulated by systems, such as the HPA-axis, the autonomic nervous system, and the immune system (McEwen 1998 i and ii). Allostatic load is:

> defined as the consequence of allodynamic regulatory wear-and-tear on the body and brain promoting ill health, involving not only the consequences of stressful experiences themselves, but also the alterations in lifestyle that result from a state of chronic stress (McEwen and Gianaros 2010:191).

Bruce McEwen, a prominent researcher in the field of stress, defines four situations associated with allostatic load (McEwen 1998 i and 2010). First, there is frequent stress. For instance, sudden BP peaks increase the risk of cerebral stroke and MI, and repeated BP elevations are atherogenic (Kaplan et al. 1991; Muller et al. 1989). Second, adaptation to repeated stressors of the same type may be inadequate. Thus, instead of gradually becoming more comfortable with dealing with a particular repeating challenge, the individual experiences surges of stress as described in the first example. Third, there may be failure to inactivate the allostatic response after the stressful situation has passed. For example, recovery of BP may be delayed in some people after acute stress, such as an arithmetic test (Gerin and Pickering 1995). Also, high glucocorticoid blood levels (e.g., during a chronic stress response) has some hazardous effects, including stimulating central accumulation of adipose tissue, and decreasing insulin sensitivity (Björntorp 1990; Després et al. 1990; Manolopoulos et al. 2010). Fourth, an inadequate response of an allostatic system to a stressor may cause compensatory increased activity in another system, in the absence of down regulating feedback stimuli from the underactive system. E.g., secretion of inflammatory cytokines increases as a response to stress if the counterregulatory cortisol secretion is attenuated.

This has, for example, been described among children with atopic dermatitis (Buske-Kirschbaum et al. 1997). Increased levels of inflammatory cytokines have also been linked to CVD (Koenig et al. 1999; Libby and Crea 2010; Ridker et al. 1998).

It is apparent that frequent and/or long-lasting stress responses can seriously damage health, including increasing the risk of CVD. The allostatic response to a stressor depends on the person's *perceived* threat of a stressful situation, and the person's general physical condition (McEwen 1998 i). Thus, an individual's unique biographical experience, perception, and interpretation are of major importance in the regulation of allostatic activity. McEwen and Gianaros state:

> [W]e will emphasize the brain as the central mediator of stress processes, insofar as distributed brain networks encode, filter, and store environmental information according to unique personal histories and life experiences to determine what is threatening and thus "stressful" to the individual. Moreover, we will emphasize the brain as the instrumental organ for regulating biological, behavioral, and social responses that are influenced by short-term (acute) and long-term (chronic) stress processes (McEwen and Gianaros 2010:191).

One of the major advantages of the "allostasis-model" is that it includes "psychological" risk factors as well as the traditional "physical" ones. Thus, smoking or alcohol consumption may lead to a similar allostatic load as a stressful job. I.e., mental and physical stressors have the same status in the model. In addition, the model emphasises the individual's experience and interpretation of stressors.

Childhood and foetal origins of cardiovascular disease

Many studies have found associations between childhood experiences and disease development in adult life. The Adverse Childhood Experiences (ACE) Study (Felitti et al. 1998), led by Vincent Felitti, was conducted in San Diego in 1995-97 and included roughly 17 000 adults which answered a detailed questionnaire on adverse childhood experiences, such as emotional neglect, living with an alcoholic or criminal parent, or suffering emotional, physical, or sexual abuse. The adverse experiences were

categorised by the nature of the experience and each participant given a score depending on the number of event categories ever experienced. The researchers found a dose-response association between the ACE score and the morbidity in adult life (Felitti et al. 1998). The same association was found with IHD (Dong et al. 2004), and premature mortality (Brown et al. 2009). Thus, findings of the ACE study suggest adverse childhood experiences, such as suffering abuse and living in a dysfunctional home, may seriously affect an individual's health in adult life, possibly through allostatic load. A childhood of constant fear and instability may mark a person permanently, not only mentally but also metabolically.

Studies have also found adverse living conditions at even earlier stages in life to be associated with poor adult health. In the 1970s, Anders Forsdahl found a remarkable correlation between premature mortality and infant mortality of the same birth cohorts in Finnmark County, Norway (Forsdahl 1973). His conclusion was that undernutrition in early life, especially when coupled with affluence in adulthood, rendered individuals more susceptible to CHD. Similar results have been reported from other studies. The Helsinki Birth Cohort Study found an association of low weight at birth and during infancy with CHD in adulthood (Eriksson et al. 2001; Eriksson 2007). Similarly, the Dutch Famine Birth Cohort Study found people who were exposed as children or even *in utero* to the Dutch famine in 1944-45 to exhibit higher mortality and prevalence of diabetes than controls not exposed to the famine (van Abeelen et al. 2011; Roseboom et al. 2011). David Barker and co-workers were probably the first to relate undernutrition in foetal life to CHD (Barker and Osmond 1986; Barker et al. 1989). The Barker hypothesis (in short) suggests that undernutrition *in utero* causes some kind of foetal programming that has long-term effects on the individual's metabolism (Barker 1995). Metabolic pathways that can be crucial to ensure the vitality of the foetus and infant may prove to increase the risk of CVD in adult life. To recognise the pioneering work of Anders Forsdahl, it has been suggested to refer to this as the Forsdahl-Barker hypothesis (Gram et al. 1995).

Epigenetics and telomeres

In recent years epigenetics have given new insights into the Forsdahl-Barker hypothesis. Even though pre-natal undernutrition and trauma cannot alter the DNA sequence, it can affect the phenotype through gene transcription. The epigenome is composed of methyl and actyl groups that are attached to the DNA molecule and result in decreased or increased transcription of the gene they are attached to (Kuzawa and Sweet 2009; Petronis 2010). The epigenome is regulated through metabolic signals and has the potential to change over time. At the same time it is also inherited (Kuzawa and Sweet 2009; Petronis 2010). Thus, undernutrition and other adversities *in utero* may not only render an individual more susceptible to diabetes and CVD through foetal epigenetic programming, but it may also affect the risk of his/her offspring through the inherited epigenome.

The telomere is another DNA-related phenomenon that has recently been associated with stress and diseases (Epel 2009; Epel et al. 2010). Telomeres are long DNA sequences at the ends of the chromosomes, made of nucleotide repetitions. They function as protective caps on the chromosome ends. While the telomeres are gradually worn out under cell divisions, they protect the genes from being harmed. Chronic stressful situations, such as being the caregiver for an Alzheimer's disease patient, have been found to accelerate telomere wear and tear, and short telomeres have been associated with cellular aging and morbidity (Epel 2009; Epel et al. 2010; Damjanovic et al. 2007; Kiecolt-Glaser et al. 2011).

I have presented examples of some of the exciting research on how stress and psychosocial factors affect the risk of CVD. These examples show how social deprivation, job strain, childhood abuse, and chronic stress can seriously damage health, alter the body's metabolism and increase the risk of CVD, even in someone's offspring. The interaction of the above-mentioned factors may be extremely potent. Thus, the inherited epigenome may render some people more vulnerable than others to traumatic childhood experiences and job strain, partly explaining the individual differences in thresholds for telomere erosion and allostatic load. This is evidence that is generally not considered when guidelines for CVD prevention are being drafted.

2.3. Evidence-based guidelines

2.3.1. Evidence-based medicine

Evidence-based medicine (EBM) is a concept that in 20 years has become a central theme in medicine (Guyatt et al. 2008). This term (and acronym) has achieved dogmatic status and is vastly overused as a label of excellence. The validity and application of the phenomenon has been much debated and both too much and too little adherence to the concept has been widely criticised (Fretheim et al. 2006; GRADE 2011; Grimen and Terum 2009; Hetlevik et al. 2008; Sackett et al. 1996; Wyller 2011). The main reason appears to be widespread misunderstanding of the term. Many of those most advocating the implementation of EBM and criticising non-adherence violate the principles of EBM themselves. In return, EBM is identified as something it is not (or should not be), which provokes scepticism and critique. But what is EBM really? And where does it come from?

The origin of EBM

The EBM movement stems from McMaster University in Hamilton, Canada. In the 1980s a group of clinical epidemiologists, led by David Sackett, taught medical students and physicians *critical appraisal* of medical articles and published a series of papers on the matter (Guyatt et al. 2008). Their ideology "evolved into a philosophy of medical practice based on knowledge and understanding of the medical literature (...) supporting each clinical decision" (Guyatt et al. 2008:xix), i.e., basing each clinical decision on the available evidence rather than tradition. In 1990, Gordon Guyatt, one of the central actors in the movement, coined the term *evidence-based medicine*. The term and the concept became widespread, not least because of the Evidence-Based Medicine Working Group, led by the McMaster team, which in the 1990s created a series of articles on EBM in the Journal of the American Medical Association (JAMA).

The definition of EBM has evolved over time. In 1996 Sackett *et al.* defined EBM in the following way:

> Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Sackett et al. 1996:71).

I.e., "EBM" refers to the process of (any given practitioner) conscientiously basing each clinical decision on the "best available evidence" (identified through a systematic search) in the light of (one's own) clinical expertise. In the book *User's guides to the medical literature* (a doctrine of EBM), Guyatt et al. define two "fundamental principles of EBM" (Guyatt et al. 2008):

> First, EBM posits a *hierarchy of evidence* to guide clinical decision making. Second, evidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits and *risks*, inconvenience, and costs associated with alternative management strategies and in doing so, consider their patients' *values* and *preferences* (Guyatt et al. 2008:6).

The hierarchy of evidence

Any empirical observation, collected systematically or not, can be regarded as evidence. The "quality" or "strength" of the evidence depends on the methods of the study (observation). "Correct" methodology increases validity of the results, i.e., decreases potential bias. Thus, the methodological quality of the study decides how trustworthy the results are as a basis for a clinical decision. For example, results of unsystematic clinical observations (e.g., case reports) are more prone to bias than well-conducted RCTs, rendering the RCT results evidence of higher quality (stronger evidence), at least, when studying intervention effect. However, RCT is not always the best method. As an example, when studying patients' preferences (e.g., if informed patients find preventive statin treatment acceptable), qualitative research methods yield stronger evidence than RCTs, although treatment drop-out (in RCTs) may be regarded as an important piece of evidence. Thus, every research question has its ideal research methodology, and EBM posits hierarchies of evidence to facilitate identification of "the

best available evidence" for different types of questions (treatment effect vs. diagnosis vs. harm etc.). Where no evidence of high quality (obtained by means of the "ideal methodology") is available to answer a given clinical question, evidence of lower levels in the hierarchy will become "the best available evidence". Likewise, a poorly conducted study using a method ranked high in the hierarchy can result in lower quality evidence than a well-conducted study using a lower ranked method. Large effect sizes, consistency and precision of results increase the strength of the evidence (Guyatt et al. 2008).

Applicability of study results is another factor requiring careful consideration before implementation in the individual consultation. Strong evidence of treatment effect may, for example, have uncertain applicability because of co-morbidities or the age of the patient (Guyatt et al. 2008).

Values and preferences

The second principle of EBM is that "evidence alone is never sufficient to make a clinical decision" (Guyatt et al. 2008:6). The values and preferences of the individual patient (and/or his/her family) have to be considered for every clinical decision. "By *values* and *preferences*, we mean the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes" (Guyatt et al. 2008:10). The implications can be either obvious or unforeseen, so patients' preferences should not be assumed to be the same as that of the physician or the majority of the population. Cardiac resuscitation of an elderly or terminally ill patient is an example of an intervention decision that can differ with values, religion, etc. Drug treatment for the prevention of CVD is another example, where side-effects, costs, and inconvenience of the treatment may exceed the potential benefit in some patients' view but not others. This is a fundamental principle of EBM but often appears to be forgotten.

Clinical expertise

Each individual evidence-based clinical decision has been described by the McMaster team to rely on four components: the clinical state and circumstances, patients'

preferences and actions, research evidence, and clinical expertise (of the physician or health-care worker) (Haynes et al. 2002). The “clinical state” refers to the symptoms, disease, or other clinical problem in question and will thus define the relevant evidence, while “circumstances” refer to the surroundings in which the “clinical state” arises. A patient with signs of acute myocardial infarction will, for example, not have the same treatment opportunities if the symptoms arise in a remote, rural area, or in the neighbourhood of a high-tech hospital. “Patients’ preferences” have been discussed above. “Patients’ actions” may also need consideration, because they are not always in aggreement with values and preferences. Lack of treatment adherence may, for example, stem from forgetfulness or misunderstanding. The “best available research evidence” will have to be considered in the context of the two previously mentioned components. “Clinical expertise” refers to the general skills and experience of the practitioner. It includes the practitioner's ability to identify, interpret, and combine the best available evidence with the patient's values and preferences in the context of his clinical state and circumstances in order to reach a clinical decision (Haynes et al. 2002).

To sum up, the essence of EBM is conscientiously basing each clinical decision on the best available evidence and the patient's values and preferences, in the context of the given circumstances. To best achieve this goal, clinical expertise is needed. Any abridgement of this statement cannot be regarded to be in true accord with EBM.

> Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough.Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients (Sackett et al. 1996:71).

2.3.2. Clinical practice guidelines

Traditional guidelines

For decades clinical practice guidelines have been made as an aid to clinicians in their everyday work. The aim is to summarise the available evidence (and expertise) in the specific field, to support recommendations aimed at clinicians. Because of the exponential increase in published research papers in recent decades, it has probably never been more important to supply clinicians with practical summaries and recommendations based on the best available evidence. Currently, countless authorities, organisations, and institutes develop and publish such guidelines for worldwide use (WHO 2007), regional (Graham et al. 2007; Mancia et al. 2007), national (Cooper et al. 2008; Norheim et al. 2009; National Cholesterol 2002), and even local use in single hospitals and clinics (Böðvarsson et al. 2011; Digranes et al. 2004). This has not always been done systematically and explicitly. The typical method has been to establish a committee of specialists in the field and other stakeholders to a varying degree. Literature search is often limited, non-systematic, and/or undisclosed. The guideline committee then reaches a consensus on the recommendations, often in a non-transparent way. These guidelines have often been of huge assistance to clinicians, offering useful recommendations based on evidence and expert insights that would otherwise not have been available to them. However, the validity and applicability of such recommendations can be hard to evaluate due to a non-transparent production process. Fortunately, guideline development processes have generally greatly improved.

Some methodological limitations still exist in many guidelines published by prominent organisations. Guideline authors often have conflicts of interest (Graham et al. 2007; Mancia et al. 2007; National Cholesterol 2002); relevant stakeholders and targeted users are not always represented, and the derivation of recommendations is not always transparent. This opens the door to excessive weight being put on guideline authors' values and opinions at the cost of evidence and, perhaps, patients' preferences.

Combined risk algorithms

The method of calculating future risk of CVD events and mortality from combining information on multiple risk factors was developed by the research team of the Framingham Study (Anderson et al. 1991). The Framingham algorithm has been used widely, and many organisations have developed their own algorithms from national or regional data, based on the Framingham methodology (Conroy et al. 2003; Selmer et al. 2008). The most famous European example is the SCORE algorithm from 2003 (Conroy et al. 2003). The algorithms vary in the risk factors included. Some include variables, such as BMI (D´Agostino et al. 2011), HDL (Reiner et al. 2011), and socioeconomic status (Hippisley-Cox et al. 2010), while others do not (Mancia et al. 2007; WHO 2007). Most algorithms do include age, sex, smoking status, BP (SBP), and (total) cholesterol (De Backer et al. 2003; Graham et al. 2007; Hippisley-Cox et al. 2010; Mancia et al. 2007; Norheim et al. 2009; WHO 2007). While the complete risk calculators are often available online (D´Agostino et al. 2011; HeartScore 2011; QRISK 2011), guidelines usually present simplified score charts for reference in clinical practice (De Backer et al. 2003; Norheim et al. 2009; Reiner et al. 2011; WHO 2007). Most of these algorithms estimate 10-year (absolute) risk of CVD event or CVD mortality.

Most of these algorithms are derived in the same way. In short (and simplified), a multiple regression analysis, using Cox or Weibull proportional hazards models, is done on data from cohort studies with follow-up (of various lengths) on fatal and/or non-fatal CVD events (or any other given end-point). The regression coefficients derived for each risk factor are used to estimate the relative risk (hazard ratio) of different combinations of risk factor levels. Age- and sex-specific incidence rates of the selected end-point in the given population and information on average levels of the risk factors are combined with the relative risk calculations to estimate the absolute risk. Thus, BP, smoking, and cholesterol are each assumed to be of the same relative importance for both sexes and all ages, and BP and cholesterol are assumed to be linearly associated with CVD events and death within the combined model (Conroy et al. 2003; Selmer et al. 2008). This assumption is challenged in section 2.2.2 (regarding cholesterol) and in Paper III and is discussed in section 4.2.2.

GRADE

Published guidelines are often touted for being *evidence-based* and referred to as representing the gold standard of clinical practice within their specific field. But the methodology of their production is not always of high standard or in coherence with EBM. For that reason the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group was established in 2000 by members of the McMaster team and collaborators worldwide (health professionals, researchers, and guideline developers) (Guyatt et al. 2011 i). The aim of the group was to establish a practical and transparent system to grade the quality of evidence and strength of recommendations. Their results have been published in a 6-part series of papers in the British Medical Journal (BMJ) in 2008 and in a 20-part series in the Journal of Clinical Epidemiology in 2011 (partially still in press) (GRADE 2011). A short overview of how to develop guidelines using the GRADE system follows below, as a reference for discussion on the limitations of current guidelines. For further information on GRADE, see www.gradeworkinggroup.org (see "Publications" for access to published articles).

A summary of how to develop evidence-based guidelines using GRADE (Guyatt et al. 2008 and 2011 ii)

1. **Define questions to be addressed**

   Consider all relevant patient groups, management options, and outcomes (including morbidity, mortality, quality of life, toxicity and adverse effects, inconvenience, psychological burden, cost to patient and/or society).

2. **Critically appraise available systematic reviews and/or prepare systematic review(s)**

   One or more systematic reviews are needed to address all of the relevant patient groups, management options, and outcomes defined in step 1.

3. **Assess the relative importance of outcomes**

   Ranking the relative importance of the outcomes (defined in step 1) is crucial for the comparison of management options and for all outcomes to be considered. Doing this explicitly improves the transparency of recommendations, making adjustments based on different ranking (values and preferences) easier.

4. **Prepare an evidence profile, including an assessment of the quality of evidence for each outcome, and a summary of the findings**
   An "evidence profile" is derived from the systematic review(s) and provides a simple and systematic summary of:
   a. the assessment of the quality of the evidence (considering risk of bias, inconsistency, indirectness, imprecision, and publication bias) for each outcome;
   b. the findings (absolute and relative risks) for each outcome.
5. **Assess the overall quality of evidence and decide on the direction and strength of the recommendation**
   The direction (for or against a management option) and the strength (strong or weak) of the recommendation is based on the quality of the evidence (high quality evidence can support strong recommendations), the effect (large effect supports strong recommendations, risk of outcomes decides the direction), and the balance of desirable vs. undesirable outcomes (the relative importance of outcomes can be crucial as well as values and preferences). Resource use may also affect the strength and direction of the recommendation, weighted according to circumstances.

Additionally, it is important for guidelines to state clearly the clinical question addressed (health problem and patient group), the targeted guideline users, and who has developed the guidelines (including information on financial support and conflicts of interest). Values and preferences underlying recommendations should be explicit (steps 3 and 5). Representatives of targeted users should preferably be involved in the guideline development. Guideline implementation should preferably be tested in a pilot project before large scale distribution takes place. Guidelines have to be relevant for and attainable by the targeted users and the recommendations acceptable for the patients.

The GRADE system has already been adopted by some guideline developers and its use is likely to increase in upcoming years (GRADE 2011). Strict adherence to the *GRADE system* is not a necessary prerequisite for good, evidence-based guidelines, but considering all the factors described above is mandatory for any guideline to be

associated with EBM. This overview thus provides a useful framework for identifying methodological limitations to the validity and relevance of clinical practice guidelines.

2.3.3. Do the guidelines work?

It is a problem that clinical practice guidelines considered to be of adequate methodological quality and based on high-quality evidence may prove difficult to implement. In the mid-1990s Irene Hetlevik, one of my mentors, and her co-workers documented significant discordance between guideline recommendations on management of BP and diabetes, and the clinical practice in mid-Norway (Hetlevik et al. 1997 i and ii). Hetlevik et al. conducted an RCT to evaluate the effect of a multifactorial implementation strategy to improve adherence to clinical guidelines on CVD prevention. At 12 and 18 months there was no clinically significant difference between the intervention group and the control group regarding patient outcomes (BP, BMI, HbA1c, smoking status) (Hetlevik 1999). A decade later another Norwegian RCT, the Rational Prescribing in Primary Care (RaPP) study (Fretheim et al. 2006), evaluated an even more extensive, sophisticated, and systematic intervention to support the implementation of guidelines for the use of antihypertensive and cholesterol-lowering drugs for primary prevention of CVD. The intervention had very limited effect on improving guideline adherence in general practice (Fretheim et al. 2006).

Low adherence to authoritative clinical guidelines on CVD prevention among GPs has been documented widely (Al-Gelban et al. 2011; Bała et al. 2011; Fhärm et al. 2009; Fretheim et al. 2006; Hetlevik et al. 1997 i and ii; Jaussi et al. 2010; Philips et al. 2001; Treweek et al. 2005), and there is no reason to assume that this is a phenomenon isolated to Norway. This suggests the existence of important barriers to guideline implementation. These barriers may be bound to the *point of care* (physicians and patients); to the guideline implementation strategy (the RaPP study suggests this is not the case); or to the guidelines themselves (quality of evidence and/or development methodology), i.e., the guideline recommendations may be unattainable. But does it really matter?

Does it matter?

Yes, it does matter, and for several reasons. If the guideline recommendations are unrealistic and unattainable it can cause serious practical and ethical dilemmas in clinical practice. My three supervisors for this thesis, Linn Getz, Johann Agust Sigurdsson and Irene Hetlevik, and their co-workers have discussed this issue (Getz et al. 2004 and 2005; Getz 2006). They estimated that according to the 2003 European CVD prevention guidelines (SCORE) (De Backer et al. 2003), a majority (76%) of the adult Norwegian general population had unfavourable risk profiles (Getz et al. 2004 and 2005; Getz 2006). This would cause immense practical problems if the recommendations were to be followed. Again, the question could be asked: does it matter? Is individual modification of the guideline recommendations not an option?

The authoritative way in which the recommendations are usually presented and the lack of transparency (especially regarding values and preferences) makes it rather difficult to make individual modification in a sensible manner. Besides, the recommendations must be valid and relevant if the guidelines are intended to be used at all.

Even if the preventive guidelines are not legal documents, they define a certain standard of care which, if deviated from, might become a basis for malpractice lawsuits when CVD events occur. But even if strict guideline adherence is not mandatory, such guidelines are used for quality assessments and as basis for pay-for-performance systems (Starfield 2011). Physicians thus have economic motives to adhere to guidelines, potentially at the cost of the patients' best interest ("person-focused care"), down-prioritising issues that may be of greater importance to the patient (Starfield 2011).

2.3.4. "Vulgar Cochranism"

The (arguably) most important reason for unrealistic and unattainable guideline recommendations to matter has to do with the mentality and the culture of the medical society. These are the greatest limitations to preventive medicine, to technologically

driven medicine and EBM – the "arrogance of preventive medicine" (Sackett 2002) and "Vulgar Cochranism" (Wyller 2011).

In 2002, David Sackett wrote about the "arrogance of preventive medicine":

> Preventive medicine displays all 3 elements of arrogance. First, it is *aggressively assertive*, pursuing symptomless individuals and telling them what they must do to remain healthy. (...) Second, preventive medicine is *presumptuous*, confident that the interventions it espouses will, on average, do more good than harm to those who accept and adhere to them. Finally, preventive medicine is *overbearing*, attacking those who question the value of its recommendations (Sackett 2002:363).

Sackett's biggest concern was the presumptions; that the assumptions of the validity and benefit of preventive medical interventions were not based on sound evidence. In 2011 Torgeir Bruun Wyller, a Norwegian geriatrician, coined the term "vulgærcochranisme" (Norwegian) (Wyller 2011) or *Vulgar Cochranism* (my translation, which I will use from here onwards, in lack of a better term) to describe the same abusive arrogance in relation to EBM. He identified three consequences of overuse and emphasis on "EBM-evidence" (RCTs and meta-analyses), such as publications of the Cochrane Collaboration (hence the term, Vulgar Cochranism). First, the available evidence is applied beyond the range of its validity. The average effect of an intervention in a study population is assumed to apply to everybody, also the elderly and multimorbid, even if such patient groups are hardly ever included in RCTs. Wyller also points out that clinical practice guidelines are often very categorical regarding how (all) patients with certain medical conditions should be treated in a concrete "evidence-based" way (Wyller 2011). Others have also pointed out that guidelines focus on specific diseases and ignore the challenge of multimorbidity (Starfield 2011). Wyller argues that this indicates inadequate understanding of biology and clinical medicine. Second, excessive emphasis on the hierarchy of evidence leads to neglect of non-pharmacological interventions. Many interventions fit poorly to the RCT model and evidence of effect is therefore regarded as less valid. In addition, it has become difficult to conduct large clinical trials without the support of the pharmaceutical industry, which leads to biased

"evidence production" in favour of pharmacological interventions. Third, *experience-based evidence* (clinical expertise) is degraded. Pattern recognition, intuition, and identification of details relevant to the care of the specific patient, i.e., clinical expertise, is explicitly placed at the bottom of the evidence hierarchy. Wyller points out two facilitating factors for the rise of Vulgar Cochranism. First, it fits the bureaucratic way of thinking perfectly, while clinical expertise, on the other hand, is a threat to bureaucracy, difficult to streamline and hard for policy-makers to count on. Second, Wyller argues that doctors are trained to learn things by heart, and they like depending on hard facts and numbers. The Vulgar Cochranism and the hierarchy of evidence is thus a simple solution to complex problems (Wyller 2011).

Tor-Johan Ekeland, a Norwegian professor in social psychology, has discussed the limitation of EBM. He addresses the *presumptuous* nature of EBM and Vulgar Cochranism (Ekeland does not use this term) simply by the title of the book chapter "What is the evidence for evidence-based practice?" (Grimen and Terum 2009:145) He points out that there is no evidence supporting that EBM (as currently practiced) results in better patient care. Barbara Starfield stated on this issue: "Adoption of guidelines, particularly those touted as preventive, fails to be consistent with the overwhelming purpose of medicine, which is the relief of suffering" (Starfield 2011:65).

Like Wyller, Ekeland points out that results of RCTs do not always apply to the individual patient. He argues that RCTs, and thus EBM, systematically underestimate and ignore the importance of the clinical context and, therefore, poorly fit the complexity of clinical reality. Psychotherapy, Ekeland argues, is especially dependent on the practitioner and the clinical context and should not be standardised to fit the RCT model. Assuming evidence from RCTs always to be more valid than other evidence (or even the only valid evidence) introduces bias in favour of pharmacological interventions. He argues that the absence of (RCT) evidence does not substantiate the absence of effect. Additionally, because it can be problematic to weigh values vs. evidence of effect, doing so is generally not considered. EBM, Ekeland states, lacks critical reflection, and evidence supersedes ethics (Grimen and Terum 2009).

EBM started out as a quality-improvement project by applying the best available evidence in everyday clinical practice. This project seems to have evolved (or to be evolving) into the authoritative Vulgar Cochranism, which demands control over clinical practice. Ekeland argues that research should be more practice-relevant for clinical practice to apply the evidence. But Vulgar Cochranism is *aggressively assertive*. Facilitated by poor resource management in the healthcare system, health-focused media and patients' expanding expectations, an "EBM-label" (e.g., for a certain drug) automatically becomes an assurance of quality and a justification for resource allocation. And in that perspective, Ekeland states, criticism of and deviation from "EBM" may be regarded as unethical and in line with quackery (Grimen and Terum 2009). Thus, Ekeland identifies the element of *overbearing* in Vulgar Cochranism.

Clinical inertia

The arrogance of preventive medicine and Vulgar Cochranism often presents itself in discussion of "clinical inertia" (Philips et al. 2001). Clinical inertia is a term introduced by Philips et al. in 2001, and defined as "failure of health care providers to initiate or intensify therapy when indicated (Philips et al. 2001:825)," i.e., when indicated by clinical practice guidelines. Giugliano and Esposito suggested the term also to apply to "the failure of physicians to stop or reduce therapy no longer needed," but, they further state: "Ironically, this neglected side of clinical inertia does not seem to generate as much concern among physicians or scientific associations" (Giugliano and Esposito 2011:1592). Some imprecision exists regarding the use of the term clinical inertia, which is sometimes referred to as "therapeutic inertia", and to varying degrees authors deem the concept to cover patient non-adherence, but, it generally refers primarily to physicians (Allen et al. 2009; Faria et al. 2009).

In their article, Philips and colleagues (Philips et al. 2001) focus on clinical inertia in the management of high BP, dyslipidaemia, and diabetes, and the term appears to be used most within this field, i.e., the field of CVD prevention. In many guidelines on CVD prevention, clinical inertia is mentioned, and ways to reduce it are discussed (JNC 2003; National Cholesterol 2002). Guidelines on CVD prevention are mostly aimed at general practitioners (GPs), while specialists in cardiology and internal medicine (hospital-

based) tend to comprise an overwhelming majority of the guideline developing committees. Guidelines may therefore be regarded authoritative by GPs, and discussion of clinical inertia (of the GPs) may be regarded as derogatory and insulting, coming from hospital specialists out of touch with the clinical reality of primary care. As an example, the 2007 European guidelines on hypertension discuss the importance of the involvement of WONCA-Europe (European society of GPs) and other professional societies in the development of guidelines: "This partnership is crucial because general practitioners are more likely to accept and to use guidelines when these are developed with the involvement of those known to them" (Mancia et al. 2007:1514). Thus this implies that WONCA was involved primarily to increase the acceptance among GPs, rather than for an important input regarding content. About clinical inertia, the JNC 7 hypertension guidelines state:

> There is a broad range of clinician commitment to optimal hypertension therapy (…) Failure to titrate or combine medications and to reinforce lifestyle modifications, despite knowing that the patient is not at goal BP, represents clinical inertia which must be overcome [my underlining]. This may be due in part to clinician focus on relieving symptoms, a lack of familiarity with clinical guidelines, or discomfort in titrating to a goal (JNC 2003:61).

The guidelines further state: "Clinicians should periodically audit their own patient files to assess their degree of compliance and success with established goals and treatment interventions" (JNC 2003:62).

In a report from the US Institute of Medicine, *A Population-Based Policy and Systems Change Approach to Prevent and Control Hypertension* (by the Committee on Public Health Priorities to Reduce and Control Hypertension in the U.S. Population), hypertension is regarded a "neglected disease" (Institute of Medicine 2010:1) and the issue of clinical inertia addressed:

> Although patient nonadherence to treatment is one reason for lack of hypertension control, the lack of physician adherence to (…) guidelines (JNC) contributes to the lack

> of awareness, lack of pharmacologic and nonpharmacologic treatment, and lack of hypertension control in the United States. (…) physicians are not providing treatment consistent with the guidelines. In particular, physicians are less aggressive in treating elevated blood pressure in older patients (…) While the reasons for physician nonadherence to JNC guidelines are unclear, lack of physician awareness and physician beliefs about the practicality and benefit of treatment may contribute. (…) Numerous questions remain regarding whether the lack of adherence is related to a lack of physician agreement with the new treatment guidelines, physician lack of knowledge regarding the guidelines, inertia based on treating at the previous guideline of 160 mm Hg/95 mm Hg, or other barriers (Institute of Medicine 2010:12-13).

And a key recommendation is given:

> **5.1 The committee recommends that the Division for Heart Disease and Stroke Prevention give high priority to conducting research to better understand the reasons behind poor physician adherence to current JNC guidelines. Once these factors are better understood, strategies should be developed to increase the likelihood that primary providers will screen for and treat hypertension appropriately, especially in elderly patients** (Institute of Medicine 2010:13).

As these examples prove, authoritative parties assert considerable pressure on physicians (GPs) to follow guidelines, questioning the professional integrity, skills, knowledge, and commitment of those deviating from the recommendations in their practice. The tone is often derogatory and guideline non-adherence is not considered compatible with good patient care. Hence, identifying the reasons for clinical inertia seems to be considered a step towards ensuring full guideline adherence, and towards "improvement in clinical practice", but not towards improvement of the "evidence-based" guidelines. But according to Sackett et al.:

> Evidence based medicine is not "cookbook" medicine. Because it requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patients' choice, it cannot result in slavish, cookbook approaches to individual patient care. External clinical evidence can inform, but can never replace, individual clinical

> expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision. Similarly, any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied (Sackett et al. 1996:72).

The question then remains whether clinical inertia is just a matter of human error, or whether GPs have valid reasons for not adhering to guidelines (Giugliano and Esposito 2011; Hetlevik et al. 2008); i.e., whether the guidelines may be erroneous. Are the guidelines for prevention of CVD valid and relevant to general practice?

3. THE PRESENT STUDY

3.1. Aims of the study

The objective of this project was to study and discuss the validity and relevance of international CVD prevention guidelines for general practice. More specifically:

- To document the CVD risk profile of a general population as defined by selected, authoritative preventive clinical guidelines, by means of modelling studies.
- To estimate the workload associated with following the recommendations of the selected guidelines for a well-defined general population in whole.
- To identify potential causes of guidelines' overestimation of risk, focusing on individual risk factors.

To meet these objectives, four different papers have been written. The aims for each of these were as follows:

Paper I:
The aim was fourfold: Firstly, to document the prevalence of identified CVD, BP lowering drug treatment, and five selected risk factors in a well-defined general population. Secondly, to document the prevalence of high BP as defined by the different cut-off points given by different guidelines. Thirdly, to identify the proportion of the population having an "unfavourable risk profile", i.e. having two or more risk factors. And, finally, to address the implications of the guidelines' recommendations in the light of the findings.

Paper II:
Aim: to model the implications of the most recent European guidelines for management of arterial hypertension (Mancia et al. 2007) in a general population by estimating the prevalence of unfavourable CVD risk levels according to the guidelines and,

subsequently, estimating the clinical workload and workforce associated with the guideline recommendations.

Paper III:
Aim: to document the strenght and validity of total serum cholesterol as a risk factor for mortality, as defined by current CVD prevention guidelines.

Paper IV:
Aim: to clarify and compare the associations of five anthropometric measures of obesity and body composition intended for use in clinical councelling of individual patients (BMI, WHR, WHtR, waist circumference, and hip circumference) with overall mortality, and specifically with CVD mortality.

3.2. Material and methods

The Nord-Trøndelag Health Study
The work presented in this dissertation is based on the database of The Nord-Trøndelag Health Study 1995-1997 (HUNT 2). The first large health survey in Nord-Trøndelag County in Norway (HUNT 1) was conducted in 1984-86 (Holmen et al. 2003). Every adult (aged 20 years or more) living in the study area was invited to participate in the HUNT 1 study, and a total of 74 599 (88.1%) of the inhabitants did so. The main objectives of this survey were to address prevalence rates and quality of health care provided to individuals with hypertension, diabetes, and tuberculosis (Holmen et al. 2003). The second wave of the HUNT study was conducted in 1995-97. Again, every adult in Nord-Trøndelag County was invited and 71.2% of the population participated. This time the scope of the survey was wider, addressing important public health issues like CVD, diabetes, obstructive lung disease, osteoporosis, and mental health. The HUNT 2 study has been described in detail by Jostein Holmen and co-workers (Holmen et al. 2003).

Participation in the HUNT 2 study consisted of a physical examination (including measurements of BP, height and weight), a non-fasting blood sample, and answering an

extensive questionnaire on demographic factors (including education and income), habits (e.g. smoking and physical activity) as well as personal and family medical histories. Further information on the HUNT studies can be found at: http://www.ntnu.edu/hunt. Likewise, the questionnaires can be found online at: http://www.ntnu.edu/hunt/data/que.

The third phase of the HUNT study (HUNT 3) was conducted in 2006-08. Three phases of a Young-HUNT survey (UngHUNT) have also been conducted, including participants aged 13-19 years. The HUNT centre holds a high-standard bio-bank with facilities for advanced bio-material analyses. In addition, the personal identity number of Norwegian citizens enables linking of HUNT participant data to various registers, such as the Cause of Death Registry, given approval by the Norwegian Data Inspectorate.

Ethics statement

Each participant in the HUNT study signed a written consent form regarding the screening and the use of data for research purposes, including linking to other registers (subject to the approval of the Norwegian Data Inspectorate). The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

Study population

The HUNT 2 population is ethnically homogenous, dominated by individuals of Nordic origin, and has been regarded as fairly representative for the Norwegian nation regarding demography, socio-economic factors, morbidity, and mortality (Holmen et al. 2003). Overall, 74% of women (34 786) and 65% of men (30 575) chose to participate. Participation rate was lowest in the youngest and oldest age groups. For both sexes combined, the participation rates for each decade of age were as follows: 20-29 years, 49%; 30-39 years, 68%; 40-49 years, 77%; 50-59 years, 81%; 60-69 years, 86%; 70-79 years, 80%; 80-89 years, 66%; 90+ years, 53% (Holmen et al. 2003). For more details on participation rates, see *Holmen et al. Norsk Epidemiologi 2003;13:19-32.*

Selective participation evidently has to be considered as a possible source of bias in the HUNT 2 study, especially in the age groups with the lowest participation rates. A non-participation study was conducted to identify causes of not attending. Among those younger than 70 years, the most frequent causes of non-participation reported were lack of time, having moved out of the county, having forgotten to turn up for the physical exam, or no special reason (Holmen et al. 2003). For those aged 70+ years the most frequently given reasons were immobilisation because of disease, regular follow-up by a physician or hospital, and having moved. A comprehensive non-participation study after HUNT 1 did not find evidence of selection in health measures in the younger age groups, but found significantly more morbidity among old non-participants than among participants of the same age (Holmen et al. 2003).

For the present study, different eligibility criteria were applied in each of the papers, regarding age, missing data, etc. Details regarding exclusion are to be found in each paper separately. A summary is presented here in Table 1.

Table 1. Sex-specific number of participants eligible for analysis and inclusion criteria for each of the paper presented.

Study	Men	Women	Total	Inclusion criteria
HUNT 2	30 575	34 786	65 361	
Paper I	29 288	32 816	62 104	- Age 20-79 years
Paper II	26 347	24 719	51 066	- Age 20-89 years - BP ≥120/80 mmHg - Data available on: BP, smoking, cholesterol, waist circumference, and family history of CVD
Paper III	24 235	27 852	52 087	- Age 20-74 years - Free from CVD at baseline - Data available on: cholesterol, BP, and smoking
Paper IV	26 461	30 510	56 971	- Age 20-79 years - Free from CVD at baseline - Data available on: weight, height, waist and hip circumference

Study variables

In the HUNT 2 study, height and weight were measured with participants wearing light clothes without shoes; height to the nearest 1.0 cm and weight to the nearest 0.5 kg. BMI was calculated as weight in kg divided by the squared value of height in meters. Waist and hip circumferences were measured with a steel band to the nearest 1.0 cm with the participant standing and with the arms hanging relaxed. The waist circumference was measured horizontally at the height of the umbilicus, and the hip circumference was measured likewise at the thickest part of the hip (Holmen et al. 2003). When analysing the anthropometric measures in Paper IV, the aim was to use clinically recognisable categorisations, rather than percentiles. BMI was categorised according to WHO definitions (WHO 2000), the waist circumference categories were defined with 10 cm interval, and the hip circumference categories with 5 cm interval. The WHR and WHtR were, however, categorised by quintiles. In Papers I and II, abdominal (waist) obesity was defined as waist circumference >102 cm for men and >88 cm for women.

In the HUNT 2 survey, total serum cholesterol was measured by an enzymatic colorimetric cholesterol esterase method (Holmen et al. 2003). The blood pressure of persons in a seated position was measured by specially trained personnel using Dinamap 845XT, based on oscillometry. The cuff size was adjusted after measuring the arm circumference, and blood pressure was recorded as the mean values of the second and third measurements performed consecutively at the same visit (Holmen et al. 2003). In Paper II, ”pulse pressure (SBP minus DBP) in the elderly”, as an independent risk factor, was defined as ≥60 mmHg in people aged >55 years.

Smoking was defined as daily smoking of cigarettes, cigars or a pipe. In Paper IV smoking status was defined as: unknown, current smoker, former, or never smoker. Levels of recreational physical activity were defined as self-reported number of hours spent on hard or light activity during one week: no activity; <3 h light activity; ≥3 h light activity or <1 h hard activity; ≥1 h hard activity; unknown. Self-reported weekly alcohol consumption (Paper IV) was categorised as: abstinence, 0-2 glasses (units), 2.1-5 glasses, 5.1-8 glasses, >8 glasses.

Established CVD was defined as self-reported angina pectoris, myocardial infarction or stroke. Likewise, information on BP lowering drug treatment and diagnosed diabetes was self-reported. Family history of CVD was defined as first-degree relatives (parents or siblings) with myocardial infarction before the age of 60 or stroke at any age.

Since blood samples were non-fasting, the decision was made not to include triglycerides, blood glucose, or calculated low-density lipoprotein (LDL) in any of the analyses included in this thesis (inclusion of postprandial measures might introduce error).

Follow-up

The personal identity number of Norwegian citizens enables linking of HUNT 2 participant data to the Cause of Death Registry at Statistics Norway (information on www.ssb.no/english/). For the analysis in Paper III, each participant contributed person-time from the date of clinical examination (August 1995-June 1997) until ten years of follow-up had been achieved (until August 2005-June 2007, depending on participation dates) or until the date of death if this occurred in the follow-up period, making the oldest participants of the study 84 years of age at the end of the follow-up. The follow-up time came to a total of 510 297 person-years. For analysis in Paper IV, each participant contributed person-time from the date of clinical examination until the date of death or end of follow-up, December 31st 2008. The mean follow-up time was 12.0 years, in total 684 644 person-years. Death from CVD was defined by the International Classification of Disease code for the primary diagnosis of death (ICD-9: 390-459; ICD-10: I 00-I 99) as well as death from IHD (ICD-9: 410-414; ICD-10: I 20-I 25).

Guidelines studied

Paper I discusses the implications of applying international clinical preventive guidelines on the HUNT 2 population, focusing on the prevalence of selected risk factors and the proportion of the population regarded to be at increased risk. Cut-off points defining risk factors were based on recommendations of four internationally renowned clinical preventive guidelines. These were: The 2002 update of the guidelines

for primary prevention of CVD by the American Heart Association (AHA) (Pearson et al. 2002); the seventh report of the (USA) Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (JNC 2003) from 2003; the 2006 update of the guidelines on hypertension by the (UK) National Institute for Clinical Excellence (NICE) (National Institute 2006); and the 2007 European guidelines on CVD prevention in clinical practice (Graham et al. 2007). The guidelines were selected as representative samples of the views and recommendations of four highly regarded associations and institutes from both sides of the Atlantic. Summary of the recommendations can be found in Table 1 in Paper I.

Paper II models the implementation of the 2007 European guidelines for management of arterial hypertension (Mancia et al. 2007) on the HUNT 2 population. These guidelines were chosen on the basis of being the most recent ones on the subject at the time of the study planning, recommended for use all over Europe. Figure 1 shows the risk stratification, as presented in the guidelines, as well as the number of recommended follow-up visits per year for each risk stratum, as interpreted by the study authors. Figure 2 (Paper II) shows the definitions of the risk factors considered in the study.

Statistical analysis

The SPSS statistical package, version 15.0 (SPSS Inc., Chicago, USA) was used for frequency analyses in Papers I and II. Stata for Windows (Version 11 StataCorp LP, TX, USA) was used for analyses of Papers III and IV. A thorough discussion of the statistical analyses performed in each paper separately follows below.

Paper I

Paper I presents simple descriptive statistics: prevalence of established CVD and risk factors in absolute numbers and percentages, as well as age standardised prevalence percentages (Europe and World standard [Waterhouse et al. 1976]) with 95% confidence intervals (CI). Age standardised prevalences are presented to enable comparison between countries. The proportions of the population having none of the risk factors studied, one of them, two, or more than two, as well as the proportion reporting established disease (CVD, diabetes, or BP treatment) are presented.

The upper age limit of 79 years was found to be of clinical relevance due to high co-morbidity and low life expectancy after that point. This coincided with considerably lower participation rates among the oldest inhabitants in Nord-Trøndelag.

Inclusion of the recently coined risk factor "prehypertension" in the analysis can be debated. However, differentiation of this factor from hypertension made the relative importance of prehypertension clearly recognisable.

Paper II

In this paper, we estimated the prevalence within each risk stratum, as defined by the 2007 European hypertension guidelines (Mancia et al. 2007). Age standardised prevalences were calculated because of inequal participation rates in different age groups, with the actual age distribution in Nord-Trøndelag (Statistics Norway 2007) as standard. The total number of recommended follow-up visits per year was calculated by multiplying the age standardised prevalence numbers with the recommended number of visits for each risk category. Number of physicians needed to take care of that workload was calculated by dividing the estimated number of visits by 3 000 – the average consultation number of a general practitioner at the time (Nossen 2007).

Since the exact number of visits per year for each risk category was not stated by the 2007 guidelines, a subjective interpretation was unavoidable. Individuals in certain risk categories were recommended to be seen more than twice a year. We interpreted this as 3-4 times a year, and used an average number of 3.5 visits/year (further explained in Paper II). Sensitivity analyses were also done, exchanging the number 3.5 with 3 and 4, respectively.

An upper age limit of 89 years was found to be appropriate because of low participation rate above that age. This cut-off point might be regarded as rather high, but the guidelines specifically emphasise that preventive treatment should be continued in old age. Including participants aged 80-89 years might, however, have introduced a selection bias, favouring the more healthy individuals in that age range. This decision

was found to be defendable since the effect of such bias would be underestimation of the workload.

The 2007 European guidelines include a risk stratification chart where the lower cut-off point for BP is 120/80 mmHg. Individuals with lower BP values are thereby not eligible for risk evaluation.

Paper III

The first part of the analysis involved making a simple CVD risk estimation chart to be compared with the charts currently recommended for clinical practice in Norway. The Systematic Coronary Risk Evaluation (SCORE) chart of the European Society of Cardiology (Conroy et al. 2003; De Backer et al. 2003), and the nationally adjusted chart used in the Norwegian National Guidelines (Norheim et al. 2009) were used as a reference. These charts are intended to depict the 10-year risk of dying from CVD, given the level of the following risk factors at baseline: sex, age, smoking status, systolic blood pressure, and total cholesterol. To obtain a meaningful amount of data for each square of the chart, we based the analysis on three age groups (20-39 years, 40-59 years, and 60-74 years), two levels of systolic blood pressure (<140 mmHg vs. ≥140 mmHg, in accordance with guidelines), smokers vs. non-smokers, and two levels of total cholesterol. Regarding cholesterol, the levels <5.5 mmol/L vs. ≥5.5 mmol/L were used (cut-off approximately 215 mg/dL). This cut-off point assigned 40% of participating males and 43% of females to the "low level" category. Using a cut-off point of 5.0 mmol/L (which guidelines [De Backer et al. 2003; Graham et al. 2007] state that cholesterol should be below) would have assigned only 24% of males, and 27% of females to the lower cholesterol stratum. The median cholesterol level of the participants was 5.7 mmol/L for both sexes. The observed mortality rates per 1 000 person-years were calculated for each square of the chart.

For the next part of the analysis, Cox proportional hazard models were used to compute hazard ratios (HRs) for overall mortality, as well as for mortality from CVD and IHD, associated with different levels of cholesterol at baseline. The precision of the estimated

associations was assessed by a 95% confidence interval. Departure from the proportional hazards assumptions was evaluated by Schoenfeld residuals.

Sex-specific HRs were computed for cholesterol as a continuous variable as well as a variable with four categories (<5.0 mmol/L, 5-5.9 mmol/L, 6.0-6.9 mmol/L, and ≥7.0 mmol/L). The other variables of the aforementioned chart were adjusted for, namely: age (in the time scale), systolic blood pressure (as a continuous variable), and smoking status.

An alternative model was also tested, including the same variables, in addition to WHR, level of physical activity, diabetes mellitus, and family history of CVD. The categorical cholesterol variable was tested for linear, as well as quadratic trend. Finally, an analysis of cholesterol as a dichotomous variable with the cut-off point of 5.5 mmol/L was conducted, stratified by smoking status, and an analysis of the effect of smoking stratified by the dichotomous cholesterol variable for comparison. Using a finer set of cholesterol-categories was not deemed to be feasible due to limited statistical power.

The upper age limit of 74 years was identified as a clinically meaningful cut-off for estimating 10-year risk of death, given the average life-expectancy in Norway (Statistics Norway 2011).

Paper IV

Associations of five anthropometric measures (BMI, waist circumference, hip circumference, WHR, and WHtR) with mortality were examined in this study. Each measure was divided in five categories (see chapter on study variables for details). Cox proportional hazard models were used to compute hazard ratios for overall mortality and CVD mortality associated with different levels of each anthropometric measure. Precision of the estimated associations was assessed by a 95% confidence interval. Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and log-minus-log plots. An interaction term between time and the appropriate variables was added to the model if the proportional hazards assumption did not hold.

The HR for participants with BMI below 18.5 kg/m^2 (104 men and 314 women) was analysed for comparison with the other BMI categories but excluded from further analysis due to the potential of reverse causality (a J-shaped mortality curve) (Berrington de Gonzalez et al. 2010; Flegal et al. 2007).

Sex specific standard deviation (SD) scores for each of the anthropometric variables were calculated and the HR associated with an increase of one SD was estimated. The data were analysed separately for men and women, and all associations were adjusted for potential confounding effects of age, smoking status and recreational physical activity. Sensitivity analyses were conducted, involving three additional models (Model 2-4). Model 2 included the same covariates as the main model but excluded participants with unknown smoking status. Model 3 was adjusted for age, smoking, and physical activity (as the main model) in addition to diabetes mellitus and weekly alcohol consumption (abstinence, 0-2 glasses [units], 2.1-5 glasses, 5.1-8 glasses, >8 glasses). Model 4 was identical to the main model but excluded the first three years of follow-up to limit the potential reverse causality effect of undiagnosed diseases.

The "relative informativeness" of each anthropometric measure was evaluated by examining the contributions made to the χ^2 likelihood ratio statistic in the Cox regression model compared with a model that only contained the confounders, as the χ^2 statistic can be used as a measure of the improvement of goodness of fit (Prospective Studies 2002). This was done both in relation to all cause mortality and CVD mortality.

To further compare the predictive properties of the different anthropometric measures for CVD death, sex-specific net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were computed when adding each anthropometric measure to two different prediction models. Model A included age as the only predictive variable, while Model B included age, smoking status, systolic blood pressure, and total cholesterol. For each model three different NRI calculations were done, using two (<5%, ≥5%), three (<1%, 1-9%, ≥10%), and four (<1%, 1-4%, 5-9%, ≥10%) levels of risk of CVD death, respectively.

In addition, an analysis of the anthropometric measures stratified by age (above and below 60 years) was conducted. Finally, mutually adjusted analyses were conducted for waist and hip circumference, as well as for BMI and WHR.

3.3. Results

3.3.1. Synopsis of Papers I-IV

Paper I

Can individuals with a significant risk for cardiovascular disease be adequately identified by combination of several risk factors? Modelling study based on the Norwegian HUNT 2 population

Petursson H, Getz L, Sigurdsson JA, Hetlevik I. *J Eval Clin Pract* 2009;15:103-9

Aims and objectives

Clinicians are generally advised to consider several risk factors (combined risk estimate) when evaluating patients' CVD risk. The aim was to study whether a combined assessment of five traditional risk factors might help demarcate a relatively distinct and manageable group of high-risk individuals in the clinical setting. Five risk factors were selected and the proportion of a well-defined population with "unfavourable" levels of at least two of them, as defined by four internationally renowned guidelines, was estimated. The impact of including so-called "prehypertension" (BP 120/80-139/89 mmHg) among the risk factors was specifically addressed. The results are discussed in a wider perspective.

Material and methods

Guideline implementation was modelled on data from the HUNT 2 study comprising 62 104 adults aged 20–79 years (29 288 men and 32 816 women). The risk factors studied were BP, cholesterol, obesity, smoking, and family history of CVD (1° relatives). Total, age- and sex-specific point prevalences of each risk factor was calculated, as well as the

prevalence of having zero, one, two, three or more factors, or having established disease (diabetes, CVD, BP treatment).

Results

One single CVD risk factor was exhibited by 12.4% of the population (age standardised, European standard); two factors by 21.5%; and three or more by 49.7%. Established CVD or diabetes mellitus was reported by 12.5%. In total, 83.7% of the population exhibited a disease or risk profile with at least two factors, if prehypertension was included. Table 4 shows the prevalences of individual risk factors.

Conclusions

If authoritative guideline recommendations are literally applied, as many as 84% of adults in Norway could exhibit two or more CVD risk factors or established disease and thus be considered in need of individual, clinical attention. This challenges the widely held presumption that "the net will close" around a manageable group of individuals-at-risk if several risk factors are jointly considered. As the finding of this study arises in one of the world's most long- and healthy-living populations, it raises several practical as well as ethical questions.

Paper II

Current European guidelines for management of arterial hypertension: Are they adequate for use in primary care? Modelling study based on the Norwegian HUNT 2 population

Petursson H, Getz L, Sigurdsson JA, Hetlevik I. *BMC Fam Pract* 2009;10:70

Aims and objectives

Previous studies (including Paper I) indicate that clinical guidelines using combined risk evaluation for CVD may overestimate risk. The aim of this study was to model and discuss implementation of the current (2007) hypertension guidelines in a general Norwegian population, with emphasis on the associated workload.

Methods

Implementation of the current *European Guidelines for the Management of Arterial Hypertension* was modelled on data from the HUNT 2 study, comprising 65 028 adults, aged 20-89, of whom 51 066 (79%) were eligible for modelling (26 347 men and 24 719 women). Based on the risk estimation chart and recommendations of the guidelines, the number of recommended follow-up visits per year was calculated, as well as the number of physicians required for this task.

Results

Among individuals with blood pressure ≥120/80 mmHg, 93% (74% of the total, adult population [HUNT 2 participants]) would need regular clinical attention and/or drug treatment, based on their total CVD risk profile. This translates into 296 624 follow-up visits/100 000 adults/year. In the Norwegian healthcare environment, 99 general practitioner (GP) positions would be required in the study region for this task alone. The number of GPs currently serving the adult population in the study area is 87 per 100 000 adults.

Conclusion

The potential workload associated with implementing the 2007 European hypertension guidelines could destabilise the healthcare system in Norway, one of the world's most long- and healthy-living nations, by international comparison. Such a large-scale, preventive medical enterprise can hardly be regarded as scientifically sound and ethically justifiable, unless issues of practical feasibility and sustainability are considered in a transparent way.

Paper III

Is the use of cholesterol in mortality risk algorithms in clinical guidelines valid? Ten years prospective data from the Norwegian HUNT 2 study

Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TIL, Getz L. *J Eval Clin Pract* 2011;18:159-68.

Aims and objectives

Many clinical guidelines for CVD prevention contain risk estimation charts/calculators. These have shown a tendency to overestimate risk, which indicates that there may be theoretical flaws in the algorithms. Total cholesterol is a frequently used variable in the risk estimates. Concerns for one's (total) cholesterol value is also widely promoted as part of a responsible lifestyle, as illustrated by the Norwegian campaign "Under 5" in 2011 (Under 5 2011). Some previous studies, however, indicate that the predictive properties of cholesterol might not be as straightforward as widely assumed. The aim of this study was to document the strength and validity of total cholesterol as a risk factor for mortality in a well-defined, general Norwegian population without known CVD at baseline.

Methods

The association of total serum cholesterol with total mortality was assessed, as well as mortality from CVD and IHD specifically, using Cox proportional hazard models. The study population comprises 52 087 HUNT 2 participants (24 235 men and 27 852 women), aged 20–74, who were followed-up on cause-specific mortality for 10 years (510 297 person-years in total).

Results

Among women, cholesterol had an inverse association with all-cause mortality (HR [95% CI]: 0.94 [0.89-0.99] per mmol/L increase) as well as CVD mortality (HR [95% CI]: 0.97 [0.88-1.07]. The association with IHD mortality (HR [95% CI]: 1.07 [0.92-1.24]) was not linear but seemed to follow a "U-shaped" curve, with the highest mortality <5.0 and ≥7.0 mmol/L. Among men, the association of cholesterol with mortality from CVD (HR [95% CI]: 1.06 [0.98-1.15]) and in total (HR [95% CI]: 0.98 [0.93–1.03]) followed a "U-shaped" pattern.

Conclusion

The study provides an updated epidemiological indication of possible errors in the CVD risk algorithms of many clinical guidelines. If our findings are generalisable, clinical and public health recommendations regarding the "dangers" of cholesterol should be

revised. This is especially true for women, for whom moderately elevated cholesterol (by current standards) may prove to be not only harmless but even beneficial.

Paper IV

Body configuration as a predictor of mortality: Comparison of five different anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study

Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TIL, Getz L. *PloS ONE* 2011;6:e26621

Aims and objectives

Distribution of body fat is more important than the amount of fat as a prognostic factor for life expectancy. Despite that, BMI still holds its status as the most used indicator of obesity in clinical work. The aim was to study the associations of five anthropometric indicators of obesity and body composition (BMI, WHR, WHtR, waist circumference, and hip circumference) with overall mortality, and specifically with CVD mortality.

Methods

We assessed the association of the five different anthropometric measures with mortality in general and CVD mortality in particular using Cox proportional hazards models. Predictive properties were compared by computing integrated discrimination improvement and net reclassification improvement for two different prediction models. The analyses were conducted on data on 56 971 HUNT 2 participants (26 461 men and 30 510 women) age 20-79 and free from CVD at baseline, followed up for mortality from 1995-1997 through year 2008 (mean follow-up 12.0 years, 684 644 person-years in total).

Results

After adjusting for age, smoking and physical activity WHR and WHtR were found to be the strongest predictors of death. HRs for CVD mortality per increase in *WHR* of one standard deviation were 1.23 for men and 1.27 for women. For *WHtR*, the corresponding HRs were 1.24 for men and 1.23 for women; for *waist circumference*, HRs were 1.19 (men) and 1.22 (women); for *BMI*, 1.12 (men) and 1.09 (women); and

finally, for *hip circumference*, 1.06 (men) and 1.09 (women). WHR offered the greatest integrated discrimination improvement to the prediction models studied, followed by WHtR and waist circumference. Hip circumference showed a strong, inverse association with mortality when adjusting for waist circumference. In all analyses, BMI had weaker association with mortality than three of the other four measures studied.

Conclusions

The study adds further weight to the evidence that BMI is not the most appropriate measure of obesity in everyday clinical practice, at least in relation to predicting mortality. WHR can reliably be measured, is as easy to calculate as BMI, and is currently a better documented measure than WHtR. It therefore appears reasonable to recommend WHR as the primary clinical measure of body composition and obesity for preventive purposes.

Conclusions of Papers I-IV in context

The results of Paper I indicate that prominent preventive clinical guidelines have a tendency to overestimate CVD risk. At least they fail to identify a clinically manageable proportion of the population as at "high risk". Paper II supports this conclusion, adding that the recommendations of the guidelines studied would introduce an overwhelming workload to the Norwegian healthcare system. These conclusions raise the question of where the problem lies. What causes the overestimation? Papers III-IV seek the answer among individual risk factors – whether flaws in definition (demarcation) of individual risk factors (we selected cholesterol and obesity for further investigation) could cause errors in the combined risk estimate. The results of Paper III indicate that the assumption of a linear association between total cholesterol and CVD mortality, as presented in most combined risk algorithms, may be erroneous. The results of Paper IV indicate that WHR and WHtR are more appropriate than BMI for defining "obesity" for CVD risk estimation.

3.3.2. Previously unpublished additional results

In the process of writing a paper presenting quantitative results, numerous potential tables and figures tend to accumulate. Some of these get published (after alterations to a varying degree) while others do not. In Appendices I present some tables and figures that were not included in the published papers I-IV but contain interesting supporting information. These results will not be discussed in great detail but are summarised in the context of the papers.

Paper I presents prevalence rates of a few risk factors in absolute numbers as well as age standardised. Figure A and Figure B (Appendix II) show the prevalence of each risk factor within each year of age, for men and women, respectively. The prevalence of most of the risk factors increased with age, most notably for serum cholesterol and hypertension. Already at age 20 some of the factors were exhibited by a considerable proportion of the population, which is reflected in Figure 2 (Paper I). An even more detailed analysis of body configuration is presented in Table A (men) and Table B (women), which show the prevalence of being overweight or obese, defined by BMI and waist circumference both separately and combined, in 5-year age groups. It is of interest to note that in both sexes, prevalence of abdominal obesity increased through all age groups, while overweight (BMI $\geq$25.0 kg/m^2) plateaued around age 50.

Figure 1 of Paper III depicts the observed ten-year mortality rates per 1 000 person-years in the HUNT 2 population, according to each level of the risk factors found in the international SCORE system. Two identical figures were made, presenting all-cause mortality (Figure C) and IHD mortality (Figure D), respectively. As stated in Paper III, the results were similar for all three analyses, the models showed a general trend towards increased mortality for an increase in any of the included risk factors, except for cholesterol, where no such association was observed.

As can be seen in Table 1 of Paper III, the number of deaths divided by the number of participants within each of the cholesterol categories yields relative risk ratios quite different from the adjusted HRs reported. Age-adjustment is the cause of this

discordance. For further clarification, age-stratified mortality rates for each of the cholesterol categories are presented in Tables C-E (Appendix I). As the Tables show, the majority of the deaths occurred among participants aged 60-74 at baseline. A larger proportion of participants aged 60-74 had total cholesterol above 6 mmol/L than below 6. Therefore, a higher number of deaths in total occurred among those with high cholesterol levels, compared to those with lower levels. The age-stratified data are more in accord with the adjusted HRs, showing the highest mortality among the oldest participants with the lowest cholesterol levels.

Figures E-N (Appendix II) were made in the preparation of Paper IV and are based on the data on the 56 971 participants included (all free from CVD at inclusion). They depict the observed sex-specific CVD death rate per 1 000 person-years during the 12 year follow-up for each anthropometric measure separately without any statistical adjustments. For each measure 20 categories were created for each sex. Each category included approximately 5% of the population, except the first and last category which included approximately 1% each. Clinically relevant cut-off points were chosen where possible. A visual appraisal identifies WHR and WHtR as having the strongest and most uniform association with mortality, of the measures studied.

4. DISCUSSION

In theory, clinical practice guidelines on prevention of CVD offer an excellent opportunity for education and quality improvement in general practice. However, a range of factors currently appears to limit their validity and relevance. Such limitations may have important effects on clinical practice and resource allocation, as well as population health. From another perspective, there seem to be plenty of opportunities for improvement. While some of the limitations involve easily adjustable technical details, others are more fundamental and even have historical, social and cultural roots and implications.

I will first present some methodological considerations regarding Papers I-IV and then reflect on the scientific and professional development of preventive medicine in general practice. I will present my reflections as an analysis of the (potential) limitations of preventive CVD guidelines, which will hopefully result in practical and useful recommendations regarding guideline improvement.

4.1. Methodological considerations

The main strength of the present study lies in the extensive database of the HUNT 2 study. The HUNT 2 population is large, compared to other population studies, and the study has good participation rates. All measurements were conducted in a standardised manner, and the mortality follow-up can be regarded as complete, with virtually the only potential exception being deaths among individuals who might have emigrated from the country during the follow-up period.

The wider generalisability of research findings, based on the HUNT studies in general and the HUNT 2 study in particular, is open to debate. The HUNT 2 population has been regarded as relatively representative of the Norwegian nation in terms of demography, socio-economic factors, morbidity, and mortality (Holmen et al. 2003). The similarities of the Nordic countries, regarding social structure, life-expectancy, etc.

(Statistics Denmark 2011; Statistics Iceland 2011; Statistics Norway 2011; Statistics Sweden 2011), suggests a certain transferability of the results, while greater uncertainty may be associated with application to other different populations. The present study, however, identified certain limitations to international preventive CVD guidelines that call for careful consideration in any population targeted for guideline implementation in the future.

Regarding the papers included in the present study, I have, in hindsight, become aware of some limitations and issues that might have been addressed. These considerations will be discussed in the chronological order of the papers.

Paper I

In hindsight, a sensitivity analysis could have been conducted, estimating, e.g., the best and worst case scenario from the missing data on individual variables. It would even have been possible to estimate the best and worst case scenario from invited non-participants living in Nord-Trøndelag County. Also, it would have been of interest to calculate the ten-year combined risk score for all participants. We refrained from doing so, mainly due to the complexity of the task, especially when considering more than a single guideline.

Paper II

The 2007 European guidelines include a risk stratification chart where the lower cut-off point for BP is 120/80 mmHg. Individuals with lower BP values were thereby not eligible for risk evaluation. In hindsight, guidelines without such lower BP cut-off might have been chosen, rendering a larger proportion of HUNT 2 participants eligible for the analysis.

It might be considered a weakness of the study that the total workload associated with the guideline recommendations was estimated without taking into account the work currently spent on BP monitoring, i.e., how much *additional* workload implementation of the 2007 guidelines would introduce. This estimation would, however, have been an extremely complicated. From clinical experience the authors know that much preventive

work takes place as opportunistic BP measurements and lifestyle recommendations during consultations initiated for other reasons. Statistics based on the number of visits with CVD or BP control as the stated reason for contact would probably underestimate the work actually performed.

Paper III

Preliminary analyses applying the Mantel-Haenszel test focused our interest on further examining the association of serum cholesterol with mortality. The study was thereby designed to address this association. It would have been of interest to explore further the predictive value of cholesterol in a combined risk estimate by means of receiver operating curves (ROC) or net reclassification improvement analyses, but this was considered more appropriate for a potential follow-up study.

As mentioned in section 3.3.2, the adjusted HRs presented in Table 1 do not seem to be in accord with the reported number of deaths, as the number of deaths increase rather than decrease with higher levels of cholesterol. The explanation for this apparent paradox lies in the correlation of cholesterol and age. This can be seen from the age-stratified mortality rates for the different cholesterol categories (Tables C-E in Appendix I). These data might have been included in Paper III for clarification. Concerns regarding this matter were raised in a Letter to the Editor of the Journal of Evaluation in Clinical Practice after publication of Paper III. Table C is included in our response to that letter. The correspondence will appear in the 2012 January issue of the journal and is presented in Appendix III.

Figure 1 presents age-stratified mortality rates, but only for a dichotomised cholesterol variable. A more detailed categorisation might have been preferable. However, that was not deemed feasible since it would have caused some of the categories (boxes) of Figure 1 to include very few participants. In hindsight, a different cut-off point for dichotomisation of cholesterol (i.e., 6.0 mmol/L) might have been chosen for more obvious coherence with the regression analysis.

A possible explanation for the high mortality observed in the lowest cholesterol category is reverse causality, i.e., low cholesterol levels at baseline might be due to undiagnosed diseases that increase the mortality in the group. Thus, excluding, for instance, the first two years of follow-up may be warranted to reduce this potential bias. At least this could have been addressed in the form of a sensitivity analysis. The aim of our study was **not** to examine the causal relationship between cholesterol and death, **but** rather to examine the association as a part of a prediction algorithm. Introducing, as a decision aid in clinical practice, a prediction algorithm estimating the risk of CVD death for the next 10 years, whilst immediately excluding the first 2-3 years, would lack clinical meaning. In the context of the present study, I therefore argue that reverse causality is not to be considered a cause of bias. Rather, it should be considered part of the complex, clinical reality.

A recent study by Mørkedal et al., also based on the HUNT 2 population, reported HRs for the association between total cholesterol and IHD mortality (Mørkedal et al. 2011). Mørkedal et al. reported the HRs in a supplementary appendix we were not aware of when Paper III was submitted. These HRs are sex-specific and refer to an increase of 1 SD (men: 1.2 mmol/L; women: 1.3 mmol/L) in total cholesterol. The resulting HRs are slightly higher than those reported in Paper III: 1.20 for men and 1.14 for women per increase in total cholesterol of one SD, compared with 1.08 for men and 1.07 for women per increase in cholesterol of 1.0 mmol/L in Paper III. Closer comparison of the studies, including a post-publication re-analysis performed jointly by the two author groups, has shown that the results of the two studies can be fully explained by different inclusion criteria. These criteria are again linked to the difference in research questions; Mørkedal et al. present a statistically oriented epidemiological investigation of causal inferences, whilst Paper III is a practically oriented modelling study of the validity and relevance of current clinical guidelines. Ideally, the apparent discrepancy between the two studies should have been addressed in Paper III.

Mørkedal included participants of all ages and excluded only those with incomplete data on the study variables or a reported history of MI or cerebral stroke, whilst we additionally excluded those who reported angina pectoris as well as individuals aged 75

years or older. More than half of the IHD deaths occurred among participants above age 74 and roughly 20% among participants that reported angina pectoris but not MI or stroke. The exclusion criteria are open to debate. Addressing primary prevention from the perspective of 10-year mortality predictions has limited clinical relevance in very old age. The mean life-expectancy in Norway was among the factors informing our decision on the upper age limit for inclusion. Since we were addressing primary prevention of CVD, we wanted to be sure not to include the participants who might already be under secondary preventive surveillance due to histories of MI and/or stroke. The validity of self-reported MI and stroke in the HUNT 2 study is difficult to evaluate in the absence of documented information from, for instance, clinical endpoint registries. To minimise the risk of including patients with established CVD, we also excluded people with self-reported angina pectoris. Thereby, some participants at high risk of CVD and truly eligible for targeted prevention (which they might in fact not have sought) could have been excluded. This would result in underestimating the true effect of high cholesterol if these participants had higher cholesterol levels than the mean for their age. However, we believe that Norwegian patients reporting angina pectoris are likely to have undergone a medical work-up and be under surveillance and receiving relevant prophylactic treatment. Thus, the direction of any possible bias related to inclusion/exclusion of self-reported angina pectoris is not obvious. A sensitivity analysis with inclusion of participants who reported angina pectoris could have shed further light on this issue.

Paper IV

It could have been of interest to seek out the cut-off points yielding the highest NRI estimates, thus identifying a risk stratification model with the best predictive properties. This was, however, considered to be outside the study aims. It would also be relevant to compare the predictive ability of the anthropometric measures as dichotomous variables, because preventive guidelines often refer to BMI and waist circumference in that manner. However, an international consensus has not been reached regarding WHR and WHtR cut-offs for obesity, in contrast to BMI and waist circumference (WHO 2011 ii). Before settling on such cut-off points, it must be specified whether they are intended

to identify high body fat percentage or, alternatively, high risk of morbidity/mortality. This question is addressed in Paper IV.

4.2. Possible limitations to guideline validity and relevance

I have presented evidence indicating that international clinical guidelines on prevention of CVD may have limited validity and relevance for general practice, at least in Norway. The guidelines appear to overestimate CVD risk and fail to correctly identify a manageable proportion of the population as "high-risk individuals", for whom individual preventive strategies would be effective and beneficial. Thus, current guidelines seem to introduce inadequate thresholds for individual-based high risk preventive strategies as an alternative (or complement) to population-based mass strategies (Buetow et al. 2007; Rose 1985). The strategy of targeting individuals at risk ("high-risk strategy") ends up being recommended at the level of mass strategy, which can hardly be regarded as sustainable or responsible.

If one takes for granted that the guidelines are not followed, that the recommendations do not translate into practice, the obvious question will be asked: Are the guidelines "good enough". Here "good enough" asks whether the guidelines are of high methodological standard, based on the best available evidence, and whether the available evidence is sufficient to support efficient, cost-effective, and realistic (obtainable) preventive strategies. To guide the reader through my analysis, a flowchart of the arguments is presented in Figure 1, below.

4.2.1. "Prevention in practice" inadequate

If it is taken for granted that the existing clinical preventive guidelines are "good enough", i.e., of good methodological quality and based on sound and sufficient evidence, potential limitations must be found where the recommendations are put into practice - meaning that the guidelines are not followed correctly or not well enough. I have identified four possible "barriers": the physicians, the number of physicians, the organisation, and the patients.

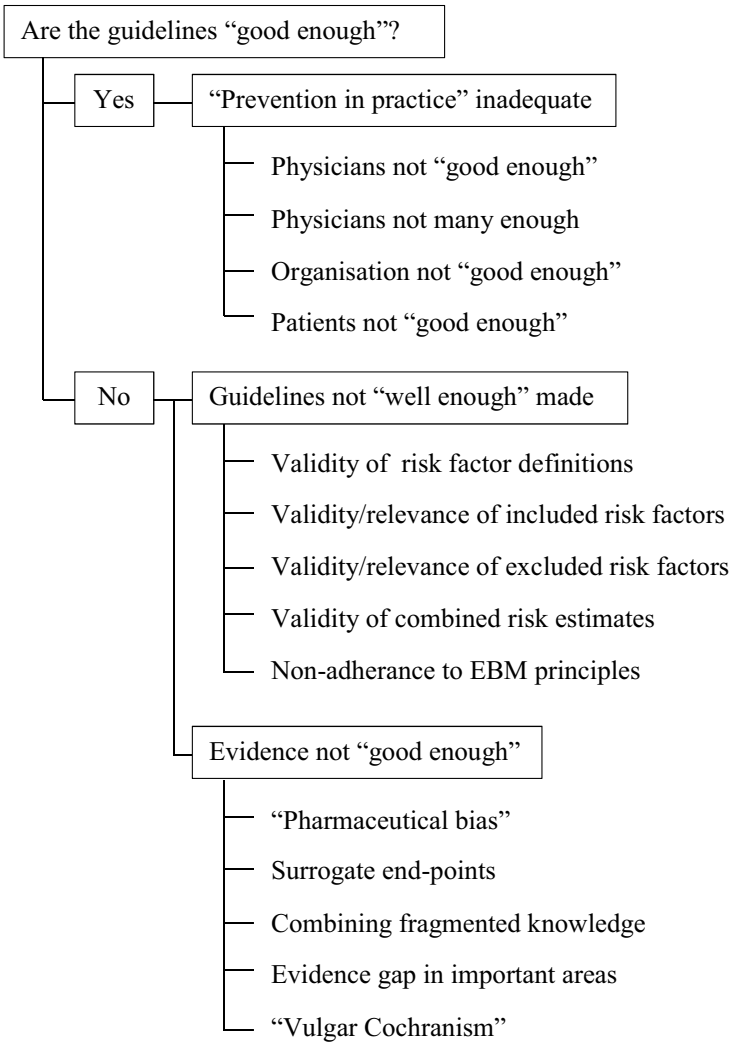

Figure 1. Potential limitations to guideline validity and relevance.

Physicians not "good enough"

Physicians may not be familiar with the current guidelines or may disagree with the recommendations; they may not have the experience and/or knowledge to adequately reach treatment goals (such as lowering BP below 140/90 mmHg); or they may not feel committed to identifying patients "at risk" and treating them to guideline-recommended

goals. This has been described as *clinical inertia*, the "failure of health care providers to initiate or intensify therapy when indicated" (Philips et al. 2001:825). Clinical inertia is discussed in chapter 2.3.4. Although clinical inertia may contribute to guideline non-adherence, I regard researchers/thinkers pointing to *professional inadequacy* as the main barrier for preventive guideline implementation as relatively arrogant and inadequately informed. The guidelines are in most instances aimed at practicing physicians, and GPs are primarily involved and responsible for primary prevention of CVD. Thus, discussion of clinical inertia can soon become an expression of distrust toward GPs. In my opinion, clinical inertia should generally be addressed in a wider context of other possible reasons for non-adherence, including organisational workload and time constraints; patient-related issues, such as "patient preferences", and competing health issues (co- and multimorbidity). The physician and his patient may find it necessary to prioritise other important issues, leading to deviation from guideline recommendations (Hetlevik et al. 2008).

Physicians not many enough

Paper II indicated that the GPs currently practicing in Nord-Trøndelag are not many enough to handle the workload associated with the guideline recommendations. A possible solution would be to increase the number of GPs. Intuitively this is, however, not a realistic option on a large scale. The investment demanded for educating and employing these additional physicians is likely to exceed the possible gain from lower CVD incidence. These investments of manpower and resources would have to be thoroughly evaluated in a larger context with other possible (preventive) societal projects worthy of investment (i.e., opportunity cost), such as maternal and neonatal care and the educational system. Also, it has to be borne in mind that CVD prevention does not seem to be the only field of medicine where disease-specific guidelines recommend allocation of unavailable resources. Clearly, the number of physicians cannot be increased to meet every potential demand. The law of diminishing returns (Fisher and Welch 1999) will eventually deem further investment in medical activity non-beneficial. Some increase in the number of physicians may be considered as part of a multifactorial solution but can hardly be regarded as the primary strategy.

Organisation not "good enough"

In Norway, individual GP consultations account for most person-based CVD primary prevention. Perhaps this organisation of preventive work might be made more efficient and cost-effective. Instead of meeting the GP 2-4 times a year for BP controls as recommended by guidelines (Mancia et al. 2007), the patient might be seen by assisting health-care personnel, giving protocol-based care including BP measurements, blood tests, lifestyle advice etc. Patients without special aberrations in test results or BP readings would meet their GP, for example, once every five years for a re-evaluation of the treatment and the treatment goals. Although such reorganisation of preventive work would decrease GPs' workload this would only mean an increased investment in other positions – an investment that would demand a thorough cost-benefit evaluation.

Patients not "good enough"

Patient adherence to treatment and willingness (motivation and capability) to follow a physician's advice can explain some of the deviation from guideline recommendations and treatment goals. These "obstacles" to guideline-adherence may be present on the individual as well as societal level. A society with high-stress levels and unreasonable work demands will not only have poor CVD risk profiles (De Vogli et al. 2007; Ferrie 2004), but might also feature decreased opportunities for leisure-time physical activity and other health-promoting activities. A society of great social inequity may limit the preventive opportunities for the lower classes. A consumption-focused market society may nurture materialism, dependence on luxuries, delicacies (high-calorie diet, overeating, alcohol and tobacco consumption), and simple solutions (drugs and surgery to lose weight), possibly making the citizens adverse to healthy living and physical exercise (Fugelli 2003 and 2008; Grimen and Terum 2009). Although such societal factors may be seen as potential targets for improvement, it can hardly be regarded as relevant to guidelines. Recommendations on motivation and how to improve individual adherence to treatment might, however, be addressed. Anyway, for guidelines to be valid and relevant they must be aimed at the population of interest, not at an *ideal* or utopic population. The guidelines must provide useful recommendations for the population in question. Thus, a discussion of patients not being "good enough" for

optimal guideline-adherence (though interesting) is of little relevance to guideline evaluation.

4.2.2. Guidelines not "well enough" made

If we look for limitations outside the "point of delivery" of health care, two obvious targets must be identified – the guidelines themselves, and the evidence they are based on. Factors underlying guidelines not being "well enough made" refer to methodological flaws, misinterpretation of evidence, and failure to translate relevant evidence into recommendations.

Validity of risk factor definitions

The risk evaluation, the treatment, and the follow-up on patients depend on valid definitions of specific risk factors, and when relevant, combinations of these (multi-factorial risk estimates). Errors in definitions and assumptions regarding any of the risk factors are bound to result in errors or imprecision in the resulting risk estimates. This will again decrease the value of follow-up measurements by over- or underestimating treatment effects, with reference to patient-important outcomes (e.g., risk of death). Paper IV addresses this error, as well as Paper III to a certain degree: The results of Paper IV indicate that defining obesity / adiposity / body configuration / body composition as a risk factor according to BMI levels will introduce an error which can be reduced by using WHR or WHtR instead – at least when considering the ability to predict patient-important outcomes. Likewise, according to Paper III, defining the risk factor *dyslipidaemia* in terms of *total cholesterol* may turn out to be invalid, but this problem may possibly be correctable by substituting some other lipid particle(s) for total cholesterol.

In recent decades there has been a constant trend of lowering cut-offs defining risk factors, such as BP (see section 2.2.1). Even though the lowering of cut-off points has been based on the available evidence at the time of redefinition, it inevitably increases the prevalence of the risk factor and the proportion of the population defined as "at risk". Since the association of most risk factors with CVD is not an on-off phenomenon

but rather a gradient one, it is possible to demonstrate an increase in relative risk to very low levels of a risk factor if there is a sufficient number of study participants (Prospective Studies 2002). Theoretically this *risk inflation* can label the majority of a population as "at risk" even if the absolute risk is low and, as a result, "normal" becomes abnormal. I.e., the academic "normal" or ideal becomes rare, and what is normal or common in the population becomes undesirable (unacceptable) and not good enough. As an example of this, the risk estimation chart of the 2007 European hypertension guidelines (Mancia et al. 2007) identifies the lowest risk category (prehypertension and no other risk factors) as "average risk" and all the other categories (BP ≥140/90 mmHg and/or coexisting risk factors) as variably "added risk", without even defining BP levels below 120/80 mmHg as "low risk". In a wider perspective, this phenomenon is further augmented with the simultaneous *risk inflation* of several risk factors for various other diseases.

The question remains whether such risk inflation affects the validity of the risk factors as such. The answer depends on the circumstances. When a continuous variable, such as BP, is treated as dichotomous (hypertension vs. normal BP), lowering the cut-off point will increase the sensitivity of the risk factor and decrease the specificity. Thus, the ability to adequately identify "high risk" individuals is likely to decrease.

Validity/relevance of included risk factors

Defining the risk factors "correctly" is not always enough. It is of fundamental importance that the risk factors included in risk estimates, discussed in guidelines, and recommended as targets for medical intervention are in fact valid and relevant - valid as risk factors for the disease in question and relevant as treatment targets. Paper III discusses the validity of total cholesterol as a risk factor for CVD.

For any factor to be valid for inclusion in a combined risk estimate, it has to improve the predictive ability of the prediction model. It does not necessarily have to be a "true risk factor" in the sense of a causal factor. Statin use may, for example, be useful in a model applied to the general population to predict CHD events, even though statin use is not a causal factor, because statins are primarily used among individuals at

considerably higher risk of CHD than the general public. The results of Paper III indicate that total cholesterol may not be valid as it is currently used in most combined risk estimates. The possibility arises that total cholesterol is merely a *risk marker* rather than a *risk factor*.

For risk factors (or markers) to be valid as targets of intervention, an effective treatment to lower the risk factor levels has to be available, and the effect has to be reflected in decreasing incidence in patient-important outcomes. Statins are the only treatment option demonstrated decisively to lower both total cholesterol and mortality (see section 2.2.2). Lowering cholesterol to a certain level with statins is more effective, regarding patient-important outcomes, than reaching the same cholesterol level with any other drug. The fact that statins have a range of documented effects, other than lowering cholesterol (Meng 2005; Vaughan et al. 1996), inhibiting atherosclerosis and atherothrombosis supports the hypothesis that cholesterol lowering in itself might be of little causal importance. Thus, total cholesterol may not be valid as a target of therapy and might perhaps be abandoned as such in the future. Replacing it with a different lipid particle (such as LDL or ApoB) might be a relevant step.

Current guidelines of CVD prevention lump together a number of *clinical outcomes* related to coronary circulation as well as the peripheral circulatory system. Emerging evidence suggests that the impact of cholesterol as a risk factor/marker might not be the same for IHD and cerebral stroke (Hamer et al. 2011; Prospective Studies 2007). There is indeed a possibility that cholesterol will in the near future be proven to have partially different roles in (or related to) the pathogenetic processes of heart and brain vascular diseases. If this is so, clinical advice related to preventing one outcome (IHD) may not have the same validity for the other and, to many people, even more threatening clinical outcome (cerebral stroke).

Validity/relevance of excluded risk factors

As discussed in section 2.2.4 there is much evidence available on various risk factors that are discussed in the guidelines only to a small degree or not at all, not to mention their inclusion in the risk estimates. Some of these are of limited relevance for practical

reasons, e.g., “risk genes” with low prevalence and/or penetrance (Levely et al. 2011), and markers that are difficult or expensive to measure, such as apolipoproteins (Sniderman et al. 2003) and air-pollution (Zhang et al. 2011). However, there are some risk factors that guideline authors tend to exclude that might be relevant. These factors may be deemed irrelevant or impractical for recommendations, or the authors might simply not be aware of their significance. Low socioeconomic status has been shown to be an important risk factor for CVD (Marmot et al. 1984 and 2008) but is hardly ever included in risk calculators and rarely discussed in guidelines. Recommendations on interventions for improving SES (or inequity in a society) would of course be beyond the scope of guidelines on CVD prevention, but information on SES is likely to improve the risk estimate (Hippisley-Cox et al. 2010).

Substantial discussion of psychosocial factors is hard to come by in the guidelines. The 2007 European hypertension guidelines (Mancia et al. 2007) studied in Paper II are a good example of this. The reference list of the guidelines includes 825 references, none of which discuss psychosocial risk factors. The discussion is often limited to recommending that depression and anxiety disorders might affect risk and should be treated. Such recommendations often get lost in these reports, which tend to be of considerable length. The importance of stress and existential trauma is rarely addressed, and the 1962 WHO recommendations of “common-sense psychotherapy” for essential hypertension (WHO 1962) are long forgotten. This is, however, not always the case, and I see signs that the situation is improving. The Norwegian CVD prevention guidelines, for example, explicitly state that psychosocial factors such as low SES, poor social network, existential trauma, and high stress levels increase the risk of CVD (as depicted by the risk estimation chart), and recommend interventions where appropriate (Norheim et al. 2009).

Co- and multimorbidity is another important aspect seldom addressed by guidelines' authors, apart from that of existing renal disease and diabetes (Boyd et al. 2005; Starfield 2011). Multimorbidity is a growing problem in the aging Western populations that needs to be considered in therapeutic management of patients (Boyd and Fortin 2010; Parekh and Barton 2010). Addressing multimorbidity specifically in the CVD

prevention guidelines may lead to recommendations on a more aggressive therapeutic approach to a patient with multiple comorbidities because the comorbidities may potentially increase the risk of CVD. Alternatively, less aggressive medical intervention may be recommended due to the risk of polypharmacy and adverse effects. Parekh and Barton state:

> The tremendous efforts in the fight against chronic disease have inadvertently created individual disease "silos," which are reinforced by specialty organizations, advocacy groups, disease management organizations, and government at all levels. Transformation from a single chronic condition approach to a multiple chronic conditions approach is needed (Parekh and Barton 2010:1304).

The "silo" approach strikes me as an excellent metaphor for describing the scope of most preventive, clinical guidelines and recommendations. Disease specific mortality and morbidity is consistently emphasised, while all-cause mortality is hardly ever mentioned. To GPs and patients, however, the statistical endpoint *death,* irrespective of cause, may be a good starting point for a nuanced discussion of potential medical interventions. The "silo-vision" may easily lead to dilemmas when multiple guidelines targeting multiple diseases in a single individual are not easily combined because of, for instance, drug interactions. The situation is further enhanced by specialists, patient organisations and other stakeholders who compete to draw attention to "their" disease. In its ultimate consequence, the "silos" may come to overshadow the individual persons' unique situation and needs. Important factors might become excluded from consideration by one silo specialist because they are dealt with in guidelines which pertain to another disease silo.

Validity of combined risk estimates

The combined risk estimate, originally developed by the Framingham research team, is an intuitively appealing idea which is currently recommended in most CVD guidelines. However, current international risk algorithms appear to have limited validity and relevance for general practice, at least in Norway and possibly in many other countries as well, if the results of Papers I-II are generalisable to similar contexts. These risk

algorithms appear to offer good sensitivity for the high-risk individuals but poor specificity. For a risk algorithm to be valid for use in a specific population it has to be based on representative data. The data has to be considered in the context of time and geographical origin, reflecting factors such as mortality rates, economy, pollution, and quality of health care systems – i.e., factors confounding the associations of traditional biological risk factors with CVD incidence/mortality on a population basis. The European SCORE risk algorithm (Conroy et al. 2003) is, for example, based on 76 cohorts from 12 countries and data gathered in the 1970s and 1980s. This seriously affects the validity of the algorithm in any population 30-40 years later.

National algorithms based on local data may possess considerably better predictive properties but, as discussed in Papers III-IV and in the paragraphs here above, these algorithms might also have significant, correctable, inherent errors. Careful critical appraisal of the current risk factor definitions (including cut-offs), and the validity and relevance of the risk factors included as well as those not included might raise the predictive value of the algorithms to higher standards. Action levels (risk levels where intervention is recommended) also have to be carefully evaluated in association with the workload likely to result.

A recent systematic review (Liew et al. 2011) reported some additional limitations of 21 CVD risk scores studied. The risk scores differed considerably in terms of population, predictors and outcomes, making them non-interchangeable. Some of the algorithms were based on cohorts with missing data on specific risk factors for substantial proportions of individuals, sometimes over 60% (Liew et al. 2011). And, thirdly, effect of treatment (i.e., treatment at baseline or treatment "drop-in") was not considered fully by any of the algorithms, which might cause an underestimation of risk, especially in the high risk category.

In a wider perspective, alternatives to the combined risk estimate approach have been suggested. In 2003, Wald and Law suggested an approach to CVD prevention more resembling a mass strategy than a high-risk approach (Wald and Law 2003). They suggested the development of "the polypill", which would combine six active

components (statin, thiazide, β-blocker, ACE-inhibitor, folic acid, and aspirin) in one pill and could lower the individual CVD risk considerably. They suggested the polypill be recommended for every adult above age 55 and younger people with symptoms of occlusive arterial disease. No measurements of BP or cholesterol would take place, either before treatment initiation, or for monitoring the treatment. This way the CVD burden of the population as a whole would be significantly decreased, and more so than by focusing specifically on high-risk individuals. At the same time, resources would be saved by dropping the usual screenings and follow-ups, making this approach more cost-effective on the whole than the usual approach. The main problem with this method is that for some individuals the risk of adverse effects of the intervention would be higher than the potential benefit, which would violate the *primum non nocere* principle. According to Wald and Law, this would be rare (Wald and Law 2003). Identifying those unlikely to benefit from the polypill (i.e., those with low CVD risk) might be suggested, but that brings us right back to the starting point with screening for high-risk individuals.

Although the polypill strategy has some important flaws and currently seems an unlikely or inappropriate option, it is thought-provoking and challenges the current standards; such challenges are necessary for progress in the field. Age is by far the most important risk factor and adding more and more risk factors to a statistical prediction model already including age, no matter how good the model is, cannot improve the prediction (discrimination) more than a few percent (Cook 2007; Wald and Law 2003). CVD risk algorithms have an (unidentified) upper limit of positive and negative predictive value, and it does not seem to be very close to 100%. It will always be a judgement call whether the improvement in prediction, obtained by measuring risk factors, is worth the resources invested.

Non-adherence to EBM principles

Although clinical guidelines are often touted as "EBM-documents", significant deviations from the principles discussed in section 2.3 are often to be found. Guidelines on prevention of CVD vary considerably in this regard. The 5-step summary of how to

develop EBM-guidelines provided in section 2.3.2 can act as a simple guideline-evaluation tool.

1. Define questions to be addressed

The defined clinical question is not always clear enough regarding the relevant patient groups, all relevant management options, and all relevant outcomes. Guidelines on primary prevention of CVD usually do not exempt patients with comorbidities (other than CVD) but rarely address practical considerations such as *frailty* and *polypharmacy*, the exception being pregnant women and patients with diabetes or renal disease (Graham et al. 2007; JNC 2003; Mancia et al. 2007; Norheim et al. 2009). Treatment of the elderly is usually discussed without considering comorbidities (Boyd et al. 2005). Discussion of psychosocial risk factors and appropriate management options tends to be minimal or none at all (JNC 2003; Mancia et al. 2007) although this is not always the case (see, e.g., the 2009 Norwegian guidelines (Norheim et al. 2009)). Regarding outcomes, guidelines tend to address the adverse effects of preventive treatment (see chapter 4.3) only to a very limited degree (including inconvenience and psychological burden), at least not in a transparent manner.

2. Critically appraise available systematic reviews and/or prepare new ones

Discussion of systematic reviews is often inadequate which makes it difficult to evaluate how extensive the literature search has been, and whether all relevant issues have been addressed (see, for instance, Graham et al. 2007; Mancia et al. 2007).

3. Assess the relative importance of outcomes

Assessment of the relative importance of outcomes depends on (all) the relevant outcomes being clearly and explicitly defined in the first place, which is usually not the case. Thus, this assessment is rarely transparent.

4. Prepare an evidence profile

Clear, schematic evidence profiles are extremely rare in CVD prevention guidelines. Invariably the guidelines present a narrative (and/or schematic) summary of the evidence supporting specific recommendations. This presentation often lacks

information on absolute risk (reduction). The guidelines depend on various systems for grading the evidence and information on limitations (of the evidence presented) is often lacking.

5. Assess the quality of evidence and decide on the direction and strength of recommendations

Since evidence profiles are usually incomplete or not presented at all, the assessment of the quality of the evidence is not transparent, and decisions on the direction and strength of recommendations become difficult to evaluate. The evaluation becomes even more difficult since guideline authors rarely adequately state the relative importance of outcomes and the values and preferences on which the recommendations are based.

Additionally, discussion on the resource use associated with the implementation of the guidelines is often scarce (Graham et al. 2007; JNC 2003; Mancia et al. 2007) or underestimated (Getz et al. 2004 and 2005). This is especially important when certain recommendations seem to be based on expert (guideline authors') opinion to a large extent, rather than objective evidence. An example of this is the recommendations on the rate of follow-up visits given in the 2007 European hypertension guidelines (Mancia et al. 2007) where no references are cited on this matter. While issues of resource allocation do not receive much attention, guideline authors rely rather on predictions of cost-effectiveness, which are usually of debatable validity (Järvinen et al. 2011).

4.2.3. Evidence not "good enough"

The third potential source of limitations of the guidelines is the available evidence they rely on. The evidence may be inadequate to support the recommendations of the guidelines; an *evidence-gap* may exist in important areas, and the current mainstream interpretation of the available evidence may not be adequate to serve the task of prevention as well as possible.

"Pharmaceutical bias"

The pharmaceutical industry has broad-based influence on medical research and practice. It is widely documented that industry-sponsored drug trials tend to yield more positive results for the drug and the pharmaceutical companies involved (i.e., show more effect) than trials with independent sponsors (Lexchin et al. 2003; Schott et al. 2010). Pharmaceutical companies have been found to deliberately avoid publishing negative results and making the data unavailable for analysis by independent researchers (Ghaemi et al. 2008). Further impact on practice is gained by advertising campaigns directed at doctors and patients (HEART UK 2011; Under 5 2011), and direct (financial) incentives to doctors, guideline authors, and policy-makers (Moynihan 2006 and 2010; Neuman et al. 2011). In addition, the pharmaceutical industry, as well as providers of other medical supplies and technology, is a major contributor to medical research. Obviously the industry will focus on trials for advertising and justifying use of their products, reflected in study designs and research fields. The synergy of all these factors causes an enormous *pharmaceutical bias* in research and practice. The result is more *evidence production* in profitable research areas, compared with less profitable ones (non-pharmacological treatment); bias of the available evidence in favour of drug treatment; influential actors (politicians, guideline authors, etc.) have conflicting interests (Moynihan 2006 and 2010; Neuman et al. 2011); patient organisations demand "the best" (new and/or expensive) treatment options and tests available; and physicians are bombarded with selective information (HEART UK 2011; Moynihan 2010; Under 5 2011).

Like any manufacturer of any other product, a pharmaceutical company benefits from increasing the number of its customers. This can be done by increasing the company's share of the existing market (marketing campaigns, etc.) or by enlarging the market. By widening the definitions of a disease or a risk factor (wider indications for drug use), the potential market can expand enormously. This has happened in many areas, such as BP- and cholesterol-lowering treatment. The JUPITER trial (Ridker et al. 2008) is a good example of this kind of a marketing strategy. Thus, the pharmaceutical industry can affect the definitions of risk factors (Moynihan 2006), diseases, and "pre-diseases" (Moynihan 2010). This is a form of medicalisation and disease mongering.

Surrogate end-points

Trials of preventive interventions are often designed to document drug effects on surrogate end-points, since (statistically significant) effect on mortality may take many years to document, while effect on, e.g., BP may take only weeks to detect. Popular surrogate markers are, e.g., BP, cholesterol, and carotid intima-media thickness (on ultrasound). While this decreases the time and costs necessary to conduct a trial, it also decreases the validity of the results. Although LDL, for example, is a documented risk factor for CVD and mortality, and many drugs have been shown to lower LDL, only statins have been shown to decisively reduce mortality (see section 2.2.2). Thus, an effective reduction in a risk factor does not necessarily translate into reduction in mortality. Basing guideline recommendations on evidence of risk factor lowering but not effect on mortality or CVD events can introduce bias.

Combining fragmented knowledge

It is obviously beneficial to minimise potential confounding effects in any research. When studying the effects of a certain drug on a specific risk factor or mortality, it can be beneficial to "isolate" the effects of the drug in question, e.g., by including only healthy participants not using any other drugs. However, such results can only be generalised to similar populations of healthy individuals. But clinical reality is far more complex (Strand et al. 2004). Inevitably, many patients evaluated for CVD prevention will have other chronic conditions with associated drug treatment, such as asthma, osteoporosis, arthritis, pain syndromes and depression. The guidelines recommend the same BP and cholesterol lowering treatment for everyone. Prescriptions that are initiated or recommended by different disease specialists (or guidelines) can, however, result in *polypharmacy*, which may prove suboptimal or even harmful with respect to some patients' overall health and safety (Boyd et al. 2005; Schuler et al. 2008). This problem is seldom addressed and documented in clinical trials. Of course, an RCT cannot be conducted for every combination of drugs and diseases, but great caution should generally be shown when "lumping together" disease-specific drug regimens in individuals with co- and multimorbidities. Polypharmacy, as widely practiced today, is not in accordance with the standards and principles of EBM.

Polypharmacy is just one of the problems associated with combining pieces of evidence obtained from narrowly focused research. The mainstream biomedical research method is to defragment the human being in a Cartesian way (Getz 2006) and combine again the pieces of evidence obtained. Although regarded methodologically correct, this may not lead to the right conclusions. The lipid-lowering drug ezetimibe can be taken as an example. Even if ezetimibe has beneficial effects on the lipid profile, it does not mean that it will have a beneficial effect on CVD development in a specific individual in his context of social surroundings, risk factors, diseases, and drugs.

Combined risk estimates can be regarded as another example. Linear relationships between risk factors and disease are assumed, without studying the possibility of, for instance, U-curve phenomena, and the risk factors combined in a mathematical prediction model. Even though the details of the models are correct, from a certain perspective, the predictive ability of the model has to be checked thoroughly for validation in the target population. Such validation analyses do not always precede the implementation of the risk estimates.

Cost effectiveness analyses are important for supporting recommendations of the use of therapeutic interventions – i.e., comparison of the cost of the treatment versus the direct and indirect gain, such as decreased mortality, morbidity, and hospitalisation. The majority of the available cost effectiveness analyses are, however, subject to considerable bias. Usually these are statistical cost prediction models based on the results of RCTs (with selective inclusion criteria, etc.), not representing the clinical reality of general practice (Järvinen et al. 2011). Such cost effectiveness analyses are thus likely to overestimate the benefit of the treatment, which may affect the validity of recommendations.

Evidence gaps in important areas

There appears to be an evidence gap regarding certain aspects of CVD and prevention. This is especially the case in non-pharmacologic intervention and the humanistic aspects of cardiovascular illness aetiology. Section 2.2.4 discusses themes where an abundance of research opportunities seems to exist. Interventions for allostatic-

overload, for violated integrity and traumatic life-events have only to a small degree been addressed in the context of CVD. Perhaps it is time for a serious evaluation of the role of *narrative-based medicine* and "common-sense psychotherapy" (WHO 1962) in CVD prevention. These interventions are, however, not immediately suited for RCTs, and they do not attract much interest from industrial sponsors.

"Vulgar Cochranism"

The recently introduced concept Vulgar Cochranism has been discussed in detail in section 2.3.4. Vulgar Cochranism does not refer to inadequate *evidence* as such, but rather to presumptuous and erroneous use of evidence. First, available evidence may be applied beyond the range of its validity (combining fragmented knowledge, see above). Second, there is excessive emphasis on RCTs and pharmaceutically biased evidence, downgrading non-pharmacological interventions and evidence involving structural, societal phenomena and psychosocial risk factors. The evidence gap discussed above is exaggerated and ignored at the same time by overlooking the available evidence in the field as well as the research opportunities. Third, the role of clinical expertise of (general) practitioners (for whom the guidelines are intended) is devaluated and, with aggressive assertiveness, attempts to adjust the guidelines to clinical reality are met with labels such as *clinical inertia*. Vulgar Cochranism is overbearing, and criticism of guidelines' shortcomings is not well tolerated.

4.3. Adverse effects of prevention

It is a common view that *prevention is better than cure*. This is often true, but not in a general sense at any cost. CVD prevention can be expensive – for the individual, the health care system, and society, both in terms of money and other resources, such as physicians' consultation time (see Paper II). For interventions to be recommended by guidelines, they preferably have to be estimated as cost-effective. However, health care systems do not have unlimited resources, and choices have to be made regarding which projects to invest in and to what degree. It seems obvious that to increase the resources invested in CVD prevention, cuts have to be made in other areas, even if the prevention is highly cost-effective. Before criticising physicians for clinical inertia and demanding

better guideline adherence, policy makers and guideline authors should perhaps suggest activities in general practice that can be decreased or abandoned.

In addition to direct pharmacological side-effects and drug interactions, preventive drug prescription exposes individuals to another potential health hazard which has not received much attention: the *nocebo effect* of being labelled as "a patient", as well as of consuming tablets, possibly without any obvious subjective (or objective) benefit (Barsky et al. 2002; Hahn 1997; Haynes et al. 1978; McCormick 1998; Olshansky 2007; Sångren et al. 2009).

The exponential increase in papers published on risk in recent decades, and the accompanying increase in defined risk factors, has been called "the risk epidemic" (Skolbekken 1995). Due to the epidemic of inflating risk factors, fuelled by enthusiastic biomedical reductionism and Vulgar Cochranism, everybody seems to becoming at risk of being diagnosed as *at risk*. It can hardly be practical to label the majority of the population "at increased risk", and ethically doing so is highly questionable. Mass stigmatisation is hardly a good preventive strategy. In the end "life itself is a universally fatal sexually transmitted disease" (McCormick 1998:166), and the risk of death and disease cannot be reduced to naught. A responsible and sustainable preventive strategy has to allow for a realistic level of acceptable risk. "The Zero-vision" is harmful to preventive medicine and harmful to the health of the population (Fugelli 2003 and 2006).

Those practicing Vulgar Cochranism usually do not take these adverse effects into account when estimating cost-effectiveness and demanding implementation of "evidence-based treatment".

The harmful effects of preventive interventions and their excessive use have raised voices of concern (Starfield et al. 2008). An emerging concept called *quaternary prevention* has even been defined as an important task of GPs (Kuehlein et al. 2010). Referring to the dangers of excessive medical activity, quaternary prevention is defined as: "an action taken to identify a patient at risk of over-medicalization, to protect him

from new medical invasion, and to suggest to him interventions which are ethically acceptable" (Bentzen 2003). The World Organization of Family Doctors (WONCA) has identified excessive implementation of interventions for therapeutic and preventive purposes, often with little or uncertain effect, as a real threat to the health of patients and populations that needs to be addressed and considered in clinical practice (Kuehlein et al. 2010; Starfield et al. 2008).

4.4 Conclusion

In theory, clinical practice guidelines on prevention of CVD offer an excellent opportunity for education and quality improvement in general practice. However, there currently appears to be a range of factors limiting the validity and relevance of such guidelines, at least in Norway. Such limitations may have important effects on clinical practice and resource allocation, as well as population health. The guidelines appear to overestimate CVD risk and fail to correctly identify a manageable proportion of the population as "high-risk individuals", for whom individual preventive strategies would be effective and beneficial. The strategy of targeting individuals at risk ("high-risk strategy") ends up being recommended at the level of mass strategy, which can hardly be regarded as sustainable or responsible.

Many factors limit the validity and relevance of current guidelines for prevention of CVD in general practice. The factors I deem most important can be summarised in three terms: *Vulgar Cochranism*, *silo-vision*, and *zero-vision*. Vulgar Cochranism refers to the presumptuous use of evidence, applying trial results and conclusions outside their range of validity, as well as arrogance and aggressive assertiveness leading to an almost unconditional justification of recommendations based on evidence that has been selectively defined as the most (or only) valid evidence. Subsequently, adherence to these recommendations may be regarded as morally and even legally mandatory, and non-adherence is harshly criticised. Silo-vision further adds to the problems of Vulgar Cochranism, with its narrow focus on a specific disease or a group of diseases (such as CVD) without addressing the person as a whole, ignoring important factors such as multimorbidity and polypharmacy. Silo-vision can lead to the exclusion of significant

factors, such as mental stress and social circumstances, based on subjective interpretation and preferences (of guideline authors) alone. Finally, zero-vision may lead to unattainable goals being set. For instance, the elimination of premature CVD mortality, say, death before age 70 in Norway, may sound like an appealing goal, but it is hardly realistic when resource allocation is considered.

Vulgar Cochranism, silo-vision, and zero-vision are factors involving mentality and culture and are, therefore, not easily altered. However, many factors have been addressed in this thesis that may prove less resistant to improvement efforts. These include, e.g., considering psychosocial risk factors in combined risk estimates, depending on evidence of patient-important outcomes rather than surrogate end-points, and re-assessing the validity of risk factor definitions, such as defining obesity with measures of central adiposity rather than with BMI.

5. WAYS TO IMPROVEMENT - A PROPOSAL

I see considerable room for improvement when it comes to clinical guidelines on CVD prevention in general practice. Some aspects might be significantly improved by relatively simple (yet potentially controversial) manoeuvres, including altering cut-off points to diminish the at-risk groups. Other aspects would require more fundamental change in thinking about the problem of CVD as a whole.

I regard eliminating *Vulgar Cochranism* to be of highest priority, not only to ameliorate clinical guidelines as such but also to safeguard the academic integrity of medicine in general. Vulgar Cochranism is, by definition, not in accord with good academic practice. Selectively down-grading or even excluding certain types of evidence and research fields is ethically unjustifiable and cannot be practical in the long run. Likewise, aggressively asserting favoured evidence, stigmatising colleagues as "clinically inert" and attempting to tyrannise professionals who raise critical voices is not consistent with academic openness and debate.

General improvement in the understanding of what *evidence-based medicine* really is and is not is needed among many professionals and policy-makers. It is also time for researchers and practitioners to raise their awareness above narrow silo perspectives on diseases and risks. I certainly acknowledge that silo-vision may be helpful, or even necessary, in many situations, particularly in organ-specialised hospital wards. But in primary health care silo-vision cannot be defended as a general approach. All stakeholders in the healthcare system must respect this fact. Furthermore, the silo approach is inadequate as a main approach in scientific medicine; since it is not compatible with real patients' lives, too much reliance on the approach is logically bound to limit advancement in the field. For optimal treatment of a person's health profile (illness, risk and disease pattern), understanding the whole person in his or her context is necessary. This comprehensive view includes the person's biological status, past and current life stressors, and social and cultural surroundings. New evidence is currently emerging which facilitates a much deeper understanding of the

interdependency of all these factors. Research in epigenetics and stress physiology (including the concept allostatic load and research on the dynamics of the chromosomes' telomeres) offers an unprecedented possibility to understand, for instance, how mental stress and/or integrity violations fuel the development of diseases in general and CVD in particular. This new evidence may also contribute considerably to explaining the fundamental and general relationship between social inequity and health. In the 2001 Harveian Oration, Iona Heath asks:

> The socio-political construction of health inequality has become undeniable (Holtz et al. 2006). As society becomes ever more economically polarised, health is systematically damaged by the structural violence this entails and yet governments still appear to believe that health inequality can be tackled in isolation from the socioeconomic inequality that drives it. Doctors have seemed content to collude in this offloading of responsibility through the rhetoric of 'lifestyle medicine' (Porter 2006), a sophisticated variant of the age-old game of victim-blaming. Paul Farmer argues that the central contributions of medicine and public health to 'future progress in human rights will be linked to the equitable distribution of the fruits of scientific advancement' (Farmer 1999). How can we ensure that this is taken to apply to scientific advances in the biology of biography just as much as to advances in biotechnology? (Heath 2011:18-19)

Continued adherence to *the silo-vision* would typically lead to focusing on pharmaceutical interventions to counteract telomere erosion, instead of increasing human support to care-givers of chronically ill patients, whose telomeres statistically tend to erode faster than "normal" (Heath 2011).

The *zero-vision* is in line with Vulgar Cochranism and silo-vision. It fits poorly with true EBM and person-focused care. With a change in the approach to CVD (and other chronic diseases), where issues like quality-adjusted life-years, resource allocation, and opportunity cost would become more important than ICD codes for causes of death, the zero-vision would be bound to fade.

Significant improvement regarding the above-mentioned factors would depend on fundamental change in the mentality of mainstream medicine: the overall focus needs to

be shifted away from the biotechnological approach to the "average body", to a more holistic approach to the unique *person*. If I am challenged to present recommendations on a more immediate and practical level, directly related to improvement of the validity and relevance of CVD prevention guidelines for general practice, I suggest the following set of relatively demarcated issues:

1. Transparency is crucial at all levels of guideline development, regarding the authors' conflicts of interest, the methods of guideline development, the critical appraisal of evidence, the values and preferences behind the recommendations, etc.
2. Adherence to a comprehensive, structured, and explicit system of guideline development, such as the GRADE system, may offer considerable advantages and decrease the likelihood of important issues being ignored. Such adherence includes:
    a. a well-defined question should be addressed covering all relevant patient groups (including the elderly and multimorbid), all relevant interventions (including non-pharmacological), and all relevant patient-important outcomes (including all-cause mortality, morbidity, and adverse effects);
    b. conducting a systematic review (or relying on an existing one);
    c. quality assessment of the available evidence;
    d. transparent assessment of all the relevant harms and benefits of interventions that the recommendations cover.
3. Adverse effects of interventions should be explicitly considered, including the harm of labelling subjectively healthy individuals as patients "at risk".
4. Efforts should be made to limit "pharmaceutical bias", by identifying and highlighting non-pharmacological intervention strategies and minimising conflicts of interest among guideline authors.
5. Evidence of effects on surrogate markers should not be regarded as equivalent to (or likely to be equivalent to) effects on patient-important outcomes.
6. Re-assessment may be needed of the validity of definitions of certain risk factors, such as the use of BMI levels to define obesity.

7. Re-assessment of the validity and relevance of risk factors addressed in the guidelines is warranted; the use of total cholesterol is a good example.
8. An extensive assessment should take place of the validity and relevance of risk factors that tend to be excluded from the guidelines, including mental stress and low SES.
9. Combined risk estimates should be validated in any given population before recommended for implementation.
10. Resource use has to be thoroughly addressed. Preferably, resource use should be discussed in relation to issues such as disease burden, quality-adjusted life-years, all-cause mortality, and opportunity cost.

This is not an exhaustive list but my recommendations on possible ways to improve the validity and relevance of guidelines on prevention of CVD for general practice.

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Paper I

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Can individuals with a significant risk for cardiovascular disease be adequately identified by combination of several risk factors? Modelling study based on the Norwegian HUNT 2 population

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Abstract

Rationale, aims and objectives Clinicians are generally advised to consider several risk factors when evaluating patients' cardiovascular disease (CVD) risk. Our aim was to study whether combined assessment of five traditional risk factors might help doctors demarcate a relatively distinct and manageable group of high-risk individuals. We selected five modifiable risk factors and estimated the proportion of a well-defined population with 'unfavourable' levels of at least two of them, as defined by four internationally renowned guidelines. The impact of including so-called 'prehypertension' among the risk factors was specifically addressed, and the results are discussed in a wider perspective.

Material and methods Guideline implementation was modelled on data from a cross-sectional Norwegian population study comprising 62 104 adults aged 20–79 years (The Nord-Tröndelag Health Study 1995–7). Total, age- and gender-specific point prevalences of individuals with zero, one, two, three or more factors, in addition to established disease, were calculated.

Results One single CVD risk factor was exhibited by 12.4% of the population; two factors by 21.5%; and three or more by 49.7%. Established CVD or diabetes mellitus was reported by 12.5%. In total, 83.7% of the population exhibited a risk or disease profile with at least two factors, if prehypertension was included.

Conclusions If guideline recommendations are literally applied, as many as 84% of adults in Norway could exhibit two or more CVD or risk factors and thus be considered in need of individual, clinical attention. This challenges the widely held presumption that 'the net will close' around a manageable group of individuals-at-risk if several risk factors are jointly considered. As the finding of this study arises in one of the world's most long- and healthy-living populations, it raises several practical as well as ethical questions.

Introduction

Cardiovascular disease (CVD) is currently the major cause of death in the Western world, including Europe (see e.g. http://www.heartcharter.eu). Mortality from CVD has, however, declined substantially since the 1970s [1], and many Western populations appear to be undergoing the resolution phase of a so-called 20th-century epidemic of CVD. This epidemic reportedly began in the 1930s and peaked in the 1950s and 1960s. The epidemic's impact on medical thought and practice has been profound, but still, the reasons behind the rise and fall of CVD in the 20th-century are far from clear [2]. In view of the new 'epidemics' of obesity and diabetes, there is a widespread concern that the burden of CVD will start to rise again.

Large-scale medical searches for factors that could predict future heart disease began shortly after World War II with the

establishment of the US Framingham study. Around 1960, hypertension, hypercholesterolemia and smoking were singled out as the three most apparent risk factors for ischaemic heart disease. Since then, increasingly detailed knowledge regarding the impact of numerous measurable and potentially modifiable biological risk factors and risk markers has been published [2]. Development and marketing of tolerable and presumably safe antihypertensive and lipid lowering drugs have contributed much to the immense interest in CVD prevention among researchers and clinicians.

In 1962, the World Health Organization published the first international report on the importance of blood pressure control [3]. After this milestone publication, subsequent generations of clinical recommendations and guidelines regarding blood pressure as well as a steadily increasing number of other measurable risk factors have been released on both sides of the Atlantic [4–13]. With time, the thresholds for clinical intervention on the basis of single risk factors have been lowered several times. Redefinition of a risk factor cut-off point inevitably leads to a corresponding change in the number of individuals that will be categorized as 'at risk' and in need of clinical attention [14,15]. In 2004, our research group documented that implementation of the 2003 European guidelines on CVD prevention could label as much as 76% of a general Norwegian population aged 20 years and older, and 90% of individuals aged 50 years and older, as having unfavourably high cholesterol and/or blood pressure levels [15]. Arising in the context of one of the world's longest-living and healthiest-living populations [16], this finding was highlighted in an editorial in the *British Medical Journal* [17]. A heated debate followed on the *BMJ* website [17]. Key authors of the European guidelines entered the debate and stated that the focus on single risk factors represented a startling lack of understanding, and argued that the European guidelines would not lead to medicalization of whole populations since CVD risk should in practice be evaluated on the basis of a *combined risk factor estimate*. This advice was (and still is) in line with mainstream clinical recommendations for good practice [7,9,13]. The crucial question, however, is how well-combined risk evaluation strategies actually work in practice. Will they, as intended, aid clinicians to define a relatively well-demarcated and manageable high-risk group who can be targeted for further follow-up?

Formal, combined risk calculators

From the viewpoint of the practicing clinician, there are in principle two ways of performing a combined CVD risk evaluation. The first method involves a formal 'risk prediction algorithm' or 'calculator' developed on the basis of epidemiological outcome data. The level of a given individual's conventional risk factors (modifiable, such as blood pressure, cholesterol and smoking; and unmodifiable, i.e. age and gender) will be fed into the algorithm and result in a computed estimate of risk (for disease events or mortality). The first algorithm of this kind was based on the US Framingham study [18]. The Framingham model has later been updated and adjusted for use both in the United States and in Europe. In 2003, a European risk system called SCORE (Systematic Coronary Risk Evaluation) was launched, based on data from 12 European cohort studies recruited from the 1970s on [9,19,20]. In 2003 and 2007, European guidelines on CVD prevention based on the SCORE system have been published [9,12].

Although a combined risk approach may often represent an adequate, general approach to CVD risk evaluation, the clinical implementation of combined CVD risk algorithms has encountered problems. It has been well documented in a variety of settings that both the US Framingham and the European SCORE models may lead to significant overestimation of risk [9,12,21–23]. In 2005, our research group went on to document that implementation of the SCORE risk system, as outlined in the 2003 European guidelines on CVD prevention, could also label a majority of the above-mentioned Norwegian population as in need of 'maximal clinical attention' due to high *combined* risk [21].

The main reason for the risk calculators' tendency to statistically overestimate risk is most likely the previously mentioned epidemiological decline in CVD incidence leading to a so-called 'retrospective risk bias' [12,21]. To tackle this dilemma, guideline authors recommend that risk calculators be calibrated against national data. But even in the presence of mathematically valid risk calculators, the size of the high-risk group might still be so large as to represent a major challenge.

Consideration of multiple risk factors

Clinicians who do not have access to a calibrated and validated risk calculator for use in their local setting are likely to apply a more straightforward approach to combined risk evaluation. The typical case would involve an otherwise healthy person who presents with a moderately increased blood pressure, or a moderately increased cholesterol. In this situation, the doctor may or should, according to guidelines, consider the level of other risk factors before deciding on further action. The presence of more than one elevated risk factor (beyond the currently recommended cut-off point) would strengthen the argument for clinical intervention, while absence of additional risk factors might justify a more expectant approach.

The aim of the present study was to examine the practical usefulness of the latter CVD risk evaluation method from a clinical viewpoint. We selected five modifiable risk factors, and with reference to recommended cut-off points in four internationally renowned guidelines, studied what proportions of a given Norwegian population would exhibit 'unfavourable' levels of at least two of them. In our analysis, we specifically addressed the emerging risk (or literally pre-risk) factor called 'prehypertension' (120–139/80–89 mmHg) which has been included in some guidelines since 2003 [8]. Other more recent guidelines avoid using this ambiguous, medical term. They label a blood pressure level of 120–129/80–84 mmHg as 'normal', but indicate that it is not optimal. The level 130–139/85–89 mmHg is termed 'high normal' [9,11,13]. Whatever terminology used, blood pressure in the ranges 120–139/80–89 have attracted increasing attention as a risk factor for CVD among researchers and clinicians in the field of CVD prevention [24–26].

Materials and methods

Based on data from a large and well-organized Norwegian population study: the Nord-Tröndelag Health Study 1995–7 (HUNT 2 study) [27], we estimated the proportions of the population who would exhibit unfavourable combinations of risk factors, if evaluated according to the following CVD prevention recommenda-

Table 1 Overview of the selected risk factors' cut-off points in four clinical guidelines on CVD: the American Heart Association (AHA), European guidelines on CVD prevention in clinical practice (EUR), National Institute of Clinical Excellence (NICE) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)

Guideline	Regular assessment by health care providers	Medical treatment or follow-up by health care providers
AHA	BP ≥ 130/80 mmHg BMI ≥ 25.0 kg m^{-2} Waist circumference Men >102 cm Women >88 cm Smoking Family history of CVD	BP ≥ 140/90 mmHg
EUR	Cholesterol ≥ 5 mmol L^{-1} BMI ≥ 25.0 kg m^{-2} Waist circumference Men >102 cm Women >88 cm Smoking Family history of CVD	BP ≥ 140/90 mmHg Cholesterol > 8 mmol L^{-1}
NICE	BP > 140/90 mmHg Smoking	BP ≥ 160/100 mmHg
JNC 7	BP ≥ 120/80 mmHg	BP ≥ 140/90 mmHg

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease.

tions: The guidelines from the American Heart Association (AHA) [7], the European Society of Cardiology [9,12], the UK National Institute for Clinical Excellence [10] and the US Joint National Committee (seventh report, JNC 7) [8], respectively. The guidelines' recommended cut-off points are listed in Table 1.

When modelling the implementation of guidelines, we started by identifying individuals with self-reported myocardial infarction, stroke, angina pectoris or on-going antihypertensive treatment. Patients with diabetes mellitus (both types I and II) were also included here, as current guidelines recommend close CVD surveillance for these patients. We categorized these people as having 'established disease' and thus as eligible for clinical attention irrespective of current risk factor levels. Subsequently, all remaining individuals were categorized as 'below' or 'above' the recommended limits for the following measured and calculated CVD risk variables: blood pressure, total serum cholesterol, waist circumference and body mass index (BMI), and daily smoking. A family history of premature CVD was also considered as a risk factor.

The HUNT 2 population study

The HUNT 2 study was designed to investigate the significance of biomedical risk factors. Its design and methods have been described in detail elsewhere [27]. The overall participation rate in HUNT 2 was 76% among women and 67% among men (for both sexes combined 20–29 years: 49%; 30–39 years: 68%; 40–49 years: 77%; 50–59 years: 81%; 60–69 years: 86%). The present study is based on data from all participants aged 20–79 years (in total 62 104 individuals, 29 288 males and 32 816 females; see Table 2). The HUNT 2 population has been considered relatively representative for the total Norwegian population regarding demography, socioeconomic factors, morbidity and mortality [27].

Table 2 Participants in the HUNT 2 (1995–7) study according to age and gender

Age groups	Men	Women	Total
20–24	1 761	2 156	3 917
25–29	2 163	2 561	4 724
30–34	2 579	2 917	5 496
35–39	2 820	3 207	6 027
40–44	3 161	3 478	6 639
45–49	3 334	3 566	6 900
50–54	3 064	3 314	6 378
55–59	2 333	2 461	4 794
60–64	2 113	2 292	4 405
65–69	2 232	2 418	4 650
70–74	2 134	2 382	4 516
75–79	1 594	2 064	3 658
Total	29 288	32 816	62 104

In the HUNT 2 survey, blood pressure was measured on persons in seated position by specially trained personnel using a Dinamap 845XT based on oscillometry. Cuff size was adjusted after measuring the arm circumference, and blood pressure was recorded as the mean values of the second and third of three measurements performed consecutively at the same visit. Total cholesterol was measured by an enzymatic colorimetric cholesterolesterase method [27]. Height was measured to the nearest 1.0 cm and weight to the nearest 0.5 kg and BMI was calculated as kg m^{-2}.

In the present analysis, smoking was defined as daily smoking of cigarettes, cigars or pipe. Family history of CVD was defined as first-degree relatives (parents or siblings) with myocardial infarction before the age of 60 or stroke at any age.

For international comparison, prevalence rates were also calculated according to the European and World age standardization (Table 3) [28].

The SPSS statistical package, version 15.0 (SPSS Inc., Chicago, IL, USA), was used for statistical frequency analyses. All surveys in HUNT 2 were approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

Results

The prevalence numbers for each separate risk factor is shown in Table 4. Unfavourably, high blood pressure (including both hypertension and prehypertension) is the single most prevalent risk factor for which medical attention would be recommended, followed by total cholesterol. In many instances, the prevalence of the risk factors varied significantly when calculated according to the European and World age standardization.

About 98% of the population had at least one of the risk factors (or established disease conditions) in question. If 'prehypertension' was excluded, and only hypertension was considered, this number remained almost unchanged, or 95% (Table 4).

Figure 1 illustrates the potential impact of different blood pressure definitions according to the guidelines studied. Even the

minimal difference between applying a hypertension definitions of >140/90 mmHg versus ≥140/90 mmHg would affect 0.8–2.5% of the people within each age group. It is evident that prehypertension is present in a considerable proportion of the population. The currently recommended blood pressure cut-off points ≥130/80 mmHg (by the AHA guidelines) and ≥120/80 mmHg (by the JNC 7 guidelines) would have the greatest consequences among people younger than 50 years.

Table 3 Standardized age distribution of inhabitants in Europe and the world, as well as age distribution of the Norwegian population in 2005

Age groups	European standard	World standard	Norway
0–4	8 000	12 000	6 277
5–9	7 000	10 000	6 663
10–14	7 000	9 000	6 800
15–19	7 000	9 000	6 275
20–24	7 000	8 000	5 946
25–29	7 000	8 000	6 301
30–34	7 000	6 000	7 411
35–39	7 000	6 000	7 710
40–44	7 000	6 000	7 135
45–49	7 000	6 000	6 896
50–54	7 000	5 000	6 494
55–59	6 000	4 000	6 524
60–64	5 000	4 000	4 855
65–69	4 000	3 000	3 712
70–74	3 000	2 000	3 320
75–79	2 000	1 000	3 053
80–84	1 000	500	2 589
85+	1 000	500	2 038
Total	100 000	100 000	100 000

The shadowed area refers to the age groups in our study.

Figure 2 shows the point prevalence of people at different ages who are identified with established CVD, or with three or more, two, one, or zero of the CVD risk factors in question. After age standardization (Europe), it turned out that only 3.9% of the total population would be labelled as free, from both disease and all the above-mentioned risk factors. One single risk factor was exhibited by 12.4% of the population; two risk factors by 21.5%; and three or more factors by 49.7%. Established CVD or diabetes mellitus was reported by 12.5%. In total, 83.7% of the population exhibited a risk or disease profile which involved at least two cardiovascular risk factors.

Discussion

More than eight of 10 Norwegians may exhibit two or more CVD risk factors – or established disease – and thus be eligible for targeted clinical attention, if current recommendations are interpreted literally. Rather than aiding practicing clinicians to demarcate a reasonable large and manageable high-risk group with respect to further evaluation and follow-up, combination of risk factors appears to inflate the population at risk.

As can be seen from Table 4, prehypertension has a substantial impact on the population at risk, as long as blood pressure is considered in isolation. However, this effect almost vanishes when all five factors are considered jointly. This means that most people with prehypertension also exhibit one or more other risk factors, such as an unfavourably high level of cholesterol.

Table 4 Prevalence and 95% CIs of CVD and selected CVD risk factors in the HUNT 2 (1995–7) study as well as calculated prevalence according to the European and World age standardizations

Risk factors and diseases	Prevalence percentage (absolute numers)	Age standardized prevalence percentage				Number missing
		Europe	95% CI	World	95% CI	
Hypertension*	43.2 (26 687/61 844)	38.6	38.2–38.9	35.2	34.8–35.6	260
Prehypertension†	37.8 (23 390/61 871)	40.3	40.0–40.7	42.1	41.7–42.5	233
Cholesterol ≥ 5 mmol L^{-1}	75.8 (46 935/61 929)	72.1	71.7–72.5	68.7	68.4–69.1	175
Body fat						
BMI = 25.0–29.9	43.3 (26 718/61 667)	42.2	41.8–42.6	41.1	40.7–41.5	437
BMI ≥ 30.0	16.6 (10 217/61 667)	15.6	15.3–15.9	14.8	14.5–15.1	437
Waist obesity‡	18.4 (11 291/61 320)	16.6	16.4–16.9	15.4	15.1–15.7	784
Smoking	33.7 (18 288/54 244)	33.6	33.2–34.0	33.5	33.1–33.9	7860
Close relatives§ with CVD	32.7 (17 797/54 437)	30.3	29.9–30.6	28.1	27.7–28.5	7667
Established disease and/or on preventive treatment	15.8 (9 754/61 769)	12.5	12.3–12.8	10.5	10.3–10.8	335
Myocardial infarction	2.9 (1 781/61 847)	2.2	2.1–2.3	1.8	1.7–1.9	257
Stroke	1.6 (1 006/61 804)	1.2	1.1–1.3	1.0	0.9–1.1	300
Angina pectoris	4.4 (2 702/61 801)	3.2	3.1–3.3	2.6	2.5–2.7	303
Diabetes	2.7 (1 653/61 863)	2.1	2.0–2.3	1.8	1.7–2.0	241
Antihypertensive treatment	10.4 (6 421/61 845)	8.3	8.1–8.5	7.0	6.8–7.2	259
One or more of the above	97.6 (60 051/61 522)	97.0	96.9–97.1	96.5	96.3–96.6	582
One or more of the above except prehypertension	94.8 (57 727/60 872)	93.3	93.1–93.5	92.0	91.8–92.2	1232

*Hypertensinon defined as ≥140/90 mmHg or on antihypertensive treatment.

†Prehypertension defined as blood pressure 120/80–139/89 mmHg without antihypertensive treatment.

‡Waist circumference: men >102 cm, women >88 cm.

§First-degree relatives with a family history of myocardial infarction before the age of 60 or stroke at any time.

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease.

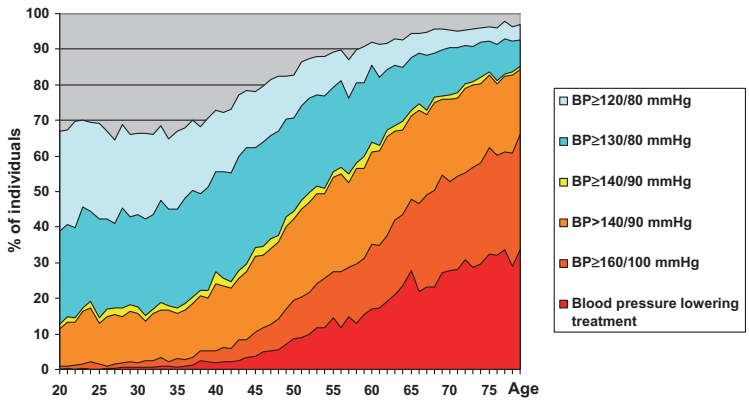

Figure 1 Point prevelence of individuals in each age group (20–79 years) who report being on antihypertensive treatment or whose measured blood pressure (BP) values exceed given limits.

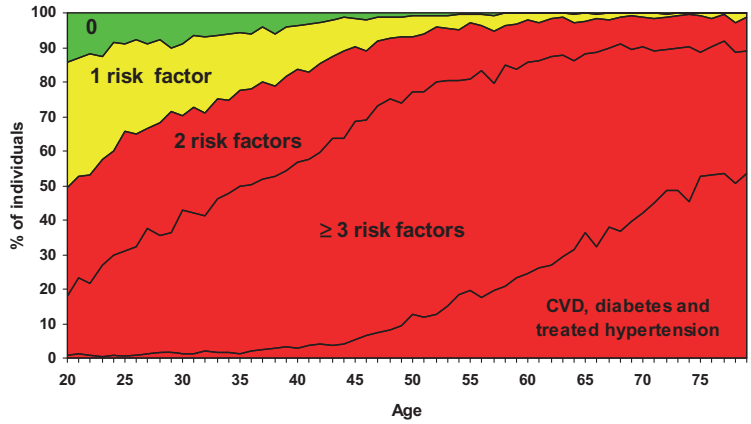

Figure 2 Point prevelence of individuals in each age group (20–79 years) who report established disease (here defined as myocardial infarction, stroke, angina pectoris, diabetes or being on antihypertensive treatment) or one or more of the risk factors studied [i.e. prehypertension or hypertension; high cholesterol; overweight or waist obesity; smoking; or close relatives with cardiovascular diseases (CVD)].

Technical strengths and limitations of the present analysis

The HUNT 2 study population is well defined, with high participation rates, and considered fairly representative for Norway as a whole. Compared with other European regions, including regions involved in the MONICA project (third phase, 1992–4) [29], it did not differ significantly with respect to cholesterol levels and smoking habits at the time of data collection. Blood pressure levels were somewhat higher in the HUNT 2 population than in most comparable countries, yet lower than in Finland. We acknowledge that since the data collection in 1995–7, changes may have taken place, both regarding lifestyle and in the distribution of biological disease risk factors in the Norwegian population [30]. We may thereby, like many other investigators in the field of CVD, be introducing a certain retrospective risk bias as we apply population data collected 10 years ago.

With respect to family risk for CVD, the HUNT 2 study enabled us to identify individuals who reported first-degree relative(s) with premature myocardial infarction. Stroke in close relatives, however, was in the HUNT 2 study reported without reference to age. As can be seen from Table 4, this potential source of overestimation has only a minor impact on the resulting risk population.

In this paper, we have deliberately chosen to outline the potential scenario of complete guideline adherence in the area of individual CVD risk assessment. We also chose to include medical surveillance for 'prehypertension' in Figs 1 and 2. It can be argued that most guidelines do not go that far in their recommendations as yet. On the other hand, opinion leaders in the medical community appear to be on the brink of accepting the idea, not only of actively monitoring prehypertension, but even to treat it with drugs [24,25]. As an illustration of the increasing focus on the subject, one may note that papers with the words 'prehypertension'/'prehypertension' in the title appeared only sporadically in PubMed until the year 2003 when it suddenly appeared in the title of four papers. In 2004, the number of publications rose to 14; in 2006, 41; and 2007 is likely to see a further increase. It can also be mentioned that Norwegian health authori-

ties in 2003 issued a fee-for-service lifestyle advice scheme 'Green prescription' where advice and individual follow-up were indicated even for people with blood pressure in the 'prehypertensive' range. It later turned out that the Green prescriptions had low legitimacy among Norwegian general practitioners [31]. One of the reasons may be that the target group was so vast. It has been calculated that literal adherence to the Green prescription initiative could in fact consume half of all consultations in Norwegian primary health care [32].

A medical 'vision zero'?

Disease prevention and health promotion are, and should remain, central goals of medicine. It is, however, a major challenge to find a reasonable balance between – on the one hand – biological, specific and risk-oriented approaches to improving health, and – on the other – more general and 'salutogenetic' approaches [2]. Definition of relevant and clinically meaningful cut-off levels for individual risk intervention is crucial in this connection. We believe that it can be demoralizing and alienating for primary health care professionals to feel obliged to inform a large majority of the individuals they serve that their current cardiovascular health is not 'good enough' according to biomedical standards [32]. The prospect of thus 'medicalizing' a large majority of an adult population such as the one in Norway, with one of the world's longest-living and healthy-living populations according to WHO statistics [1,16], evokes several epistemological and ethical challenges [15]. Resource allocation and workload are also among issues that need careful consideration before authoritative clinical recommendations are launched [2,15,21].

We believe the present study serves as a vivid illustration of a piecemeal biomedical empirism that may have become both *too good* and at the same time *not good enough* [33–35]. By 'too good', we mean that the statistical impact of traditional, biological risk factors for CVD has now been investigated so extensively that almost every citizen can find empirical arguments for concern related to his or her bodily risk profile. By 'not good enough', we mean that a narrow and reductive biological perspective which labels almost every citizen as in need of personalized, medical care, may divert both clinicians' and politicians' attention away from more comprehensive, adequate and sustainable scientific approaches to population health and disease [2].

As primary health care doctors and researchers in two of the richest countries in the Western world, we see it as a duty of the medical community not only to care for the health status of the local individuals we serve, but also to consider our chosen aims and means from a global perspective. We are not convinced that the current trend in direction of an authoritative 'vision zero' in the area of CVD prevention represents realistic and sound medicine [2]. Peter Kosso, philosopher of science, has argued that 'good' science which really brings humankind forwards tends to have a distinct aesthetical quality to it [35]. If the 'ethos' of scientifically based medicine becomes too dominated by surveillance and control of individual's isolated biological factors, down to the lowest levels of risk, it may lose its appeal as an impressive, human endeavour.

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Paper II

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Research article

Current European guidelines for management of arterial hypertension: Are they adequate for use in primary care? Modelling study based on the Norwegian HUNT 2 population

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Abstract

Background: Previous studies indicate that clinical guidelines using combined risk evaluation for cardiovascular diseases (CVD) may overestimate risk. The aim of this study was to model and discuss implementation of the current (2007) hypertension guidelines in a general Norwegian population.

Methods: Implementation of the current *European Guidelines for the Management of Arterial Hypertension* was modelled on data from a cross-sectional, representative Norwegian population study (The Nord-Trøndelag Health Study 1995-97), comprising 65,028 adults, aged 20-89, of whom 51,066 (79%) were eligible for modelling.

Results: Among individuals with blood pressure ≥120/80 mmHg, 93% (74% of the total, adult population) would need regular clinical attention and/or drug treatment, based on their total CVD risk profile. This translates into 296,624 follow-up visits/100,000 adults/year. In the Norwegian healthcare environment, 99 general practitioner (GP) positions would be required in the study region for this task alone. The number of GPs currently serving the adult population in the study area is 87 per 100,000 adults.

Conclusion: The potential workload associated with the European hypertension guidelines could destabilise the healthcare system in Norway, one of the world's most long- and healthy-living nations, by international comparison. Large-scale, preventive medical enterprises can hardly be regarded as scientifically sound and ethically justifiable, unless issues of practical feasibility, sustainability and social determinants of health are considered.

Background

The interest in preventive measures for cardiovascular diseases (CVD) has escalated in the last decades [1]. Apart from smoking and elevated cholesterol, hypertension has for the last fifty years been considered the most predictive CVD risk factor. The first international report highlighting the importance of blood pressure control was published in 1962 by the World Health Organisation (WHO) [2].

After this milestone publication several generations of clinical hypertension guidelines have followed on both sides of the Atlantic [3-13]. In 2003, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) published their own guidelines on hypertension treatment, having until then endorsed the guidelines issued by the WHO and the International Society of Hypertension (ISH) [9]. The 2003 hypertension guidelines became the most quoted paper in the medical literature [13], and the guidelines were updated in 2007 [13].

For the last decade, combined CVD risk evaluation instruments have gained an important role in CVD prevention guidelines [8,12,14-16]. First prominent in the 1999 guidelines from the WHO/ISH [4], and followed by the 2003 [9] and 2007 [13] publications by the ESH/ESC, such estimates have also become central in hypertension guidelines. During the same time period, however, the threshold for intervention in relation to individual risk factors has also been lowered. The 2007 ESH/ESC guidelines also present a new risk factor, high pulse pressure (systolic minus diastolic blood pressure) in the elderly, in its combined risk model.

To be implementable in the everyday clinical setting, it is essential that guidelines harmonise with clinical and practical realities. Both the number of patients in need of treatment and the treatment goals should appear reasonable, both from a societal and a local clinical perspective. When the approach of guidelines to CVD risk identification and stratification changes, it is hard to foresee the consequences in terms of the population-at-risk and the clinical workload. One way to address this important topic would be to conduct modelling studies as an integral part of guideline development. Empirical modelling studies of clinical guidelines, however, are surprisingly rare. Some recent papers [17-20], including studies from our own group [21] have shown that the 2003 European Guidelines on CVD Prevention [8] significantly overestimated CVD risk in several European regions. Consequently, there is a strong argument for assessing the potential impact of new clinical guidelines.

The aim of the present study was to model the implications of the most recent European guidelines for the management of arterial hypertension [13] in a general Norwegian population. We primarily estimated the prevalence of individuals with unfavourable CVD risk levels according to the guidelines. Subsequently, the potential clinical workload and workforce associated with reaching recommended treatment goals in this group were calculated. We finally reflect upon the implications of our findings.

Methods

Data from a large and renowned population study (the HUNT 2 Study, see http://www.ntnu.no/hunt/english) [22] allowed us to calculate the proportion of the population with an unfavourable combination of risk factors, as defined by the 2007 guidelines [13]. Based on these figures, we estimated the number of follow-up visits needed to achieve the guidelines' recommended treatment goals. This number was again translated into the number of general practitioners (GP) potentially needed to carry out this work.

Norway is a country with a solid primary healthcare system, and every citizen is listed with a GP. Care is mostly delivered by the GPs and rarely by other trained staff, such as nurse practitioners. Our model was designed to fit into this context. In the following, we will present some essential details about the HUNT 2 data and our modelling of the clinical workload associated with the 2007 guidelines.

The HUNT 2 population data

The Nord-Trøndelag Health Study 1995-97 (HUNT 2) has been described in detail elsewhere [22]. The overall participation rate in HUNT 2 was 76% among women and 67% among men. The HUNT 2 population has been considered representative of the total Norwegian population regarding demography, socio-economic factors, morbidity and mortality, including mortality from CVD [22].

Our model is based on data from all HUNT 2 participants aged 20-89 years, in total 65,028 individuals (30,447 males and 34,581 females), see Table 1.

Of these, 12,139 individuals (3,085 men and 9,054 women) had to be excluded because they had blood pressure levels below 120/80 mmHg (the 2007 guidelines do not address this group). Additionally, 1,015 men and 808 women had missing data regarding blood pressure or other factors of the six risk factors considered. In total, this rendered 51,066 HUNT 2 participants (79%) eligible for our modelling procedure. Among the 13,962 excluded participants, however, 788 (5.6%) did report established CVD, diabetes or receiving blood-pressure-lowering treatment. Our study thus underestimates the population-in-need-of-attention and associated workload at this point.

The participation rates in the HUNT 2 study were different in different age groups, with lower rates among the younger participants. When estimating the annual number of follow-up visits, this unequal participation rate was corrected for by age-standardising the HUNT 2 data with the 2007 age distribution in Nord-Trøndelag, which is similar to Norway in general [23,24]. This gives the younger age-groups, and hence the lower risk levels, increased weight in our calculations.

Table 1: Participants in the study

Age groups	Participants in HUNT-2			Eligible		
	Men	Women	Total	Men	Women	Total
20-24	1761	2156	3917	1293	1085	2378
25-29	2163	2561	4724	1703	1202	2905
30-34	2579	2917	5496	2085	1362	3447
35-39	2820	3207	6027	2315	1645	3960
40-44	3161	3478	6639	2670	2140	4810
45-49	3334	3566	6900	2920	2520	5440
50-54	3064	3314	6378	2748	2631	5379
55-59	2333	2461	4794	2121	2086	4207
60-64	2113	2292	4405	1934	2057	3991
65-69	2232	2418	4650	2095	2249	4344
70-74	2134	2382	4516	1980	2240	4220
75-79	1594	2064	3658	1474	1942	3416
80-84	820	1231	2051	726	1127	1853
85-89	339	534	873	283	433	716
Total	30447	34581	65028	26347	24719	51066

Participants in the HUNT-2 (1995-7) study and those eligible for modelling in the present study according to age and gender.

Variables studied

The basis for our model is the definition and classification of blood pressure levels, as defined by the guidelines, see Figure 1. The determination of an individuals' risk level however also depends on the presence of other relevant risk factors. Figure 2 gives an overview of these, including the cut-off points applied in our modelling procedure.

In the present dataset, smoking was defined as daily smoking of cigarettes, cigars or a pipe. Family history of CVD was defined as 1st-degree relatives (parents, brothers and/or sisters) with myocardial infarction before age 60 or stroke at any age. Established CVD was defined as self-reported myocardial infarction, stroke or angina pectoris. Methods for measurement of blood pressure and body composition are described elsewhere [22].

Some risk factors listed in the guidelines had to be omitted from our model as they were not assessed in the HUNT 2 study. These were: abnormal glucose tolerance test, fasting plasma glucose, LDL-cholesterol and triglyceride levels (HUNT 2 participants were not fasting). People with renal disease and/or subclinical organ damage were not accounted for separately.

The 2007 guidelines give no details regarding the cut-off points for 'levels of pulse pressure (in the elderly)'. After reviewing the literature, we defined 'elderly' as above 55 years of age (the same definition as the guidelines used for age as an independent risk factor in men) and 'high' pulse pressure level as ≥60 mmHg [25-35].

Estimation of clinical workload

Our estimates of the clinical workload related to each CVD risk category have been inserted in Figure 1. The number of follow-up visits are based on the guidelines' specific recommendations [13], when possible. As the follow-up frequency is not always accurately specified, we needed to make some interpretations, which we justify in detail below.

- Individuals at the lowest risk level (called 'average risk') are said to need no blood pressure intervention, and therefore we set the number of yearly visits to zero for this category.

- The guidelines' Box 22 ('Patients' follow-up', p. 1513) states that "Patients at low risk or with grade 1 hypertension may be seen every 6 months...". We therefore use 2 visits per year for these categories.

- The guidelines subsequently state that "Visits should be more frequent in high or very high risk patients. This is the case also in patients under non-pharmacological treatment alone due to the variable antihypertensive response and the low compliance with this intervention". We defined the term "more frequent" (than 2 visits per year) to mean 3-4 visits per year. Based on the above quote, we allocated an average of 3.5 visits per year for the categories 'high added risk,' 'very high added risk' and individuals with 'low added risk' who exhibit BP <140/90 under non-pharmacological surveillance due to the presence of other risk factors.

Since the choice of 3.5 visits per year on average for the most demanding follow-up categories can be discussed, we analysed our model's sensitivity to changes regarding this number. Alternative analyses based on 3.0 and 4.0 visits per year are also presented.

Other risk factors, OD or disease		Blood pressure (mmHg) Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factor	Risk level	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
	Follow up visits /year	0	0	2	2	3.5
1-2 risk factors	Risk level	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
	Follow up visits /year	3.5	3.5	2	2	3.5
3 or more risk factors, MS, OD or Diabetes	Risk level	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
	Follow up visits /year	3.5	3.5	3.5	3.5	3.5
Established CV or renal disease	Risk level	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk
	Follow up visits /year	3.5	3.5	3.5	3.5	3.5

Figure 1

Cardiovascular risk stratification chart with recommended follow-up frequency for each category. A reconstruction of Figure 1 from the 2007 Guidelines for Management of Arterial Hypertension [13], with inserted recommendations regarding the number of follow-up visits per year in each risk category. Low, moderate, high and very high risk refer to the 10-year risk of a CV fatal or non-fatal event. The term 'added' indicates in all categories that risk is greater than average. The risk factors referred to in the left column are: age, smoking, dyslipidaemia, elevated fasting plasma glucose, abnormal glucose tolerance test, abdominal obesity, a family history of premature CVD and 'high pulse pressure in the elderly'. Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; HT: hypertension. OD: subclinical organ damage; MS: metabolic syndrome.

The guidelines recommend that "patients should be seen often (e.g., every 2 to 4 weeks)" [13] during the blood pressure drug titration phase. Our model however does *not* include visits needed to formally diagnose hypertension, nor the series of visits associated with initial drug titration. As we include only follow-up visits beyond that point, our model will underestimate workload.

As mentioned, the guidelines only address individuals with blood pressure levels of at least 120/80 mmHg, and people with lower blood pressure are excluded from this model, regardless of their medical history.

Estimating the necessary primary care workforce

The prevalence of individuals assigned to each of the risk categories outlined in Figure 2 was calculated as a basis for analysis of clinical workforce needed.

In 2007 (January 1st), the Nord-Trøndelag County had 129,069 inhabitants. The population aged 20-89 accounts for about 72% of the total [23]. Nord-Trøndelag County was served by 112 GPs in 2007 [36]. This translates into 87 GPs per 100,000 inhabitants. This GP density is quite comparable to Norway as a whole (90 GPs per 100,000 inhabitants). We estimated the same number of GPs (87) to take care of every 100,000 adults (i.e., individuals eligible for our study). When calculating the medical workforce needed, we assumed that each GP in Nord-Trøndelag would conduct an average of 3000 consultations per year, which is equal to the Norwegian average [36].

Statistics

The SPSS statistical package, version 15.0, was used for statistical frequency analyses.

Ethical approval

The HUNT 2 survey in the Nord-Trøndelag health study was approved by the Norwegian Data Inspectorate and the regional committee for ethics in medical research.

Risk factors	Cut-off points
Pulse pressure in the elderly	≥ 60 mmHg in people > 55 years of age
Age	M > 55 years W > 65 years
Smoking	Daily smoking of cigarettes, cigars or pipe
Dyslipidaemia	TC > 5.0 mmol/l or HDL < 1.0 mmol/l
Abdominal obesity	Waist circumference > 102 cm (M), > 88 cm (W)
Family history of premature cardiovascular disease	Having a 1st-degree relative with MI before age 60 or stroke at any age

Figure 2
Risk factors and cut-off points. The risk factors and the cut-off points used in the present study, based on the 2007 Guidelines for the Management of Arterial Hypertension [13]. Abbreviations: M: men; W: women; TC: total cholesterol; MI: myocardial infarction.

Results

The 2007 European Guidelines for Management of Arterial Hypertension [13] covered 79% of the total HUNT 2 population, aged 20-89. Figure 3 shows age-standardised prevalence (percentage and absolute numbers) in each risk category, as well as the associated number of follow-up visits recommended per 100,000 adults per year.

As shown in Figure 3, only 6.6% of all individuals with a blood pressure of ≥120/80 mmHg were classified as "average risk". The rest, or 93.4% (i.e., 74% of the total, adult population), were classified as eligible for regular clinical attention and/or drug treatment in the near future, based on their total CVD risk profile, according to guideline recommendations. In the subgroup aged 50-64, the proportion eligible for clinical attention reached 99%.

Implementing the aforementioned model of clinical follow-up visits to our population of 65,028 adults, we found that 296,624 visits per 100,000 adults would be needed per year (Figure 3). This means that 99 GPs per 100,000 adults would be needed in Nord-Trøndelag County to implement these hypertension guidelines. This figure can be compared with the estimated number of 87 GPs per 100,000 adults, who in 2007 served the adult population in the county for all contact reasons.

If individuals in the higher risk categories and those under specific lifestyle supervision were to be seen 3.0 times or alternatively 4.0 times yearly instead of 3.5 times, as previously discussed, the total number of visits would be 260,035 or alternatively 333,212 visits per year. This corresponds to 87 or 111 GP positions, respectively.

Figure 4 shows the proportion of individuals at different risk levels by age and gender. As expected, the proportion of individuals at higher risk increases with age for both men and women.

Discussion

Modelling the implementation of current European guidelines on arterial hypertension [13] on a general population of Norwegian adults, aged 20-89, we found that 93.4% of all individuals with blood pressure of ≥120/80 mmHg (i.e., 74% of the total, adult population) would be eligible for regular clinical attention and/or drug treatment, based on their total CVD risk profile. In terms of the primary care workforce, a larger number of GPs would be needed for the sole purpose of implementing the hypertension guidelines, than the number of doctors who currently serve all primary care needs of this population - which is affluent as well as long-lived and healthy-living, by international comparison. These findings raise important questions related to the scientific validity, clinical sustainability and social responsibility of the guidelines.

Some limitations and other methodological considerations related to our implementation model have to be taken into consideration. Compared with other European regions, including regions involved in the MONICA project (third phase, 1992-94) [37], HUNT 2 did not differ significantly with respect to cholesterol levels and smoking habits at the time of data collection. The blood pressure levels, however, were somewhat higher in the HUNT 2 population than in most comparable countries, yet lower than in Finland [37,38].

Our sensitivity analysis of 3.0 and 4.0 follow-up visits instead of 3.5 for those in the higher risk levels and those with lifestyle changes shows that our concerns remain valid, even if the conservative estimate is chosen.

It would obviously have been of interest to qualify the total workload in terms of 'additional preventive measures' as opposed to 'already established workload related to clinical disease'. Our data are however not suited to make valid and transparent calculations of these sub-categories of workload. For instance, we know that a good deal of blood pressure follow-up in Norway takes place in consultations taking place for other contact reasons.

It may be argued that follow-up of known CVD risk patients may demand less, or alternatively more, than the average consultation time. The guideline authors emphasise that blood pressure control is a demanding, clinical task: "Indeed, health providers sometimes wrongly con-

Blood pressure (mmHg)						
Other risk factors, OD or Disease		**Normal** SBP 120-129 or DBP 80-84	**High normal** SBP 130-139 or DBP 85-89	**Grade 1 HT** SBP 140-159 or DBP 90-99	**Grade 2 HT** SBP 160-179 or DBP 100-109	**Grade 3 HT** SBP ≥180 or DBP ≥110
No other risk factor	**Standardized prevalence**	3.8% (3 772)	2.8% (2 799)	1.6% (1 645)	0.2% (162)	0.0% (22)
	Follow up visits /year	0	0	3 291	324	76
1-2 risk factors	**Standardized prevalence**	17.2% (17 189)	16.4% (16 366)	15.1% (15 117)	3.3% (3 326)	0.9% (904)
	Follow up visits /year	60 161	57 282	30 235	6 652	3 164
3 or more risk factors, MS, OD or Diabetes	**Standardized prevalence**	3.6% (3 577)	5.0% (5 025)	10.9% (10 925)	7.2% (7 217)	4.2% (4 190)
	Follow up visits /year	12 520	17 587	38 238	25 259	14 665
Established CV or renal disease	**Standardized prevalence**	0.9% (904)	1.3% (1 347)	2.6% (2 642)	1.9% (1 854)	1.0% (1 016)
	Follow up visits /year	3 163	4 715	9 248	6 490	3 556

Figure 3

Age-standardised prevalence of individuals in each risk category and associated number of follow-up visits. Age-standardised prevalence for each risk category in relation to blood pressure levels (absolute numbers within brackets) as well as the calculated number of follow-up visits needed each year according to the 2007 Guidelines for the Management of Arterial Hypertension [13] per 100,000 adults, aged 20 to 89 in the HUNT 2 Study, Norway. Abbreviations: OD: subclinical organ damage; HT: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; MS: metabolic syndrome; CV: cardiovascular disease.

sider the management of hypertension as the matter of few minute visits and reimburse doctors accordingly" [13]. In the presence of doubt, we chose to base our calculations on the average Norwegian GP patient turnover rate. These calculations are however transparent and can easily be adapted to fit healthcare models with higher GP turnover rates or, alternatively, more contact with auxiliary staff and fewer doctor visits.

The aforementioned adjustments made to accommodate the nature of the HUNT 2 data as well as the exclusion of visits related to initial diagnosis and drug titration, will all tend to underestimate the population-at-risk and clinical workload. This, however, does not mean that our final results represent an underestimate. As said, the average blood pressure in the HUNT 2 population was slightly higher than in comparable countries, and the use of ten-year-old population data in our model may also imply a tendency to overestimation as blood pressure levels in the Norwegian population may have decreased since 1995-7. Such trends have at least been observed in some other European regions [39,40]. But even if our model were to overestimate the population-at-risk somewhat, important theoretical, practical and ethical issues need to be addressed.

One crucial question that is hard to answer, and which is not specific for the 2007 hypertension guidelines, is whether the guideline's recommended approach would prove clinically effective if implemented in the general population, just as recommended. We have previously demonstrated how the 2003 European CVD prevention guidelines inflated the high-risk group, most likely due to a phenomenon called retrospective risk bias [17,20,21,24,41], resulting from the fact that mortality from CVD has decreased steadily in Western Europe during recent decades [42]. The reasons for this decline are

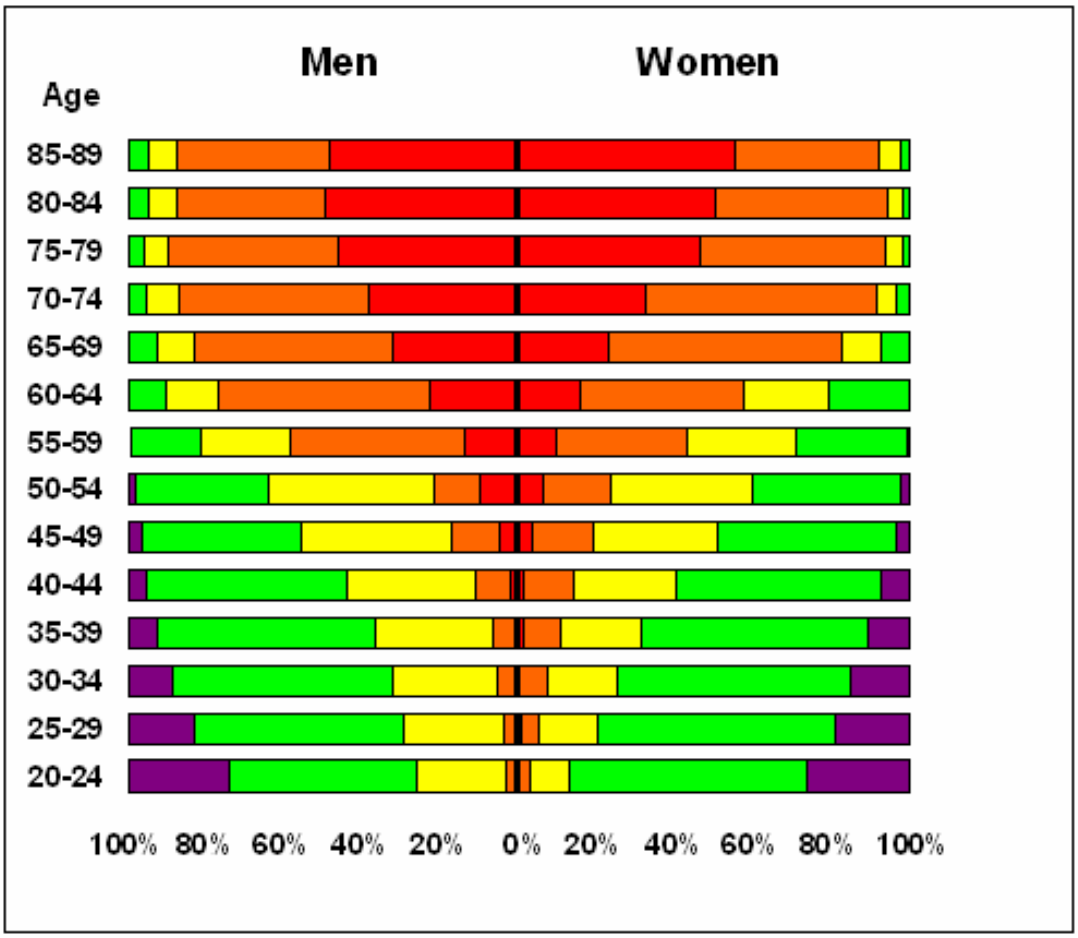

Figure 4
Gender-specific proportions of individuals within 5-year age groups, labelled at different risk levels. Gender-specific proportions of individuals within 5-year age groups, labelled at different risk levels according to the 2007 Guidelines for the Management of Arterial Hypertension [13]: average risk (purple), low added risk (green), moderate added risk (yellow), high added risk (orange), and very high added risk (red).

complex and cannot be accounted for by changes in conventional risk factors and medical interventions alone.

Recently, a prestigious, Norwegian study was conducted on evidence-based implementation of a CVD preventive guideline in general practice [43,44]. It turned out that even motivated GPs receiving tailored information, prompting and feedback showed surprisingly low concordance with the recommendations. This finding accords well with previous studies in national and international settings [45,46]. The lack of adherence, as is usually the case, was interpreted as proof that practicing clinicians are not 'good enough'. This interpretation may however be unsatisfactory. An alternative, or additional, interpretation is that contemporary CVD prevention *guidelines* are not good enough, in the sense that they are not in reasonable concordance with human nature and the realities of clinical practice [47].

The 2007 guideline's evidence-base contains 825 references. None of these discuss how medical professionals may address societal, political, work-related and relational factors, which have all been documented to play significant roles in CVD aetiology and prognosis [47,48].

We realise that it would be a challenging task to accommodate such perspectives in clinical guidelines, but ignoring evidence because it fits poorly with the mainstream, established biomedical understanding of hypertension is neither scientifically nor morally defendable.

Conclusion

Our findings indicate that the 2007 European blood pressure guidelines have an inherent potential to destabilise the healthcare system in Norway, one of the world's most long- and healthy-living nations, by international comparison. In our view, such a large-scale, preventive medical enterprise can only be regarded as scientifically sound and truly evidence-based, as long as issues of practical feasibility and sustainability are made transparent and discussed [45].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JAS and LG conceived the study idea. HP analysed the data and wrote the first draft. All authors (HP, LG, JAS, and IH) contributed to interpretation and discussion of the findings. All authors participated in further revisions of the paper and approved the final version.

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Paper III

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Is the use of cholesterol in mortality risk algorithms in clinical guidelines valid? Ten years prospective data from the Norwegian HUNT 2 study

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Abstract

Rationale, aims and objectives Many clinical guidelines for cardiovascular disease (CVD) prevention contain risk estimation charts/calculators. These have shown a tendency to overestimate risk, which indicates that there might be theoretical flaws in the algorithms. Total cholesterol is a frequently used variable in the risk estimates. Some studies indicate that the predictive properties of cholesterol might not be as straightforward as widely assumed. Our aim was to document the strength and validity of total cholesterol as a risk factor for mortality in a well-defined, general Norwegian population without known CVD at baseline.

Methods We assessed the association of total serum cholesterol with total mortality, as well as mortality from CVD and ischaemic heart disease (IHD), using Cox proportional hazard models. The study population comprises 52 087 Norwegians, aged 20–74, who participated in the Nord-Trøndelag Health Study (HUNT 2, 1995–1997) and were followed-up on cause-specific mortality for 10 years (510 297 person-years in total).

Results Among women, cholesterol had an inverse association with all-cause mortality [hazard ratio (HR): 0.94; 95% confidence interval (CI): 0.89–0.99 per 1.0 mmol L^{-1} increase] as well as CVD mortality (HR: 0.97; 95% CI: 0.88–1.07). The association with IHD mortality (HR: 1.07; 95% CI: 0.92–1.24) was not linear but seemed to follow a 'U-shaped' curve, with the highest mortality <5.0 and ≥7.0 mmol L^{-1}. Among men, the association of cholesterol with mortality from CVD (HR: 1.06; 95% CI: 0.98–1.15) and in total (HR: 0.98; 95% CI: 0.93–1.03) followed a 'U-shaped' pattern.

Conclusion Our study provides an updated epidemiological indication of possible errors in the CVD risk algorithms of many clinical guidelines. If our findings are generalizable, clinical and public health recommendations regarding the 'dangers' of cholesterol should be revised. This is especially true for women, for whom moderately elevated cholesterol (by current standards) may prove to be not only harmless but even beneficial.

Introduction

It has long been considered 'common knowledge' that total serum cholesterol is an important and strong, independent risk factor for cardiovascular disease (CVD) [1–4]. This association has been deemed to be linear, meaning 'the lower the total cholesterol level, the better'. During the last decades, CVD prevention has been marked by a trend of gradually lowering thresholds of risk definitions regarding cholesterol levels [2,5–8], in parallel with other CVD risk factors such as hypertension and blood sugar [5,7,9–12]. Campaigns aimed at the general public have underlined the risks associated with total cholesterol above 5.0 mmol L^{-1} (see, for

instance, the 2011 Norwegian campaign 'Under 5' at http://www.under5.no).

In recent years, a 'combined estimate' [2,7,8,13–17] has become the most widespread method for CVD risk evaluation, as it is believed to have better predictive properties than the single risk factor approach. Most combined estimates include the risk factors of age, sex, smoking, blood pressure and serum cholesterol. Additionally, the algorithms include, to a varying degree, other factors such as diabetes, obesity, family history and cholesterol subfractions [low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol] [2,5,7,8,12–17].

Some studies [18–22], including papers from our research group [23,24], have problematized overestimation of CVD risk in authoritative, preventive clinical guidelines. Both single risk factors [24,25] and combined risk estimates have been addressed [23,26]. We have shown that according to authoritative CVD guidelines, 75% of the adult Norwegian population would be deemed at risk for CVD and in need of clinical attention (advice and supervision) [25,26]. Consequently, we have questioned the theoretical basis of the guidelines. In the present study, we look specifically at the validity of guidelines' risk estimations involving cholesterol. In particular, we challenge the widespread assumption of a linear relationship between total cholesterol levels and disease development (expressed as mortality in our analysis).

We are well aware of evidence indicating that cholesterol subparticles, including various lipoproteins, may have stronger associations with CVD development than total cholesterol [27–34]. However, the emphasis on total cholesterol (as both a single risk factor and an element in multiple risk estimates) still prevails in many authoritative, clinical guidelines [1,7,17]. For instance, both the 2003 and the 2007 European Guidelines on CVD prevention state that 'in general, total plasma cholesterol should be below 5,' [2,16] and the risk charts in the same guidelines include total cholesterol.

In the past decades, a number of studies have found a strong and graded association between serum cholesterol and mortality from ischaemic heart disease (IHD) [14,35–48]. Regarding total mortality, however, the association has not been clear. Some studies have found no association, and others have even suggested an inverse relationship [38–41,43,49–61]. Some studies have shown an inverse or a U-shaped association between cholesterol and death from causes other than CVD, such as cancer [52,56,62,63]. The phrase 'U-shaped association' (alternatively 'J-shaped') indicates that higher mortality (or incidences) can be observed both in individuals with low and high levels of cholesterol compared with individuals with levels in between. It is important to note, however, that the phrase 'U-shaped' does not necessarily indicate that both arms of the 'U' are equal in terms of mortality rates or the proportion of the population belonging to each arm.

Regarding the association between cholesterol and overall CVD mortality, some studies have found no association or a U-shaped or even an inverse association [37,58,61,64–67]. This has been explained by an association with cerebral strokes (primarily haemorrhagic strokes), as opposed to heart disease [34,46,67–72]. Interestingly, some studies have also found an inverse [55,67,73] or a U-shaped [61,74–78] association with IHD incidence and mortality, primarily among individuals, aged 60 years and older.

The incidence, prevalence and mortality from CVD have decreased substantially throughout the Western world in recent decades [79,80]. There are also significant time trend changes regarding various risk factors for CVD [81–83]. Changes have occurred, both regarding risk factors frequently included in combined risk estimates [83–85] and for factors such as societal structure [86,87], pollution [88], television viewing [89] and dietary habits [90,91]. These on-going changes are likely to alter the predictive value of risk algorithms based on observational data collected years or even decades ago (retrospective risk bias). As cholesterol has become an essential part of lay-people's basic understanding of their health, and the prevalence of slightly 'elevated' cholesterol levels is so high, we believe that it is important to re-examine old assumptions regarding cholesterol as a risk factor.

The aim of the present study was to document the strength and validity of total serum cholesterol as a risk factor for mortality, as defined by current CVD prevention guidelines. For this purpose, we used data from a well-defined, general Norwegian population without known CVD at baseline. We focused on deaths from cardiovascular disease, IHD and death from all causes (total mortality) within a follow-up period of 10 years.

Methods

Study population

All adults, aged 20 years or older and living in Nord-Trøndelag County in Norway in 1995–1997, were invited to participate in the second wave of the Nord-Trøndelag Health Study (HUNT 2). Overall, 74% of women (34 786) and 65% of men (30 575) chose to participate. The HUNT 2 population is ethnically homogeneous (dominated by individuals of Nordic origin) and has been considered fairly representative of the total Norwegian population with respect to demography, socio-economic factors, morbidity and mortality, including mortality from CVD [92]. The HUNT 2 study has been described in detail elsewhere (see http://www.ntnu.no/hunt/english) [92].

For the purpose of the present analysis, the following HUNT 2 participants were excluded: 6780 individuals aged 75 years or more at baseline (2815 men and 3965 women); 3430 individuals (2207 men and 1223 women) with established CVD at baseline (self-reported myocardial infarction, stroke or angina pectoris); and 3064 persons with missing data on one or more of the following variables: serum cholesterol, systolic blood pressure and smoking status. Our calculations are thereby based on information from 52 087 individuals (24 235 men and 27 852 women) aged 20–74 years and free from known CVD at baseline.

Study variables

In the HUNT 2 survey, total serum cholesterol was measured by an enzymatic colorimetric cholesterol esterase method [92]. The blood pressure of persons in a seated position was measured by a specially trained personnel using Dinamap 845XT, based on oscillometry. The cuff size was adjusted after measuring the arm circumference, and blood pressure was recorded as the mean values of the second and third measurements performed consecutively at the same visit. Smoking was defined as daily smoking of cigarettes, cigars or a pipe.

Follow-up

The personal identity number of Norwegian citizens enabled linking of HUNT 2 participant data to the Cause of Death Registry at Statistics Norway (information on http://www.ssb.no/english/). For the present analysis, each participant contributed person–time from the date of clinical examination (August 1995–June 1997) until 10 years of follow-up had been achieved (until August 2005–June 2007, depending on participation dates) or until the date of death if this occurred in the follow-up period, making the oldest participants of the study 84 years of age at the end of the follow-up. The follow-up time came to a total of 510 297 person-years. Death from CVD was defined by the International Classification of Disease code for the primary diagnosis of death (ICD-9: 390-459; ICD-10: I 00-I 99) as well as death from IHD (ICD-9: 410-414; ICD-10: I 20-I 25).

Statistical analysis

The first part of our analysis involved making a simple CVD risk estimation chart to compare with the charts currently recommended for clinical practice in Norway. We used the Systematic Coronary Risk Evaluation (SCORE) chart of the European Society of Cardiology [2,15] and the nationally adjusted chart used in the Norwegian National Guidelines [17] as a reference. These charts are intended to depict the 10-year risk of dying from CVD, given the level of risk factors at baseline: sex, age, smoking status, systolic blood pressure and total cholesterol. To have a meaningful amount of data for each square of our chart, we based it on three age groups (20–39, 40–59 and 60–74 years), two levels of systolic blood pressure (<140 mm Hg vs. ≥140 mm Hg, in accordance with guidelines), smokers vs. non-smokers, and two levels of total cholesterol. Regarding cholesterol, the levels <5.5 mmol L^{-1} vs. ≥5.5 mmol L^{-1} were used (cut-off approximately 215 mg dL^{-1}). This cut-off point assigns 40% of participating males and 43% of females to the 'low level' category. Using a cut-off point of 5.0 mmol L^{-1} (which guidelines [2,16] state that cholesterol should be below) would have assigned only 24% of males and 27% of females to the lower cholesterol stratum. The median cholesterol level of the participants was 5.7 mmol L^{-1} for both genders. The observed mortality rates per 1000 person-years were calculated for each square of the chart.

For the next part of our analysis, we used Cox proportional hazard models to compute hazard ratios (HRs) for overall mortality and mortality from CVD and IHD, associated with different levels of cholesterol at baseline. The precision of the estimated associations was assessed by a 95% confidence interval (CI). Departure from the proportional hazard assumptions was evaluated by Schoenfeld residuals.

We computed sex-specific HRs for cholesterol as a continuous variable as well as a variable with four categories (<5.0, 5–5.9, 6.0–6.9 and ≥7.0 mmol L^{-1}). We adjusted for the other variables of the aforementioned chart, namely age (in the timescale), systolic blood pressure (as a continuous variable) and smoking status. We also ran an alternative model including the same variables, in addition to waist-to-hip ratio (WHR), level of physical activity, self-reported diabetes mellitus and family history of CVD. The categorical cholesterol variable was tested for linear as well as quadratic trend. Finally, we conducted an analysis of cholesterol as a dichotomous variable with the cut-off point of 5.5 mmol L^{-1}, stratified by smoking status, and an analysis of the effect of smoking stratified by the dichotomous cholesterol variable for comparison.

All statistical tests were two-sided and all analyses were performed using STATA for Windows (version 11; StataCorp LP, TX, USA).

Ethics statement

Each participant in the HUNT study signed a written consent regarding the screening and the use of data for research purposes as well as linking their data to other registers (subject to the approval of the Norwegian Data Inspectorate). The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

Results

Figure 1 shows CVD mortality for the HUNT 2 population during the 10-year follow-up period (mortality rates per 1000 person-years), according to each level of the risk factors found in the international SCORE system. This model showed a general trend towards increased mortality for an increase in any of the included risk factors, except for cholesterol, where no such association was observed. The results were similar regarding all-cause mortality and IHD mortality (data not shown).

Table 1 shows the sex-specific associations of different levels of serum cholesterol with mortality, both total mortality and CVD and IHD mortality. Among women, serum cholesterol had an inverse association with all-cause mortality as well as CVD mortality (although not reaching statistical significance) (Table 1). The association with IHD mortality appeared to follow a U-shaped curve. Test for quadratic trend did not support the existence of a U-shaped curve ($P = 0.16$).

Among men, cholesterol did not seem to be linearly associated with mortality but rather the association followed a U-shaped pattern, with the lowest mortality appearing in the second cholesterol category (5.0–5.9 mmol L^{-1}). This was apparent in all mortality categories. Consequently, cholesterol analysed as a continuous variable did not show a statistically significant linear association with mortality. Test for quadratic trend yielded $P = 0.01$ for all-cause mortality (indicating a true U-curve), $P = 0.055$ for CVD (approaching statistical significance) and $P = 0.80$ for IHD (practically excluding a U-curve). The associations between cholesterol and mortality are visualized in Figs 2–4.

A sensitivity analysis adjusting for four additional risk factors (WHR, physical activity and family history) revealed results of no considerable difference from the first model (adjusting for age, smoking and systolic blood pressure) for either sex.

The association of a dichotomous cholesterol variable with mortality, stratified by smoking status, is shown in Table 2. The HRs relate to the risk of dying among individuals with high serum cholesterol (≥5.5 mmol L^{-1}) compared with those with lower levels (<5.5 mmol L^{-1}). Having cholesterol levels above 5.5 mmol L^{-1} was not associated with increased mortality, either among smokers or among non-smokers.

Smoking, on the other hand, was strongly associated with increased mortality in all mortality categories among both sexes

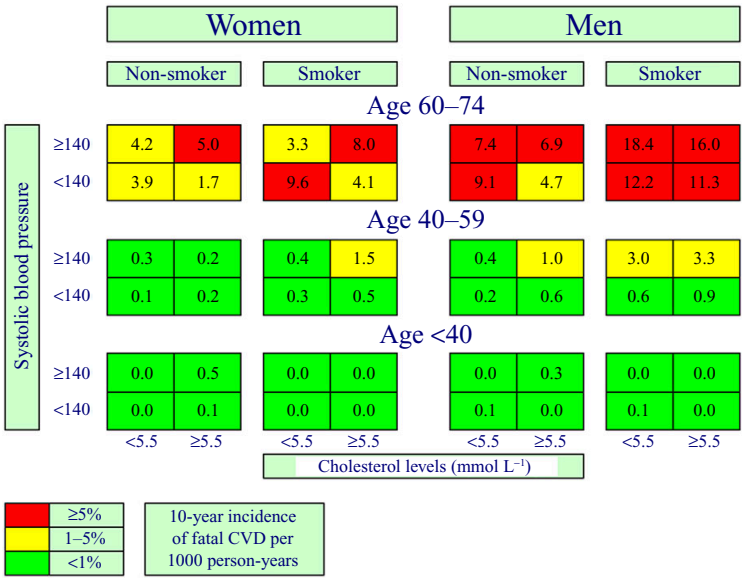

Figure 1 Ten-year incidence of fatal cardiovascular disease per 1000 person-years in the population of Nord-Trøndelag (HUNT 2 study).

Table 1 Risk of death from all causes, cardiovascular disease and ischaemic heart disease among individuals aged 20–74; associations of total cholesterol with mortality

		All causes			Cardiovascular disease			Ischaemic heart disease		
Cholesterol (mmol L^{-1})	No. of persons	No. of deaths	Adjusted* HR (95% CI)	P_{trend}	No. of deaths	Adjusted* HR (95% CI)	P_{trend}	No. of deaths	Adjusted* HR (95% CI)	P_{trend}
Men										
<5.0	5 918	208	1.00 (Reference)		58	1.00 (Reference)		24	1.00 (Reference)	
5.0–5.9	8 021	410	0.77 (0.65–0.92)		132	0.80 (0.59–1.09)		65	0.94 (0.59–1.50)	
6.0–6.9	6 658	500	0.84 (0.71–0.99)		168	0.87 (0.64–1.18)		85	1.06 (0.67–1.67)	
≥7.0	3 638	329	0.89 (0.74–1.06)	0.90	128	1.05 (0.76–1.44)	0.25	57	1.12 (0.69–1.81)	0.39
per unit increase	24 235	1447	0.98 (0.93–1.03)	0.35	486	1.06 (0.98–1.15)	0.17	231	1.08 (0.96–1.22)	0.18
Women										
<5.0	7 613	98	1.00 (Reference)		19	1.00 (Reference)		9	1.00 (Reference)	
5.0–5.9	8 565	243	0.92 (0.72–1.17)		59	0.90 (0.53–1.52)		19	0.61 (0.27–1.38)	
6.0–6.9	6 404	327	0.84 (0.66–1.06)		91	0.81 (0.49–1.35)		32	0.60 (0.28–1.30)	
≥7.0	5 270	375	0.72 (0.57–0.92)	0.001	121	0.74 (0.44–1.22)	0.13	56	0.72 (0.34–1.51)	1.00
per unit increase	27 852	1043	0.94 (0.89–0.99)	0.02	290	0.97 (0.88–1.07)	0.53	116	1.07 (0.92–1.24)	0.37

*Adjusted for age (in the timescale), smoking (current vs. not) and systolic blood pressure (continuous).
CI, confidence interval; HR, hazard ratio.

(Table 3). Among women, the association was somewhat stronger for those with cholesterol below 5.5 mmol L^{-1}.

Discussion

In this validation study of current guidelines for CVD prevention, which is based on new epidemiological data from a large and representative Norwegian population, we found total cholesterol to be an overestimated risk factor.

Regarding the association between total cholesterol and mortality, our results generally indicated U-shaped or inverse linear curves for total and CVD mortality. Only the association with IHD among men could be interpreted as suggesting a positive, linear trend.

Our results contradict the guidelines' well-established demarcation line (5 mmol L^{-1}) between 'good' and 'too high' levels of cholesterol. They also contradict the popularized idea of a positive, linear relationship between cholesterol and fatal disease. Guideline-based advice regarding CVD prevention may thus be outdated and misleading, particularly regarding many women who have cholesterol levels in the range of 5–7 mmol L^{-1} and are currently encouraged to take better care of their health.

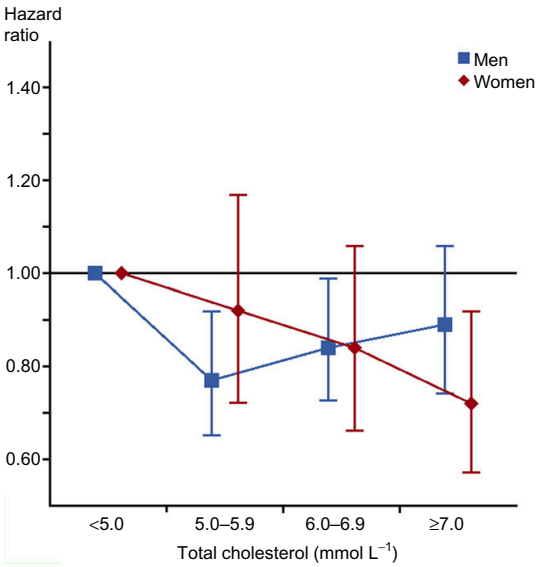

Figure 2 Risk of death (all causes) associated with different levels of total cholesterol. Hazard ratios and 95% confidence intervals for men (blue box) and women (red diamond) separately. Adjusted for age, smoking and systolic blood pressure.

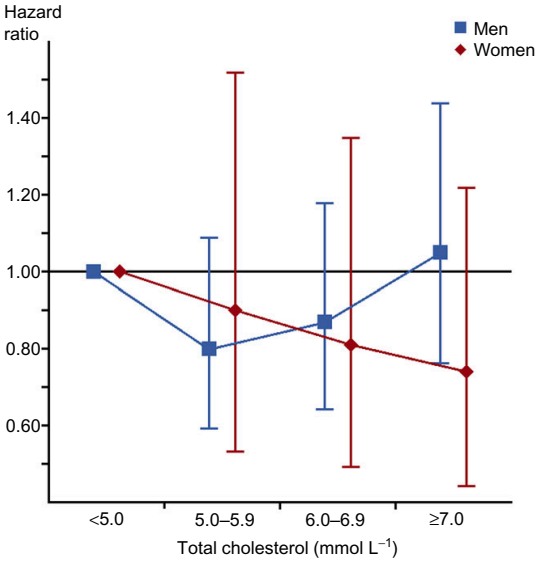

Figure 3 Risk of death from cardiovascular disease associated with different levels of total cholesterol. Hazard ratios and 95% confidence intervals for men (blue box) and women (red diamond). Adjusted for age, smoking and systolic blood pressure.

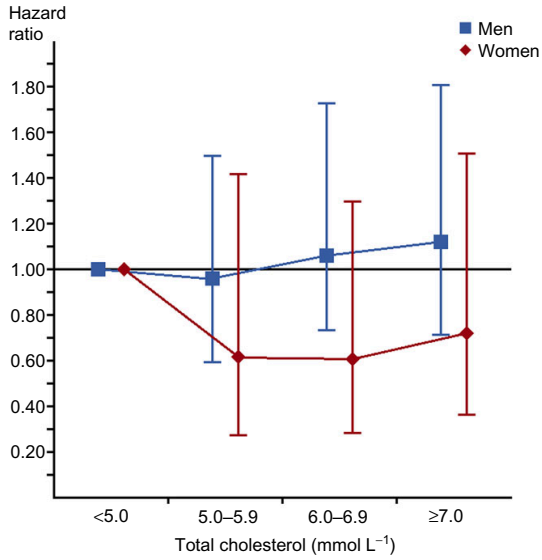

Figure 4 Risk of death from ischaemic heart disease associated with different levels of total cholesterol. Hazard ratios and 95% confidence intervals for men (blue box) and women (red diamond). Adjusted for age, smoking and systolic blood pressure.

Our finding of significant discrepancies between epidemiological data and clinical guidelines [2,16,17], suggesting a linear relation between total cholesterol and mortality from CVD is in accord with other studies [61,66,67].

The main strengths of our study are the prospective and comprehensive nature of the HUNT 2 survey, its good participation rates, and representativeness of the entire Norwegian population of similar, i.e. Nordic, origin. A corresponding weakness is the lack of immediate generalizability to Norwegians with other ethnic backgrounds. Another potential weakness of our study is the lack of information about cholesterol-lowering drug treatment among the participants. However, this is unlikely to be an important source of bias as our population was free from CVD at baseline, and cholesterol-lowering drugs were not recommended for primary prevention in the study period.

It is possible that the Norwegian HUNT 2 population differs somewhat from earlier study populations in levels of CVD risk factors and mortality, and that this may affect (or confound) the association of cholesterol with mortality. Norway is an affluent country, and Norwegians are currently one of the longest lived people in the world [93]. The rate of smoking among men is relatively low, by international comparison [93]. The stable social structure could also play a part, including a well-functioning health care system with good access and coverage for all.

Various studies have shown cholesterol, smoking and high blood pressure to have a multiplicative effect on IHD risk rather than an additive effect [94–97]. It may be that cholesterol acts differently as a risk factor for IHD than previously believed, at least in certain risk factor combinations and/or under certain

Table 2 Risk of death from all causes, cardiovascular disease and ischaemic heart disease depending on smoking status for individuals 20–74 years old; hazard ratios for high* total cholesterol compared with low cholesterol levels

		Men			Women		
Cause of death	Level of cholesterol*	No. of persons	No. of deaths	Adjusted† HR (95% CI)	No. of persons	No. of deaths	Adjusted† HR (95% CI)
All causes							
Smokers	High	4726	476	0.87 (0.73–1.03)	5 406	339	1.00 (0.77–1.31)
	Low	2680	180	1.00 (Reference)	3 795	75	1.00 (Reference)
Non-smokers	High	9724	573	0.94 (0.80–1.10)	10 485	503	0.74 (0.60–0.91)
	Low	7105	218	1.00 (Reference)	8 166	126	1.00 (Reference)
CVD							
Smokers	High	4726	181	0.92 (0.68–1.24)	5 406	94	1.09 (0.60–2.00)
	Low	2680	58	1.00 (Reference)	3 795	13	1.00 (Reference)
Non-smokers	High	9724	182	0.91 (0.68–1.21)	10 485	160	1.00 (0.63–1.57)
	Low	7105	65	1.00 (Reference)	8 166	23	1.00 (Reference)
IHD							
Smokers	High	4726	89	1.03 (0.66–1.59)	5 406	46	1.19 (0.48–2.93)
	Low	2680	26	1.00 (Reference)	3 795	6	1.00 (Reference)
Non-smokers	High	9724	88	1.00 (0.65–1.53)	10 485	56	0.96 (0.45–2.06)
	Low	7105	28	1.00 (Reference)	8 166	8	1.00 (Reference)

*Comparison of high (≥5.5 mmol L^{-1}) vs. low (<5.5 mmol L^{-1}) total cholesterol.
†Adjusted for age (in the timescale), smoking (current vs. not) and systolic blood pressure.
CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; IHD, ischaemic heart disease.

Table 3 Risk of death from all causes, cardiovascular disease and ischaemic heart disease depending on levels of total cholesterol for individuals 20–74 years old; hazard ratios for smoking compared with non-smoking

		Men			Women		
Cause of death	Smoking status	No. of persons	No. of deaths	Adjusted* HR (95% CI)	No. of persons	No. of deaths	Adjusted* HR (95% CI)
All causes							
High† cholesterol	Smoking	4726	476	2.09 (1.71–2.55)	5 406	339	1.72 (1.29–2.30)
	Non-smoking	2680	180	1.00 (Reference)	3 795	75	1.00 (Reference)
Low‡ cholesterol	Smoking	9724	573	1.99 (1.76–2.24)	10 485	503	2.16 (1.87–2.48)
	Non-smoking	7105	218	1.00 (Reference)	8 166	126	1.00 (Reference)
CVD							
High cholesterol	Smoking	4726	181	2.30 (1.61–3.29)	5 406	94	1.82 (0.91–3.64)
	Non-smoking	2680	58	1.00 (Reference)	3 795	13	1.00 (Reference)
Low cholesterol	Smoking	9724	182	2.44 (1.98–3.00)	10 485	160	2.24 (1.73–2.91)
	Non-smoking	7105	65	1.00 (Reference)	8 166	23	1.00 (Reference)
IHD							
High cholesterol	Smoking	4726	89	2.28 (1.34–3.90)	5 406	46	2.35 (0.80–6.95)
	Non-smoking	2680	26	1.00 (Reference)	3 795	6	1.00 (Reference)
Low cholesterol	Smoking	9724	88	2.42 (1.80–3.25)	10 485	56	3.08 (2.07–4.58)
	Non-smoking	7105	28	1.00 (Reference)	8 166	8	1.00 (Reference)

*Adjusted for age (in the timescale), smoking (current vs. not) and systolic blood pressure.
†High total cholesterol ≥5.5 mmol L^{-1}.
‡Low total cholesterol <5.5 mmol L^{-1}.
CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; IHD, ischaemic heart disease.

developmental and contextual circumstances, such as those mentioned earlier. At least in some settings, cholesterol may represent a risk marker and/or a weak risk factor rather than an important one. More valid risk factors might be found by further investigation of lipoproteins and/or other subparticles of cholesterol, but the same dilemmas may arise in relation to those entities. What appears evident, however, is that more updated and complex disease prediction models are needed.

Regarding the immediate future of guidelines and combined risk estimates for CVD, we envisage three options: first, IHD

mortality (and not overall CVD mortality) might be considered an appropriate end point for the current risk estimates. However, our results (Table 1) indicate that even such a limited focus would be problematic, at least for women. Alternatively, total cholesterol could be excluded from the risk estimates, potentially being replaced either by nothing or by some different subparticle(s) of cholesterol with better predictive properties, such as HDL or HDL/total cholesterol [2,8,16]. Finally, future risk estimates may be based on more nuanced statistical models, allowing for gender- and age-specific associations between cholesterol and disease development (mortality).

The Norwegian guidelines for prevention of CVD [17] include a risk estimation model developed on the basis of Norwegian population data [21]. This model assumes a linear association of cholesterol with CVD mortality, and the authors do not indicate that any evaluation of the linearity of the association has taken place, i.e. an evaluation of a possible U-shaped association. Selmer *et al*. included participants, aged 20–67, in their study, while we included people up to 74 years old, and the U-shaped association has been most prominent in studies, including participants over age 60. This difference should, however, be minimized by the statistical adjustments made for the effects of age. Besides the included age groups, there is no reason to believe that the Norwegian population data underlying the Norwegian guidelines differ considerably from the HUNT 2 population.

To address the question of whether the U-shaped association was age-dependent in the HUNT population, we performed an age-stratified Cox-regression analysis post-hoc. The results indicated a U-shaped association of cholesterol with CVD mortality among men aged 40–74, and an inverse association among women aged 60–74. Because of limited statistical power, we refrain from emphasizing these results. Seen in the light of previous studies [37,55,58,61,64–66,73–77], it is possible that a U-shaped association is primarily a phenomenon related to people aged 60 years and older.

Our smoking-stratified analysis (Table 2) indicated that the U-shaped association can possibly be found among both smokers and non-smokers, as no considerable difference was observed between these two strata. Analysis with more categories of cholesterol levels would have been preferable here, but due to limited statistical power, we refrain from further analyses post-hoc.

In contrast to cholesterol, the detrimental effect of smoking was clearly evident even after stratifying for cholesterol levels (Table 3). This emphasizes the importance of smoking as a CVD risk factor compared with cholesterol.

Conclusions

Based on epidemiological analysis of updated and comprehensive population data, we found that the underlying assumptions regarding cholesterol in clinical guidelines for CVD prevention might be flawed: cholesterol emerged as an overestimated risk factor in our study, indicating that guideline information might be misleading, particularly for women with 'moderately elevated' cholesterol levels in the range of 5–7 mmol L^{-1}. Our findings are in good accord with some previous studies. A potential explanation of the lack of accord between clinical guidelines and recent population data, including ours, is time trend changes for CVD/IHD and underlying causal (risk) factors.

'Know your numbers' (a concept pertaining to medical risk factor levels, including cholesterol) is currently considered part of responsible citizenship, as well as an essential element of preventive medical care. Many individuals who could otherwise call themselves healthy struggle conscientiously to push their cholesterol under the presumed 'danger' limit (i.e. the recommended cut-off point of 5 mmol L^{-1}), coached by health personnel, personal trainers and caring family members. Massive commercial interests are linked to drugs and other remedies marketed for this purpose. It is therefore of immediate and wide interest to find out whether our results are generalizable to other populations.

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Conflicts of interest

The authors declare no conflicts of interest.

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Paper IV

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PLoS one

Body Configuration as a Predictor of Mortality: Comparison of Five Anthropometric Measures in a 12 Year Follow-Up of the Norwegian HUNT 2 Study

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Abstract

Background: Distribution of body fat is more important than the amount of fat as a prognostic factor for life expectancy. Despite that, body mass index (BMI) still holds its status as the most used indicator of obesity in clinical work.

Methods: We assessed the association of five different anthropometric measures with mortality in general and cardiovascular disease (CVD) mortality in particular using Cox proportional hazards models. Predictive properties were compared by computing integrated discrimination improvement and net reclassification improvement for two different prediction models. The measures studied were BMI, waist circumference, hip circumference, waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). The study population was a prospective cohort of 62,223 Norwegians, age 20–79, followed up for mortality from 1995–1997 to the end of 2008 (mean follow-up 12.0 years) in the Nord-Trøndelag Health Study (HUNT 2).

Results: After adjusting for age, smoking and physical activity WHR and WHtR were found to be the strongest predictors of death. Hazard ratios (HRs) for CVD mortality per increase in WHR of one standard deviation were 1.23 for men and 1.27 for women. For WHtR, these HRs were 1.24 for men and 1.23 for women. WHR offered the greatest integrated discrimination improvement to the prediction models studied, followed by WHtR and waist circumference. Hip circumference was in strong inverse association with mortality when adjusting for waist circumference. In all analyses, BMI had weaker association with mortality than three of the other four measures studied.

Conclusions: Our study adds further knowledge to the evidence that BMI is not the most appropriate measure of obesity in everyday clinical practice. WHR can reliably be measured and is as easy to calculate as BMI and is currently better documented than WHtR. It appears reasonable to recommend WHR as the primary measure of body composition and obesity.

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Introduction

It is well documented that distribution of body fat is more important than the amount of fat as a prognostic factor for metabolic disturbance, cardiovascular diseases (CVD) and life expectancy [1–6]. Central or abdominal fat has been associated with the highest risk [7], with visceral fat being of special importance [8,9]. Increased waist-to-hip ratio (WHR) as a risk factor for CVD and mortality was first reported from the Swedish population studies in Gothenburg in 1984 where WHR was shown to be a stronger prognostic factor than body mass index (BMI) [3,4]. These results have repeatedly been confirmed since [10–14]. The specific protective effect of increased peripheral (lower body) fat in the form of hip and thigh [15] circumference in contrast to waist girth has also been reported [9], both for men [13,16] and women [17,18]. The more recent measure waist-to-height ratio (waist circumference divided by height [WHtR]) disregards the peripheral fat but takes the height into account. Some researchers have found WHtR to be an even stronger predictor of death, CVD [19–22] and CVD risk factors [23,24] than the above mentioned measures. Others have suggested the difference of these anthropometric measures to be insignificant or none at all, regarding predictive ability for CVD [25,26].

In recent years an increasing amount of knowledge has been gathered regarding the metabolic basis for the special importance of central fat distribution. Various metabolic, endocrine and neural factors appear to influence where the body fat accumulates and how this affects the individual's physiology and disease risk [5,8,9,27].

In the wake of the increasing prevalence of obesity in most parts of the world [28–32], there has been a debate about which anthropometric measures are best suited to define and monitor obesity for medical purposes. Despite the evidence of abdominal obesity being far more important than body weight regarding mortality and CVD, definitions of overweight and obesity based on BMI continue to be the most widely used measures in publications, including clinical guidelines designed for individual, preventive or therapeutic counselling [28,33–35]. Many guidelines mention WHR and/or waist circumference as interchangeable with BMI although the correlation is questionable [10,11,21,23]. This practical approximation decreases the specificity of the obesity definition and undermines the predictive precision of CVD risk estimates.

The aim of this study was to further clarify the associations of anthropometric indicators of obesity and body composition (BMI, WHR, WHtR, waist circumference, and hip circumference) with overall mortality, and specifically with CVD mortality.

Methods

Study population

All adults aged 20 years or older and living in Nord-Trøndelag County in Norway were in 1995 to 1997 invited to participate at the second wave of the Nord-Trøndelag Health Study (HUNT 2). Overall, 74% of women (34,786) and 65% of men (30,575) chose to participate. The HUNT 2 population is ethnically homogenous (dominated by individuals of Nordic origin) and has been considered representative of the total Norwegian population regarding demography, socio-economic factors, morbidity and mortality, including mortality from CVD [36]. The HUNT 2 study has been described in detail elsewhere [36] (see www.ntnu.no/hunt/english).

For the purpose of the present analysis, 3,138 participants aged 80 years or more at baseline (1,231 men and 1,907 women) were excluded. Individuals with established CVD at baseline (self-reported myocardial infarction, stroke or angina pectoris) were excluded, 4,571 in total (2,780 men and 1,791 women), as well as 681 person with missing data on one or more of the following variables: height, weight, waist circumference, and hip circumference. Our calculations are thus based on information from 56,971 individuals (26,461 men and 30,510 women) aged 20–79 years who were without any known CVD at baseline. Baseline characteristics are depicted in the supporting information (Table S1).

Study variables

In the HUNT 2 study, height and weight were measured with participants wearing light clothes without shoes; height to the nearest 1.0 cm and weight to the nearest 0.5 kg. Based on these measures we calculated BMI as weight in kg divided by the squared value of height in meters. Waist and hip circumferences were measured with a steel band to the nearest 1.0 cm with the participant standing and with the arms hanging relaxed. The waist circumference was measured horizontally at the height of the umbilicus, and the hip circumference was measured likewise at the thickest part of the hip [36]. When analysing the anthropometric measures, we aimed at using clinically recognisable categorisations, rather than percentiles. BMI was categorised according to WHO definitions [28], the waist circumference categories were defined with 10 cm interval, and the hip circumference categories with 5 cm interval. The WHR and WHtR were, however, categorised by quintiles.

In the present analysis smoking was defined as daily smoking of cigarettes, cigars or a pipe. Smoking status was defined as unknown, current smoker, former, or never smoker. Levels of recreational physical activity were defined as self-reported number of hours spent on hard or light activity during one week: no activity; <3 h light activity; ≥ 3 h light activity or <1 h hard activity; ≥ 1 h hard activity; unknown.

Follow-up

The personal identity number of Norwegian citizens enabled linkage of HUNT 2 participant data to the Cause of Death Registry at Statistics Norway (information on www.ssb.no/english/). For the present analysis, each participant contributed person-time from the date of clinical examination (August 1995–June 1997) until the date of death or end of follow-up (December 31st 2008). The mean follow-up time was 12.0 years, in total 684,644 person-years. Death from CVD was defined by the International Classification of Disease code for the primary diagnosis of death (ICD-9: 390–459; ICD-10: I 00-I 99).

Ethics statement

Each participant in the HUNT study signed a written consent regarding the screening and the use of data for research purposes as well as to linking their data to other registers (subject to approval of the Norwegian Data Inspectorate). The study was approved by the Norwegian Data Inspectorate and by the Regional Committee for Ethics in Medical Research.

Statistical analysis

We used Cox proportional hazard models to compute hazard ratios (HRs) for overall mortality and CVD mortality associated with different levels of each anthropometric measure. Precision of the estimated associations was assessed by a 95% confidence interval. Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and log-minus-log plots. An interaction term between time and the appropriate variables was added to the model if the proportional hazards assumption did not hold.

We analysed the HR for participants with BMI below 18.5 kg/m^2 (104 men and 314 women) for comparison with the other BMI categories but excluded them from further analysis due to the potential of reverse causality (a J-shaped mortality curve) [37,38].

We calculated sex specific standard deviation (SD) scores for each of the anthropometric variables and estimated the HR associated with an increase of one SD.

We analysed the data separately for men and women, and all associations were adjusted for potential confounding effects of age, smoking status and recreational physical activity. We conducted sensitivity analyses involving three additional models (Model 2–4). Model 2 included the same covariates as the main model but excluded participants with unknown smoking status. Model 3 was adjusted for age, smoking, and physical activity (as our main model) in addition to self-reported diabetes mellitus and weekly alcohol consumption (abstinence, 0–2 glasses [units], 2.1–5 glasses, 5.1–8 glasses, >8 glasses). Model 4 was identical to our main model but excluded the first three years of follow-up to limit the reverse causality effect of undiagnosed diseases.

The "relative informativeness" of each anthropometric measure was evaluated by examining the contributions made to the χ^2 likelihood ratio statistic in the Cox regression model compared with a model that only contained the confounders, as the χ^2 statistic can be used as a measure of the improvement of goodness of fit [39]. This was done both in relation with all cause and CVD mortality, respectively.

To further compare the predictive properties of the different anthropometric measures for CVD death, sex-specific net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were computed when adding each anthropometric measure to two different prediction models. Model A included age as the only predictive variable, while Model B included age, smoking status, systolic blood pressure, and total cholesterol. For each model three different NRI calculations were done, using two (<5%, ≥5%), three (<1%, 1–9%, ≥10%), and four (<1%, 1–4%, 5–9%, ≥10%) levels of risk of CVD death, respectively.

In addition, we conducted an analysis of the anthropometric measures stratified by age (above and below 60 years). Finally, mutually adjusted analyses were conducted for waist and hip circumference, as well as for BMI and WHR.

All statistical tests were two-sided and all analyses were performed using Stata for Windows (Version 11 StataCorp LP, TX, USA).

Results

We present the risk of death from all causes and from CVD among men and women aged 20–79 (Tables 1 and 2) with absolute numbers and HRs in association with each of the anthropometric measures studied, after adjusting for age, smoking and physical activity. For men, WHR and WHtR had the highest (and similar) predictive power, both regarding mortality from CVD and from all causes, followed by waist circumference (Table 1). BMI had considerably weaker association, with HRs only reaching statistical significance for death from CVD but not overall mortality.

All cause mortality was for both sexes statistically significantly lower in the BMI range 25.0–29.9 compared to the reference group (BMI 18.5–24.9), given the above adjustments.

Overall the results were similar for both sexes except for WHR appearing as a somewhat stronger predictor among women, as compared to men, while HRs for WHtR seemed more comparable with that of waist circumference than WHR (Table 2). This was apparent in both mortality categories.

The sensitivity analyses did not deviate considerably from the primary results. Among men, the HRs per one SD increase in anthropometric measures never differed more than 0.02 from the main model (Table S2). Among women, adjustment for self-reported diabetes and alcohol consumption resulted in a slight decrease in all HRs (Table S3). The decrease was in the range of 0.04–0.06 for CVD mortality and 0.03–0.04 for total mortality. Less deviation from the main model was seen in other parts of the analysis.

Table 3 shows the χ^2 likelihood ratio statistic for each measure. Within brackets the informativeness is given in percentage relative to WHR which was the most informative measure. The table shows results from analysis of the anthropometric measures as continuous variables. Our sensitivity analysis, examining the measures as categorical variables, gave similar results (data not shown).

The results from our analysis of reclassification and discrimination improvement are shown in Table 4 and Table 5. Among men (Table 4), WHtR offered most improvement to the prediction models studied, judging from the IDI, followed closely by WHR. Among women (Table 5), most improvement was associated with WHR, followed by WHtR and waist circumference. BMI and hip circumference seemed to add little or no information to the prediction models. Waist circumference, WHR and WHtR alternately produced the highest NRI, depending on the model and cut-points used. Some discordance between NRI and IDI estimates were noted.

Risk of death from CVD associated with the measures studied stratified by age is shown in Table 6. HRs are given both for men and women, aged 20–59 years versus 60–79 at baseline, for each of the measures. The strongest association was between CVD mortality and WHtR for men and WHR for women. For all measures the HRs were somewhat higher for the younger stratum.

The results for CVD mortality from the mutual adjustment analysis of hip and waist circumferences are shown in Table 7. Adjusting for hip circumference strengthened the association of waist girth with CVD mortality considerably for both sexes. Increasing hip circumference, on the other hand, seemed to be protective when adjusting for the waist. The results were similar for all cause mortality (not shown in table). The results from a corresponding analysis of BMI and WHR, mutually adjusted, are shown in Table 8. Adjusting BMI for WHR attenuated the association of BMI with mortality significantly, while adjusting WHR for BMI had no significant effect on the association.

Discussion

Of the five anthropometric measures studied, WHR and WHtR were most strongly associated with mortality, after adjusting for confounding factors. This was true both regarding overall mortality and death from CVD specifically. In accordance with other studies, our results show that BMI is a poorer predictor of death than the other measures [2–7,10–13,40]. These results underscore the advantage of assessing body configuration rather than body weight when estimating mortality risk. Furthermore, when controlling for waist circumference, increasing hip circumference appears to be protective in both genders. In our study, obesity emerged as a more important risk factor among young people, in comparison to older. This is in coherence with earlier studies [41].

In all parts of our analysis, BMI showed weaker associations with both all cause mortality and CVD mortality, when compared to waist circumference, WHR and WHtR. Furthermore, BMI was the only among these four measures which failed to show a statistically significant association with all cause mortality. BMI also contributed less additional information to the prediction models studied (Tables 4 and 5), and offered poorer fitting models (Table 3). Hence, BMI seems to be a poorer indicator of disease risk than the other measures studied, being superior only to hip circumference. When adjusting for WHR, BMI seemed even less predictive, while adjusting for BMI had no effect on WHR mortality associations. This emphasises the superiority of the alternative measures over BMI as indicators of CVD risk.

Waist circumference proved to be a statistically significant risk factor in all analyses, but still showed weaker associations with mortality than both WHR and WHtR. In particular, it emerged as a strong risk factor when adjusting for hip circumference. This underlines the significance of considering body configuration rather than the abdominal girth alone.

Hip circumference showed a weak positive association with mortality. However, when adjusting for waist circumference, it proved to be inversely related to CVD mortality in both genders. This finding is in accordance with previous research [9,13,16–18].

Both in the presence (Table 6) and absence of age stratification (Tables 1 and 2), WHR turned out to be a stronger risk factor than WHtR among women, whilst the two measures had similar predictive power among men. This gender difference favoured the

Table 1. Risk of death from all causes and from cardiovascular disease among men aged 20–79; associations with anthropometric measures.

		All causes			Cardiovascular disease		
Anthropometric measures	**No. of persons**	**No. of deaths**	**Adjusted[a] HR (95% CI)**	P_{trend}	**No. of deaths**	**Adjusted[a] HR (95% CI)**	P_{trend}
Body mass index (kg/m^2)							
<18.5[b]	104	31	2.48 (1.73–3.54)		9	2.23 (1.15–4.33)	
18.5–24.9	9,575	970	1.00 (Reference)		300	1.00 (Reference)	
25.0–29.9	13,138	1,320	0.86 (0.79–0.93)		492	1.04 (0.90–1.21)	
30.0–34.9	3,154	445	1.10 (0.98–1.23)		175	1.42 (1.17–1.71)	
≥35.0	490	70	1.34 (1.05–1.72)	0.16	28	1.78 (1.20–2.64)	<0.001
per 5 kg/m^2	26,357	2,805	1.04 (0.98–1.10)	0.21	995	1.19 (1.08–1.30)	<0.001
per SD (3.4 kg/m^2)	26,357	2,805	1.02 (0.99–1.06)	0.21	995	1.12 (1.06–1.20)	<0.001
Waist circumference (cm)							
<80	1,882	116	1.17 (0.96–1.42)		33	1.06 (0.74–1.53)	
80–89	9,466	723	1.00 (Reference)		233	1.00 (Reference)	
90–99	10,378	1,134	1.01 (0.92–1.11)		404	1.10 (0.93–1.29)	
100–109	3,625	588	1.11 (0.99–1.24)		226	1.27 (1.05–1.53)	
≥110	1,006	244	1.64 (1.41–1.90)	<0.001	99	1.99 (1.56–2.53)	<0.001
per 10 cm	26,357	2,805	1.11 (1.07–1.16)	<0.001	995	1.21 (1.13–1.29)	<0.001
per SD (9.1 cm)	26,357	2,805	1.10 (1.06–1.14)	<0.001	995	1.19 (1.12–1.26)	<0.001
Hip circumference (cm)							
<95	2,360	275	1.18 (1.02–1.36)		80	0.96 (0.75–1.25)	
95–99	6,158	639	1.00 (Reference)		225	1.00 (Reference)	
100–104	9,203	925	0.89 (0.80–0.99)		335	0.92 (0.77–1.09)	
105–109	5,471	546	0.86 (0.76–0.96)		200	0.89 (0.73–1.08)	
≥110	3,165	420	1.17 (1.03–1.33)	0.52	155	1.23 (1.00–1.51)	0.24
per 10 cm	26,357	2,805	1.01 (0.95–1.07)	0.76	995	1.11 (1.00–1.23)	0.05
per SD (6.2 cm)	26,357	2,805	1.01 (0.97–1.05)	0.76	995	1.06 (1.00–1.13)	0.05
Waist-to-hip ratio							
<0.85	5,301	254	1.07 (0.90–1.26)		75	1.11 (0.82–1.50)	
0.86–0.87	5,126	328	1.00 (Reference)		97	1.00 (Reference)	
0.88–0.89	5,287	493	1.12 (0.97–1.29)		167	1.25 (0.97–1.60)	
0.90–0.93	5,367	646	1.14 (0.99–1.30)		233	1.33 (1.05–1.69)	
≥0.94	5,276	1,084	1.38 (1.21–1.56)	<0.001	423	1.70 (1.36–2.13)	<0.001
per 0.1 unit	26,357	2,805	1.28 (1.20–1.36)	<0.001	995	1.43 (1.29–1.59)	<0.001
per SD (0.06)	26,357	2,805	1.15 (1.11–1.19)	<0.001	995	1.23 (1.16–1.30)	<0.001
Waist-to-height ratio							
<0.47	5,286	239	1.10 (0.93–1.30)		63	1.09 (0.79–1.50)	
0.48–0.49	5,219	334	1.00 (Reference)		94	1.00 (Reference)	
0.50–0.51	5,360	501	1.11 (0.96–1.27)		173	1.34 (1.04–1.72)	
0.52–0.54	5,264	663	1.07 (0.94–1.23)		238	1.31 (1.03–1.67)	
≥0.55	5,228	1,068	1.24 (1.09–1.40)	0.005	427	1.65 (1.32–2.08)	<0.001
per 0.1 unit	26,357	2,805	1.24 (1.15–1.33)	<0.001	995	1.50 (1.33–1.68)	<0.001
per SD (0.05)	26,357	2,805	1.12 (1.08–1.16)	<0.001	995	1.24 (1.16–1.31)	<0.001

Abbreviations: HR = hazard ratio, CI = confidence interval, SD = standard deviation.

[a]Adjusted for age (in the time scale), smoking (never, former, current, unknown) and physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown).

[b]This category was excluded from the remainder of the analysis presented in the table.

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use of WHtR among younger men. In any case, our results show that WHR and WHtR are superior to the other measures in relation to prediction of mortality.

Based on the IDIs (Tables 4 and 5), WHR and WHtR offered the greatest improvement to our prediction models, followed closely by waist circumference for women. The improvement

Table 2. Risk of death from all causes and from cardiovascular disease among women aged 20–79; associations with anthropometric measures.

		All causes			Cardiovascular disease		
Anthropometric measures	**No. of persons**	**No. of deaths**	**Adjusted[a] HR (95% CI)**	**P_{trend}**	**No. of deaths**	**Adjusted[a] HR (95% CI)**	**P_{trend}**
Body mass index (kg/m^2)							
<18.5[b]	314	44	2.02 (1.49–2.74)		9	1.39 (0.71–2.71)	
18.5–24.9	13,895	819	1.00 (Reference)		230	1.00 (Reference)	
25.0–29.9	10,947	872	0.81 (0.74–0.90)		308	0.93 (0.78–1.10)	
30.0–34.9	3,961	469	0.93 (0.83–1.05)		181	1.10 (0.90–1.35)	
≥35.0	1,393	204	1.24 (1.06–1.45)	0.26	74	1.41 (1.08–1.85)	0.02
per 5 kg/m^2	30,196	2,364	1.03 (0.98–1.07)	0.27	793	1.10 (1.03–1.19)	0.009
per SD (4.5 kg/m^2)	30,196	2,364	1.02 (0.98–1.07)	0.27	793	1.09 (1.02–1.17)	0.009
Waist circumference (cm)							
<70	3,981	126	1.11 (0.92–1.35)		25	0.94 (0.62–1.44)	
70–79	11,122	566	1.00 (Reference)		152	1.00 (Reference)	
80–89	8,589	761	1.00 (0.90–1.12)		265	1.14 (0.93–1.40)	
90–99	4,330	537	1.11 (0.99–1.23)		207	1.36 (1.10–1.68)	
≥100	2,174	374	1.48 (1.30–1.70)	<0.001	144	1.80 (1.43–2.27)	<0.001
per 10 cm	30,196	2,364	1.11 (1.07–1.16)	<0.001	793	1.20 (1.12–1.27)	<0.001
per SD (11.3 cm)	30,196	2,364	1.13 (1.09–1.18)	<0.001	793	1.22 (1.14–1.31)	<0.001
Hip circumference (cm)							
<95	6,457	348	1.10 (0.95–1.27)		96	1.17 (0.89–1.54)	
95–99	6,639	428	1.00 (Reference)		115	1.00 (Reference)	
100–104	6,840	499	0.86 (0.75–0.98)		173	1.04 (0.82–1.31)	
105–109	4,498	410	0.87 (0.76–1.00)		151	1.07 (0.84–1.36)	
≥110	5,762	679	1.02 (0.90–1.15)	0.33	258	1.27 (1.01–1.58)	0.14
per 10 cm	30,196	2,364	1.03 (0.98–1.07)	0.20	793	1.10 (1.02–1.18)	0.01
per SD (9.4 cm)	30,196	2,364	1.03 (0.99–1.07)	0.20	793	1.09 (1.02–1.17)	0.01
Waist-to-hip ratio							
<0.74	6,040	191	1.01 (0.84–1.22)		46	0.94 (0.65–1.35)	
0.74–0.77	6,011	282	1.00 (Reference)		83	1.00 (Reference)	
0.78–0.79	5,988	413	1.08 (0.93–1.26)		134	1.11 (0.84–1.46)	
0.80–0.83	6,125	572	1.16 (1.00–1.34)		189	1.17 (0.90–1.51)	
≥0.84	6,032	906	1.48 (1.29–1.69)	<0.001	341	1.65 (1.30–2.10)	<0.001
per 0.1 unit	30,196	2,364	1.34 (1.25–1.43)	<0.001	793	1.49 (1.33–1.66)	<0.001
per SD (0.06)	30,196	2,364	1.19 (1.15–1.24)	<0.001	793	1.27 (1.18–1.36)	<0.001
Waist-to-height ratio							
<0.43	6,001	156	1.29 (1.05–1.59)		30	1.29 (0.83–2.02)	
0.43–0.46	6,114	235	1.00 (Reference)		55	1.00 (Reference)	
0.47–0.49	6,010	407	1.19 (1.01–1.40)		121	1.35 (0.98–1.86)	
0.50–0.54	6,014	606	1.15 (0.99–1.34)		218	1.42 (1.05–1.91)	
≥0.55	6,057	960	1.35 (1.16–1.56)	0.005	369	1.71 (1.28–2.28)	<0.001
per 0.1 unit	30,196	2,364	1.20 (1.14–1.27)	<0.001	793	1.34 (1.21–1.47)	<0.001
per SD (0.07)	30,196	2,364	1.14 (1.10–1.19)	<0.001	793	1.23 (1.15–1.32)	<0.001

Abbreviations: HR = hazard ratio, SD = standard deviation, CI = confidence interval.

[a]Adjusted for age (in the time scale), smoking (never, former, current, unknown) and physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown).

[b]This category was excluded from the remainder of the analysis presented in the table.

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was in the range of 2–5‰. In comparison, smoking and systolic blood pressure produced IDIs in the range of 5–6‰ for men and 1.7–2.5‰ for women, using the same models. Some discrepancies was noted between the IDIs and the NRIs (e.g. a negative NRI 2 for WHtR among men, Table 4). This can be explained by the choice of cut-points in combination with low

Table 3. Relative "informativeness" of different anthropometric measures in relation to mortality; χ^2 likelihood ratio statistics for each measure and, within brackets, percentage of χ^2 for waist-to-hip ratio.

	Informativeness	
Anthropometric measures	**All cause mortality**	**Cardiovascular disease mortality**
Men		
Body mass index	1.5 (3%)	13.3 (31%)
Waist circumference	26.3 (48%)	30.4 (70%)
Hip circumference	0.1 (0.2%)	3.7 (8%)
Waist-to-hip ratio	54.7 (100%)	43.5 (100%)
Waist-to-height ratio	34.4 (63%)	45.0 (104%)
Women		
Body mass index	1.2 (2%)	6.6 (15%)
Waist circumference	33.4 (47%)	30.7 (69%)
Hip circumference	1.6 (2%)	6.3 (14%)
Waist-to-hip ratio	71.5 (100%)	44.4 (100%)
Waist-to-height ratio	38.7 (54%)	33.2 (75%)

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precision of the NRI estimates. The variation in NRIs highlights the importance of careful selection of cut-points, depending on the purpose. Identification of optimal cut-points depends on chosen background factors as well as considerations related to clinical relevance. Our results indicate that the best discrimination is obtained by use of waist circumference, WHR or WHtR.

The main strength of our investigation lies in the prospective and comprehensive nature of the HUNT 2 study, its good participation rates, and it being fairly representative for the entire Norwegian nation. The fact that the HUNT population is ethnically homogenous may also be considered a strength in this context, since ethnic differences (genetic and epigenetic factors) may influence the predictive properties of anthropometric measures [42–44].

The HUNT 2 database lacks comprehensive information on the participants' dietary habits and cancer history. However, the exclusion of participants with BMI <18.5 kg/m^2 and the sensitivity analysis which excludes the first three years of follow-up minimise the potential for confounding by cancer. Our sensitivity analysis indicates that the impact of other potential confounders is minimal.

Our study adds further knowledge to the evidence that BMI is not the most appropriate measure of obesity in everyday clinical practice. WHR is as easy to calculate as BMI and is presently better documented than WHtR. It therefore appears reasonable

Table 4. Risk reclassification improvement among men[a]; anthropometric measures and risk of death from cardiovascular disease.

Anthropometric measures	**IDI (‰)**	***P***	**NRI 1[b] (‰)**	***P***	**NRI 2[c] (‰)**	***P***	**NRI 3[d] (‰)**	***P***
Model A[e]								
Body mass index	0.59	0.20	1.50	0.64	1.64	0.78	5.74	0.39
Waist circumference	1.99	0.009	4.32	0.28	1.09	0.88	9.62	0.23
Hip circumference	0.10	0.58	1.24	0.48	−0.79	0.81	0.73	0.84
Waist-to-hip ratio	3.45	<0.001	4.20	0.35	5.88	0.42	15.44	0.07
Waist-to-height ratio	3.64	<0.001	2.86	0.52	5.39	0.47	13.37	0.12
Model B[f]								
Body mass index	0.40	0.42	−1.94	0.61	−4.16	0.39	−2.41	0.69
Waist circumference	1.59	0.04	7.33	0.14	0.67	0.91	12.76	0.10
Hip circumference	0.09	0.72	−0.04	0.99	4.20	0.27	5.78	0.21
Waist-to-hip ratio	2.63	0.007	3.69	0.46	4.32	0.53	13.64	0.11
Waist-to-height ratio	2.77	0.005	7.23	0.17	−6.18	0.36	6.84	0.43

Abbreviations: IDI = integrated discrimination improvement, NRI = net reclassification improvement.
[a]Participants with body mass index <18.5 kg/m^2 were excluded from the analysis.
[b]NRI when adding a given anthropometric measure to a prediction model using two risk categories (<5%, ≥5%).
[c]Three risk categories (<1%, 1–9%, ≥10%).
[d]Four risk categories (<1%, 1–4%, 5–9%, ≥10%).
[e]Variable included in model: Age.
[f]Variables included in model: Age, smoking status, systolic blood pressure, and total cholesterol.
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Table 5. Risk reclassification improvement among women[a]; anthropometric measures and risk of death from cardiovascular disease.

Anthropometric measures	IDI (‰)	*P*	NRI 1[b] (‰)	*P*	NRI 2[c] (‰)	*P*	NRI 3[d] (‰)	*P*
Model A[e]								
Body mass index	0.94	0.07	0.28	0.95	−8.41	0.23	−6.63	0.43
Waist circumference	4.12	<0.001	2.73	0.67	8.42	0.37	15.00	0.19
Hip circumference	1.12	0.03	−0.98	0.81	−7.35	0.28	−7.38	0.35
Waist-to-hip ratio	5.01	<0.001	2.15	0.77	26.76	0.009	32.21	0.01
Waist-to-height ratio	4.36	<0.001	−4.39	0.51	10.77	0.26	9.10	0.43
Model B[f]								
Body mass index	0.84	0.15	−3.27	0.42	5.90	0.35	5.36	0.48
Waist circumference	3.46	0.002	7.09	0.26	30.25	0.001	43.01	<0.001
Hip circumference	1.11	0.07	−2.80	0.53	6.36	0.34	6.98	0.38
Waist-to-hip ratio	3.90	0.002	−3.95	0.49	33.30	<0.001	36.08	<0.001
Waist-to-height ratio	3.65	0.001	4.37	0.47	25.41	0.006	35.50	0.001

Abbreviations: IDI = integrated discrimination improvement, NRI = net reclassification improvement.
[a]Participants with body mass index <18.5 kg/m^2 were excluded from the analysis.
[b]NRI when adding a given anthropometric measure to a prediction model using two risk categories (<5%, ≥5%).
[c]Three risk categories (<1%, 1–9%, ≥10%).
[d]Four risk categories (<1%, 1–4%, 5–9%, ≥10%).
[e]Variable included in model: Age.
[f]Variables included in model: Age, smoking status, systolic blood pressure, and total cholesterol.
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to recommend WHR as the primary measure of body composition and obesity, at least when it comes to assessing risk of CVD. There is, however, need for further clarification before determining whether WHtR should be considered an even better alternative than WHR. Single (waist circumference in isolation) or additional measures (involving weight and/or height) may also be added to nuance estimations of CVD risk when indicated, for instance in relation to clearly obese or

Table 6. Risk of death from cardiovascular disease among men and women aged 20–79 years[a]; associations with anthropometric measures stratified by age at baseline.

	Adjusted[b] HR (95% CI)			
	Men		Women	
Anthropometric measures	**20–59 years**	**60–79 years**	**20–59 years**	**60–79 years**
Body mass index, per 5 kg/m^2	1.55 (1.27–1.89)	1.11 (1.00–1.23)	1.26 (0.97–1.64)	1.09 (1.01–1.18)
Waist circumference, per 10 cm	1.49 (1.28–1.74)	1.15 (1.07–1.24)	1.36 (1.12–1.66)	1.18 (1.10–1.26)
Hip circumference, per 10 cm	1.45 (1.14–1.84)	1.04 (0.93–1.17)	1.12 (0.86–1.47)	1.09 (1.01–1.18)
Waist-to-hip ratio, per 0.1 unit	1.96 (1.52–2.53)	1.35 (1.20–1.51)	2.15 (1.60–2.89)	1.42 (1.26–1.60)
Waist-to-height ratio, per 0.1 unit	2.25 (1.73–2.93)	1.37 (1.21–1.55)	1.69 (1.23–2.33)	1.30 (1.18–1.44)
Per one SD increase				
Body mass index[c]	1.35 (1.18–1.55)	1.08 (1.00–1.15)	1.23 (0.97–1.56)	1.08 (1.01–1.16)
Waist circumference[d]	1.44 (1.26–1.66)	1.14 (1.06–1.22)	1.42 (1.14–1.77)	1.20 (1.12–1.30)
Hip circumference[e]	1.25 (1.08–1.45)	1.03 (0.96–1.10)	1.11 (0.86–1.44)	1.09 (1.01–1.17)
Waist-to-hip ratio[f]	1.47 (1.27–1.69)	1.18 (1.11–1.26)	1.58 (1.33–1.89)	1.24 (1.15–1.33)
Waist-to-height ratio[g]	1.54 (1.34–1.76)	1.18 (1.10–1.26)	1.46 (1.16–1.84)	1.21 (1.13–1.30)

Abbreviations: HR = hazard ratio, SD = standard deviation, CI = confidence interval.
[a]Participants with body mass index <18.5 kg/m^2 were excluded from the analyses.
[b]Adjusted for age (in the time scale), smoking (never, former, current, unknown) and physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown).
[c]One SD: men 3.5 kg/m^2, women 4.5 kg/m^2.
[d]One SD: men 9.2 cm, women 11.5 cm.
[e]One SD: men 9.2 cm, women 9.4 cm.
[f]One SD: 0.06 for both sexes.
[g]One SD: men 0.05, women 0.07.
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Table 7. Risk of death from cardiovascular disease among men and women aged 20–79 years[a]; associations with waist and hip circumferences mutually adjusted.

		Men			Women		
Anthropometric measures		**No. of persons**	**No. of deaths**	**Adjusted[b] HR (95% CI)**	**No. of persons**	**No. of deaths**	**Adjusted[b] HR (95% CI)**
Waist circumference (cm)							
Men	**Women**						
<80	<70	1,882	33	0.98 (0.67–1.42)	3,981	25	0.86 (0.56–1.32)
80–89	70–79	9,466	233	1.00 (Reference)	11,122	152	1.00 (Reference)
90–99	80–89	10,378	404	1.20 (1.00–1.44)	8,589	265	1.26 (1.02–1.56)
100–109	90–99	3,625	226	1.52 (1.20–1.93)	4,330	207	1.65 (1.28–2.14)
≥110	≥100	1,006	99	2.64 (1.91–3.67)	2,174	144	2.54 (1.81–3.58)
Waist circumference, per 10 cm		26,357	995	1.42 (1.28–1.58)	30,196	793	1.44 (1.29–1.61)
Hip circumference (cm)							
<95		2,360	80	1.16 (0.89–1.50)	6,457	96	1.40 (1.06–1.84)
95–99		6,158	225	1.00 (Reference)	6,639	115	1.00 (Reference)
100–104		9,203	335	0.75 (0.63–0.90)	6,840	173	0.88 (0.69–1.12)
105–109		5,471	200	0.61 (0.49–0.76)	4,498	151	0.77 (0.60–1.01)
≥110		3,165	155	0.65 (0.49–0.86)	5,762	258	0.67 (0.50–0.91)
Hip circumference, per 10 cm		26,357	995	0.73 (0.62–0.86)	30,196	793	0.77 (0.68–0.88)

Abbreviations: HR = hazard ratio, CI = confidence interval.
[a]Participants with body mass index <18.5 kg/m^2 were excluded from all analyses.
[b]Adjusted for age (in the time scale), smoking (never, former, current, unknown), physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown), and either waist circumference or hip circumference.
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under-weight individuals with a favourable WHR. A certain weakness of the approach suggested here is the documented, inter-personal variance in measurement of waist and hip circumferences [45]. This problem can be addressed by standardised measurement procedures [46] and adequate training [45].

Table 8. Risk of death from cardiovascular disease among men and women aged 20–79 years[a]; associations with body mass index and waist-to-hip ratio mutually adjusted.

		Men			Women		
Anthropometric measures		**No. of persons**	**No. of deaths**	**Adjusted[b] HR (95% CI)**	**No. of persons**	**No. of deaths**	**Adjusted[b] HR (95% CI)**
Body mass index (kg/m^2)							
18.5–24.9		9,575	300	1.00 (Reference)	13,895	230	1.00 (Reference)
25.0–29.9		13,138	492	0.91 (0.78–1.07)	10,947	308	0.81 (0.68–0.97)
30.0–34.9		3,154	175	1.08 (0.87–1.34)	3,961	181	0.88 (0.71–1.08)
≥35.0		490	28	1.23 (0.81–1.86)	1,393	74	1.07 (0.81–1.42)
per SD (M: 3.4, W: 4.5)		26,357	995	1.01 (0.94–1.09)	30,196	793	1.00 (0.93–1.08)
Waist-to-hip ratio							
Men	**Women**						
<0.85	<0.74	5,286	75	1.14 (0.85–1.53)	6,040	46	0.82 (0.55–1.21)
0.86–0.87	0.74–0.77	5,219	97	1.00 (Reference)	6,011	83	1.00 (Reference)
0.88–0.89	0.78–0.79	5,360	167	1.25 (0.96–1.62)	5,988	134	1.15 (0.87–1.51)
0.90–0.93	0.80–0.83	5,264	233	1.35 (1.07–1.70)	6,125	189	1.11 (0.88–1.40)
≥0.94	≥0.84	5,228	423	1.64 (1.30–2.07)	6,032	341	1.59 (1.27–2.00)
per SD (both sexes: 0.06)		26,357	995	1.22 (1.14–1.31)	30,196	793	1.27 (1.18–1.36)

Abbreviations: HR = hazard ratio, CI = confidence interval, SD = standard deviation.
[a]Persons with body mass index <18.5 kg/m^2 were excluded from all analyses.
[b]Adjusted for age (in the time scale), smoking (never, former, current, unknown), physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown), and either body mass index or waist-to-hip ratio.
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It is hard to determine how much effort should be put into training healthcare workers to measure WHR or WHtR in a standardised and reproducible manner, as the potential for predictive improvement will depend on the selected cut-off points and also the choice of prediction model. In relation to combined risk algorithms [47,48], our results indicate that a NRI of up to 4% might be reached for women and 1.5% for men, depending on cut-off points, by replacing BMI with waist circumference, WHR or WHtR. Identification of the most appropriate cut-offs for a given prediction model could eventually be addressed in a future study. Most preventive CVD guidelines [33,34,49,50] however do not include markers of obesity in their combined risk algorithms. Authoritative guidelines currently treat body composition/configuration as an isolated risk factor and usually lack clear specifications regarding the numerical impact on disease risk. As long as this approach is recommended for use in clinical practice, we argue for the use of the anthropometric measure with the best predictive properties. From this perspective, it appears rational to replace BMI by WHR or WHtR when evaluating CVD mortality risk.

Supporting Information

Table S1 Baseline characteristics of the study population.
(DOCX)

Table S2 Risk of death from all causes and from cardiovascular disease among men aged 20–79; associations with anthropometric measures (hazard ratios per increase in anthropometric measures of one standard deviation). Sensitivity analysis involving different models.
(DOCX)

Table S3 Risk of death from all causes and from cardiovascular disease among women aged 20–79; associations with anthropometric measures (hazard ratios per increase in anthropometric measures of one standard deviation). Sensitivity analysis involving different models.
(DOCX)

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Author Contributions

Conceived and designed the experiments: HP CB JAS TILN LG. Analyzed the data: HP CB TILN. Wrote the paper: HP JAS LG CB TILN.

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Supporting information

Table S1. Baseline characteristics of the study population aged 20-79[a].

Variable	Men (N = 26,463)		Women (N = 30,505)	
Mean age, years (SD)	46.7	(15.1)	47.5	(15.6)
Mean weight, kg (SD)	83.6	(12.2)	70.8	(12.4)
Mean body mass index, kg/m^2 (SD)	26.4	(3.4)	26.2	(4.5)
Mean waist circumference, cm (SD)	91.5	(9.1)	81.1	(11.3)
Mean hip circumference, cm (SD)	102.3	(6.2)	101.9	(9.4)
Mean waist-to-hip ratio (SD)	0.89	(0.06)	0.79	(0.06)
Mean waist-to-height ratio (SD)	0.51	(0.05)	0.49	(0.07)
Mean systolic blood pressure, mmHg (SD)	138.9	(18.0)	133.8	(22.3)
Mean serum cholesterol, mmol/L (SD)	5.8	(1.2)	5.9	(1.3)
Diabetes mellitus[b] (%)	564	(2.1)	610	(2.0)
University degree (%)	5,392	(21.1)	6,153	(20.3)
Smoking (%)				
Never smokers	10,298	(39.1)	13,595	(45.0)
Current smokers	7,582	(28.8)	5,680	(18.8)
Former smokers	7,224	(27.4)	9,116	(30.2)
Unknown smoking status	1,253	(4.8)	1,805	(6.0)
Physical activity[c] (%)				
No activity	1,810	(6.9)	1,712	(5.7)
<3 h easy	6,157	(23.4)	9,664	(32.0)
3+ h easy, <1 h hard	8,100	(30.7)	9,409	(31.2)
1+ h hard	8,556	(32.5)	6,275	(20.8)
Unknown	1,734	(6.6)	3,136	(10.4)
Alcohol consumption, glasses/week[d] (%)				
Total abstinence	1,756	(6.7)	4,050	(13.4)
0-2	14,983	(56.8)	21,675	(71.8)
2.1-5	6,718	(25.5)	3,801	(12.6)
5.1-8	2,384	(9.0)	619	(2.0)
>8	516	(2.0)	51	(0.2)

SD = standard deviation.

[a]Participants with body mass index lower than 18.5 kg/m^2 are not included in the table.

[b]Number of persons with self-reported diabetes.

[c]Self-reported physical activity per week.

[d]Self-reported weekly alcohol consumption (beer, wine, strong liqour), number of glasses.

Table S2. Risk of death from all causes and from cardiovascular disease among men aged 20-79[a]; associations with anthropometric measures (hazard ratios per increase in anthropometric measures of one standard deviation[b]). Sensitivity analysis involving different models.

		All causes			Cardiovascular disease		
Anthropometric measures	**No. of persons**	**No. of deaths**	**Adjusted HR (95% CI)**	P_{trend}	**No. of deaths**	**Adjusted HR (95% CI)**	P_{trend}
Model 2[c]	25,104	2,621			919		
Body mass index			1.03 (0.99-1.07)	0.11		1.13 (1.06-1.21)	<0.001
Waist circumference			1.10 (1.06-1.15)	<0.001		1.20 (1.13-1.28)	<0.001
Hip circumference			1.01 (0.97-1.05)	0.73		1.06 (0.99-1.13)	0.08
Waist-to-hip ratio			1.15 (1.11-1.19)	<0.001		1.25 (1.17-1.33)	<0.001
Waist-to-height ratio			1.13 (1.08-1.17)	<0.001		1.25 (1.18-1.33)	<0.001
Model 3[d]	26,357	2,805			995		
Body mass index			1.02 (0.98-1.06)	0.38		1.12 (1.05-1.19)	0.001
Waist circumference			1.09 (1.05-1.13)	<0.001		1.18 (1.11-1.25)	<0.001
Hip circumference			1.00 (0.96-1.04)	0.87		1.05 (0.99-1.12)	0.11
Waist-to-hip ratio			1.14 (1.10-1.18)	<0.001		1.22 (1.15-1.29)	<0.001
Waist-to-height ratio			1.11 (1.07-1.15)	<0.001		1.22 (1.15-1.30)	<0.001
Model 4[e]	25,942	2,390			835		
Body mass index			1.04 (1.00-1.09)	0.05		1.12 (1.05-1.20)	<0.001
Waist circumference			1.11 (1.07-1.16)	<0.001		1.19 (1.11-1.27)	<0.001
Hip circumference			1.02 (0.98-1.06)	0.41		1.08 (1.00-1.15)	0.04
Waist-to-hip ratio			1.15 (1.11-1.20)	<0.001		1.22 (1.14-1.30)	<0.001
Waist-to-height ratio			1.13 (1.09-1.18)	<0.001		1.23 (1.15-1.32)	<0.001

Abbreviations: HR = hazard ratio, CI = confidence interval.

[a]Participants with body mass index lower than 18.5 kg/m^2 were excluded from all analyses.

[b]Body mass index: 3.4 kg/m^2; Waist circumference: 9.1 cm; Hip circumference 6.2 cm; Waist-to-hip ratio: 0.06; Waist-to-height ratio: 0.05.

[c]Model 2: Adjusted for age (in the time scale), smoking (never, former, current), and physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown). Participants with unknown smoking status were excluded.

[d]Model 3: Adjusted for age, smoking (never, former, current, unknown), physical activity, diabetes mellitus (yes, no), and weekly alcohol consumption (abstinence, 0-2 glasses [units], 2.1-5 glasses, 5.1-8 glasses, >8).

[e]Model 4: Adjusted for age, smoking, (never, former, current, unknown), and physical activity. The first three years of follow up were excluded.

Table S3. Risk of death from all causes and from cardiovascular disease among women aged 20-79[a]; associations with anthropometric measures (hazard ratios per increase in anthropometric measures of one standard deviation[b]). Sensitivity analysis involving different models.

		All causes			Cardiovascular disease		
Anthropometric measures	**No. of persons**	**No. of deaths**	**Adjusted HR (95% CI)**	P_{trend}	**No. of deaths**	**Adjusted HR (95% CI)**	P_{trend}
Model 2[c]	28,391	2,104			696		
Body mass index			1.02 (0.98-1.07)	0.30		1.12 (1.05-1.21)	0.002
Waist circumference			1.13 (1.08-1.18)	<0.001		1.24 (1.15-1.34)	<0.001
Hip circumference			1.02 (0.98-1.07)	0.28		1.12 (1.04-1.21)	0.01
Waist-to-hip ratio			1.19 (1.14-1.24)	<0.001		1.26 (1.17-1.36)	<0.001
Waist-to-height ratio			1.14 (1.09-1.19)	<0.001		1.26 (1.17-1.36)	<0.001
Model 3[d]	30,196	2,364			793		
Body mass index			0.99 (0.95-1.03)	0.69		1.05 (0.98-1.12)	0.19
Waist circumference			1.09 (1.05-1.14)	<0.001		1.16 (1.08-1.25)	<0.001
Hip circumference			1.00 (0.96-1.04)	0.87		1.05 (0.97-1.12)	0.21
Waist-to-hip ratio			1.16 (1.12-1.21)	<0.001		1.23 (1.15-1.31)	<0.001
Waist-to-height ratio			1.10 (1.06-1.15)	<0.001		1.17 (1.09-1.26)	<0.001
Model 4[e]	29,907	2,075			699		
Body mass index			1.02 (0.98-1.07)	0.27		1.08 (1.01-1.17)	0.04
Waist circumference			1.13 (1.08-1.18)	<0.001		1.22 (1.13-1.32)	<0.001
Hip circumference			1.02 (0.98-1.07)	0.28		1.08 (1.00-1.16)	0.04
Waist-to-hip ratio			1.19 (1.14-1.24)	<0.001		1.28 (1.19-1.38)	<0.001
Waist-to-height ratio			1.14 (1.09-1.19)	<0.001		1.23 (1.15-1.33)	<0.001

Abbreviations: HR = hazard ratio, CI = confidence interval.

[a]Participants with body mass index lower than 18.5 kg/m^2 were excluded from all analyses.

[b]Body mass index: 4.5 kg/m^2; Waist circumference: 11.3 cm; Hip circumference 9.4 cm; Waist-to-hip ratio: 0.06; Waist-to-height ratio: 0.07.

[c]Model 2: Adjusted for age (in the time scale), smoking (never, former, current), and physical activity per week (no, <3 hours light, ≥3 hours light or <1 hour hard, ≥1 hour hard, unknown). Participants with unknown smoking status were excluded.

[d]Model 3: Adjusted for age, smoking (never, former, current, unknown), physical activity, diabetes mellitus (yes, no), and weekly alcohol consumption (abstinence, 0-2 glasses [units], 2.1-5 glasses, 5.1-8 glasses, >8).

[e]Model 4: Adjusted for age, smoking, (never, former, current, unknown), and physical activity. The first three years of follow up were excluded.

Appendix I
Tables

Table A. Prevalence of overweight[a], obesity[b], and abdominal obesity[c] among men in 5-year age groups.

		Overweight[a]		Obesity[b]			Abdominal obesity[c]			Overweight or obesity[d]	
Age	**N1[e]**	**N**	**%**	**n**	**%**	**N2[f]**	**n**	**%**	**N3[g]**	**n**	**%**
20-24	1 755	533	30.4	130	7.4	1 755	79	4.5	1 761	664	37.7
25-29	2 158	914	42.4	200	9.3	2 159	109	5.0	2 163	1 115	51.5
30-34	2 572	1 230	47.8	321	12.5	2 570	184	7.2	2 579	1 552	60.2
35-39	2 815	1 421	50.5	366	13.0	2 812	198	7.0	2 820	1 788	63.4
40-44	3 155	1 639	51.9	417	13.2	3 153	264	8.4	3 161	2 057	65.1
45-49	3 327	1 805	54.3	513	15.4	3 324	340	10.2	3 334	2 322	69.6
50-54	3 053	1 670	54.7	564	18.5	3 052	426	14.0	3 064	2 237	73.0
55-59	2 327	1 262	54.2	393	16.9	2 324	297	12.8	2 333	1 655	70.9
60-64	2 107	1 160	55.1	369	17.5	2 105	348	16.5	2 113	1 531	72.5
65-69	2 214	1 171	52.9	383	17.3	2 212	418	18.9	2 232	1 558	69.8
70-74	2 108	1 092	51.8	350	16.6	2 105	421	20.0	2 134	1 447	67.8
75-79	1 539	804	52.2	245	15.9	1 545	353	22.8	1 594	1 054	66.1
Total	29 130	14 701		4 251		29 116	3 437		29 288	18 980	

[a]Body mass index (BMI) = 25.0-29.9 kg/m^2.
[b]BMI ≥ 30.0 kg/m^2.
[c]Waist circumference >102 cm.
[d]BMI ≥ 25.0 kg/m^2 and/or waist circumference >102 cm.
[e]Number of participants with information on BMI.
[f]Number of participants with information on waist circumference.
[g]Number of participants with information on either BMI or waist circumference.

Table B. Prevalence of overweight[a], obesity[b], and abdominal obesity[c] among women in 5-year age groups.

		Overweight[a]		Obesity[b]			Abdominal obesity[c]			Overweight or obesity[d]	
Age	**N1[e]**	**N**	**%**	**n**	**%**	**N2[f]**	**n**	**%**	**N3[g]**	**n**	**%**
20-24	2 140	535	25.0	194	9.1	2 072	176	8.5	2 156	734	34.0
25-29	2 537	753	29.7	300	11.8	2 412	322	13.3	2 561	1 062	41.5
30-34	2 896	867	29.9	355	12.3	2 782	392	14.1	2 917	1 236	42.4
35-39	3 195	1 028	32.2	364	11.4	3 149	475	15.1	3 207	1 406	43.8
40-44	3 471	1 155	33.3	466	13.4	3 464	593	17.1	3 478	1 631	46.9
45-49	3 559	1 384	38.9	560	15.7	3 558	756	21.2	3 566	1 960	55.0
50-54	3 303	1 326	40.1	669	20.3	3 303	891	27.0	3 314	2 006	60.5
55-59	2 455	1 089	44.4	518	21.1	2 453	727	29.6	2 461	1 616	65.7
60-64	2 279	979	43.0	616	27.0	2 279	778	34.1	2 292	1 607	70.1
65-69	2 387	1 080	45.2	640	26.8	2 389	891	37.3	2 418	1 739	71.9
70-74	2 333	985	42.2	676	29.0	2 349	980	41.7	2 382	1 694	71.1
75-79	1 982	836	42.2	608	30.7	1 994	873	43.8	2 064	1 481	71.8
Total	32 537	12 017		5 966		32 204	7 854		32 816	18 172	

[a]Body mass index (BMI) = 25.0-29.9 kg/m^2.
[b]BMI ≥ 30.0 kg/m^2.
[c]Waist circumference >88 cm.
[d]BMI ≥ 25.0 kg/m^2 and/or waist circumference >88 cm.
[e]Number of participants with information on BMI.
[f]Number of participants with information on waist circumference.
[g]Number of participants with information on either BMI or waist circumference.

Table C. Mortality rate (all causes) by age and total cholesterol (mmol/L) at baseline.

	Total cholesterol (mmol/L)											
	<5.0			5.0-5.9			6.0-6.9			≥7.0		
Age	N	Deaths	Rate*	N	Deaths	Rate*	N	Deaths	Rate*	N	Deaths	Rate*
Men												
20-29	2 196	24	1.10	1 067	4	0.38	333	1	0.30	94	0	0.00
30-39	1 621	13	0.80	1 923	11	0.57	1 111	8	0.72	428	2	0.47
40-49	1 046	23	2.22	2 103	29	1.38	1 910	43	2.27	1 025	34	3.37
50-59	562	25	4.54	1 530	74	4.93	1 650	100	6.22	1 018	57	5.74
60-69	346	64	20.31	990	150	16.20	1 155	186	17.37	779	133	18.47
70-74	147	59	49.18	408	142	40.37	499	162	37.93	294	103	41.25
Total	5 918	208	3.57	8 021	410	5.22	6 658	500	7.77	3 638	329	9.42
Women												
20-29	2 591	9	0.35	1 343	4	0.30	421	1	0.24	166	1	0.60
30-39	2 582	8	0.31	2 076	9	0.43	853	7	0.82	292	2	0.69
40-49	1 692	15	0.89	2 671	49	1.85	1 607	27	1.69	717	8	1.12
50-59	516	15	2.95	1 495	53	3.59	1 725	60	3.53	1 551	58	3.79
60-69	174	35	22.31	689	68	10.32	1 269	127	10.47	1 712	157	9.51
70-74	58	16	31.46	291	60	22.50	529	105	21.58	832	149	19.23
Total	7 613	98	1.29	8 565	243	2.87	6 404	327	5.22	5 270	375	7.32

*Mortality rate per 1000 personyears.

Table D. Mortality rate (cardiovascular disease) by age and total cholesterol (mmol/L) at baseline.

	Total cholesterol (mmol/L)											
	<5.0			5.0-5.9			6.0-6.9			≥7.0		
Age	N	Deaths	Rate*	N	Deaths	Rate*	N	Deaths	Rate*	N	Deaths	Rate*
Men												
20-29	2 196	2	0.09	1 067	0	0.00	333	1	0.30	94	0	0.00
30-39	1 621	1	0.06	1 923	2	0.10	1 111	0	0.00	428	1	0.23
40-49	1 046	6	0.58	2 103	6	0.29	1 910	5	0.26	1 025	11	1.09
50-59	562	6	1.09	1 530	16	1.07	1 650	35	2.18	1 018	19	1.91
60-69	346	22	6.98	990	59	6.37	1 155	62	5.79	779	55	7.64
70-74	147	21	17.47	408	49	13.93	499	65	15.22	294	42	16.82
Total	5 918	58	1.00	8 021	132	1.68	6 658	168	2.61	3 638	128	3.66
Women												
20-29	2 591	1	0.04	1 343	0	0.00	421	0	0.00	166	1	0.60
30-39	2 582	0	0.00	2 076	1	0.05	853	0	0.00	292	0	0.00
40-49	1 692	2	0.12	2 671	4	0.15	1 607	4	0.25	717	1	0.14
50-59	516	1	0.20	1 495	13	0.88	1 725	5	0.29	1 551	14	0.92
60-69	174	9	5.74	689	19	2.88	1 269	35	2.88	1 712	53	3.21
70-74	58	6	11.80	291	22	8.25	529	47	9.66	832	52	6.71
Total	7 613	19	0.25	8 565	59	0.70	6 404	91	1.45	5 270	121	2.36

*Mortality rate per 1000 personyears.

Table E. Mortality rate (ischaemic heart disease) by age and total cholesterol (mmol/L) at baseline.

	Total cholesterol (mmol/L)											
	<5.0			5.0-5.9			6.0-6.9			≥7.0		
Age	N	Deaths	Rate*	N	Deaths	Rate*	N	Deaths	Rate*	N	Deaths	Rate*
Men												
20-29	2 196	0	0.00	1 067	0	0.00	333	0	0.00	94	0	0.00
30-39	1 621	0	0.00	1 923	0	0.00	1 111	0	0.00	428	0	0.00
40-49	1 046	3	0.29	2 103	4	0.19	1 910	3	0.16	1 025	9	0.89
50-59	562	3	0.54	1 530	7	0.47	1 650	25	1.56	1 018	11	1.11
60-69	346	8	2.54	990	32	3.46	1 155	25	2.33	779	21	2.92
70-74	147	10	8.32	408	22	6.25	499	32	7.49	294	16	6.41
Total	5 918	24	0.41	8 021	65	0.83	6 658	85	1.32	3 638	57	1.63
Women												
20-29	2 591	1	0.04	1 343	0	0.00	421	0	0.00	166	0	0.00
30-39	2 582	0	0.00	2 076	1	0.05	853	0	0.00	292	0	0.00
40-49	1 692	0	0.00	2 671	1	0.04	1 607	2	0.13	717	0	0.00
50-59	516	0	0.00	1 495	5	0.34	1 725	2	0.12	1 551	6	0.39
60-69	174	6	3.82	689	3	0.46	1 269	12	0.99	1 712	30	1.82
70-74	58	2	3.93	291	9	3.37	529	16	3.29	832	20	2.58
Total	7 613	9	0.12	8 565	19	0.22	6 404	32	0.51	5 270	56	1.09

*Mortality rate per 1000 personyears.

Appendix II
Figures

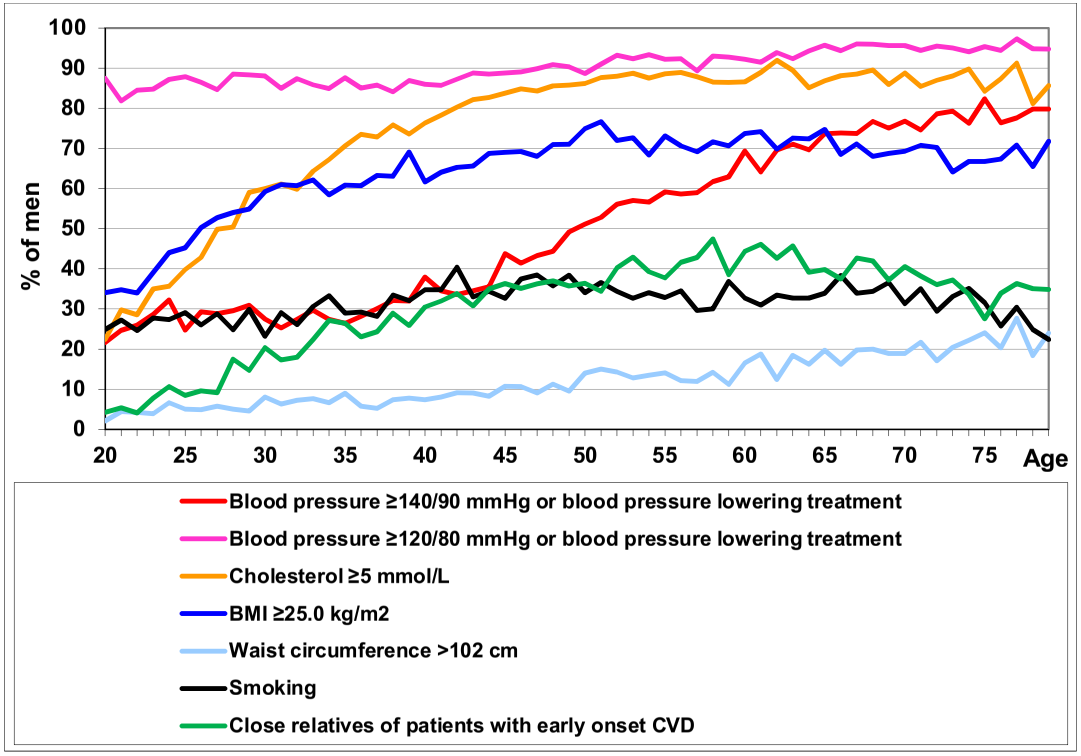

Figure A. Age-specific prevalence of some major cardiovascular risk factors among men in the HUNT 2 Study.

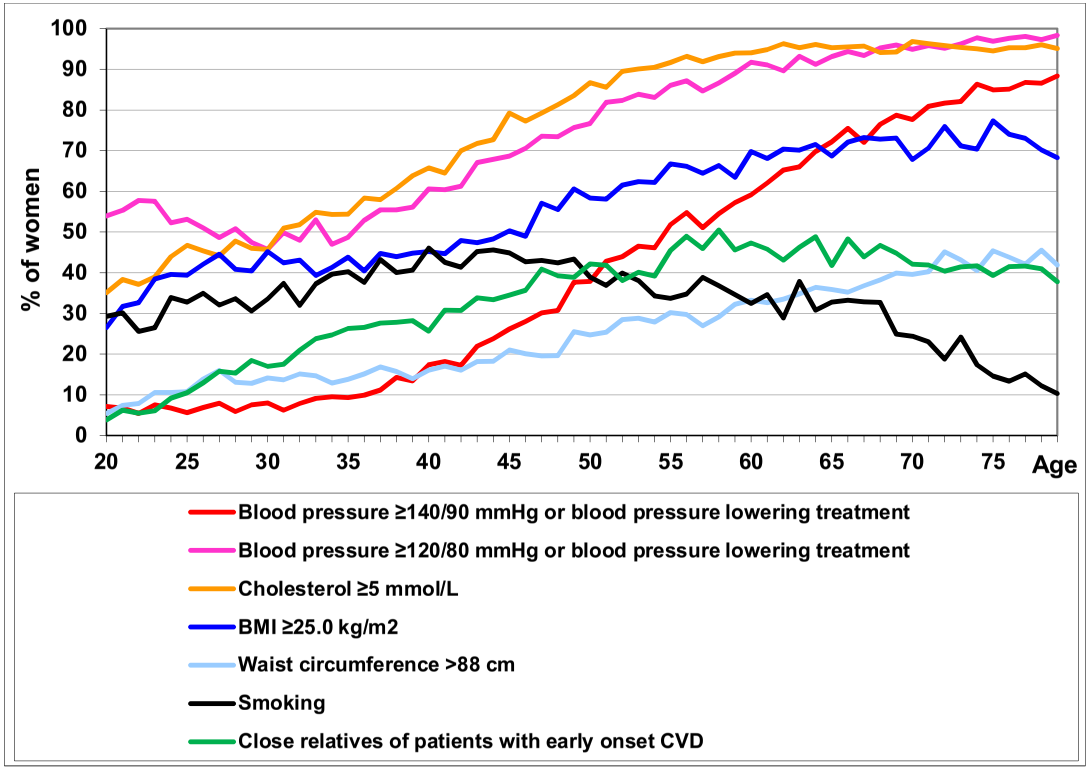

Figure B. Age-specific prevalence of some major cardiovascular risk factors among women in the HUNT 2 Study.

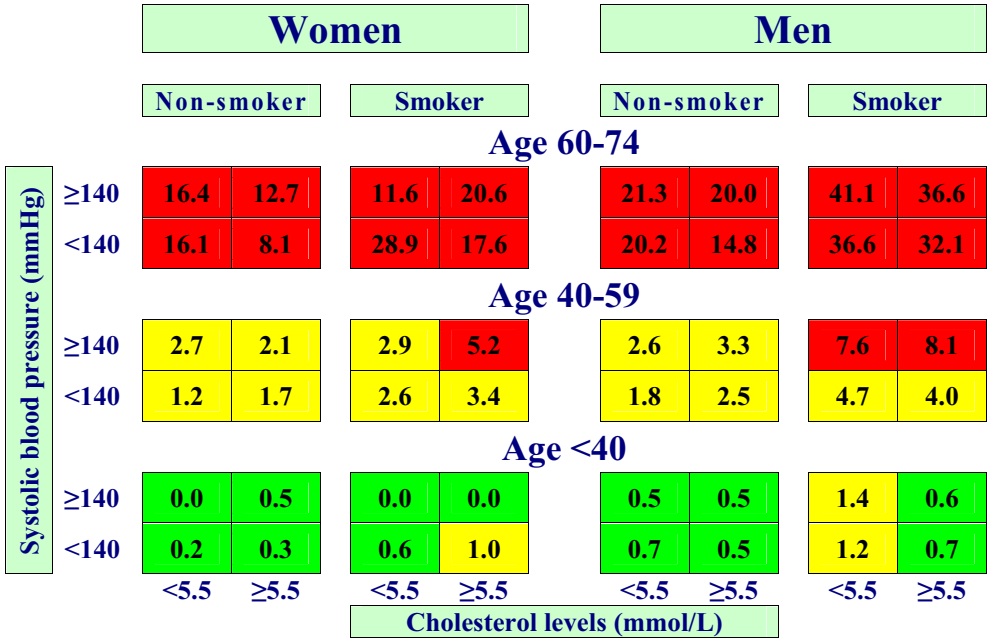

Figure C
Ten-year all-cause mortality per 1,000 person-years in the Nord-Trøndelag Health Study (HUNT 2).

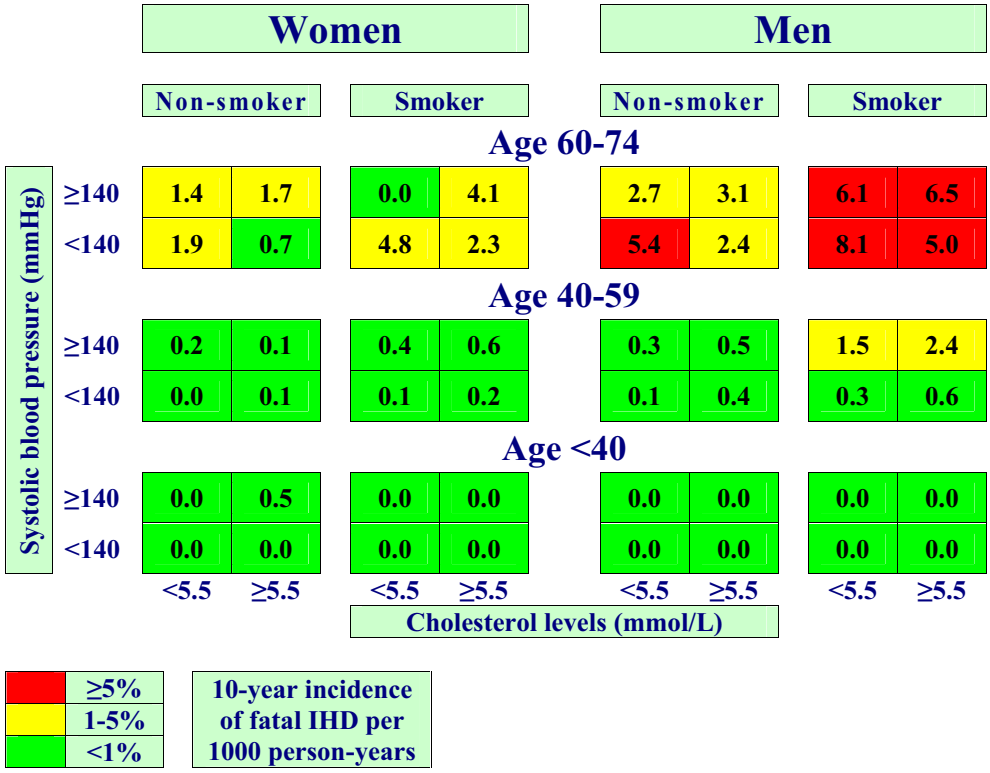

Figure D
Ten-year incidence of fatal ischaemic heart disease (IHD) per 1,000 person-years in the Nord-Trøndelag Health Study (HUNT 2).

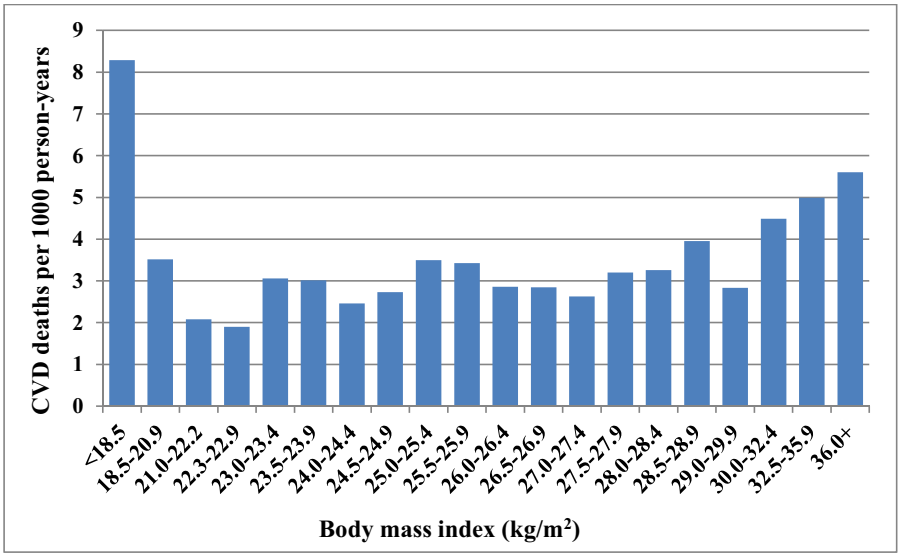

Figure E. CVD mortality per 1000 person-years among men in different BMI categories.

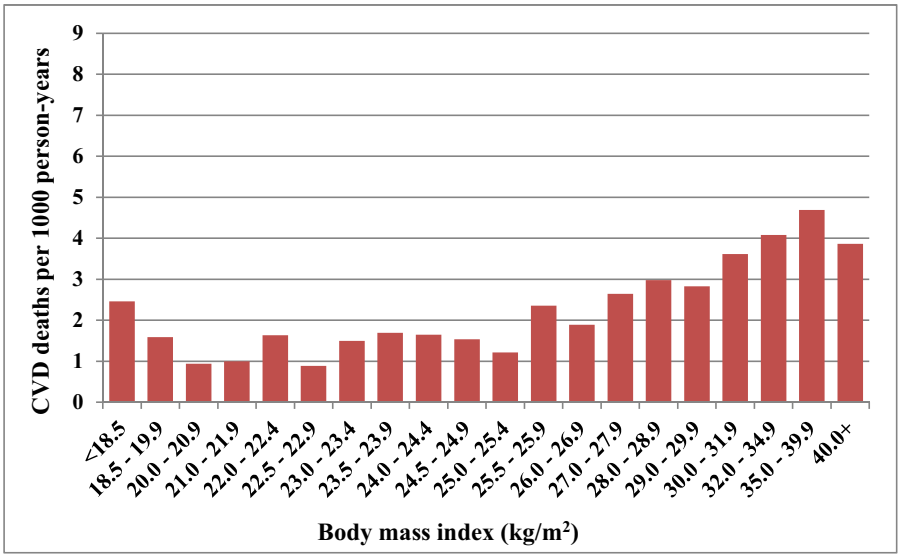

Figure F. CVD mortality per 1000 person-years among women in different BMI categories.

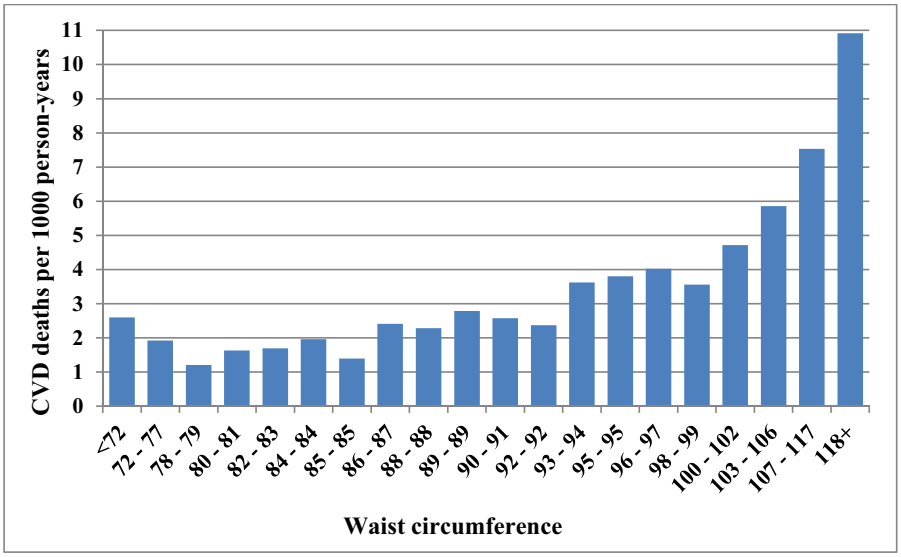

Figure G. CVD mortality per 1000 person-years among men depending on waist circumference.

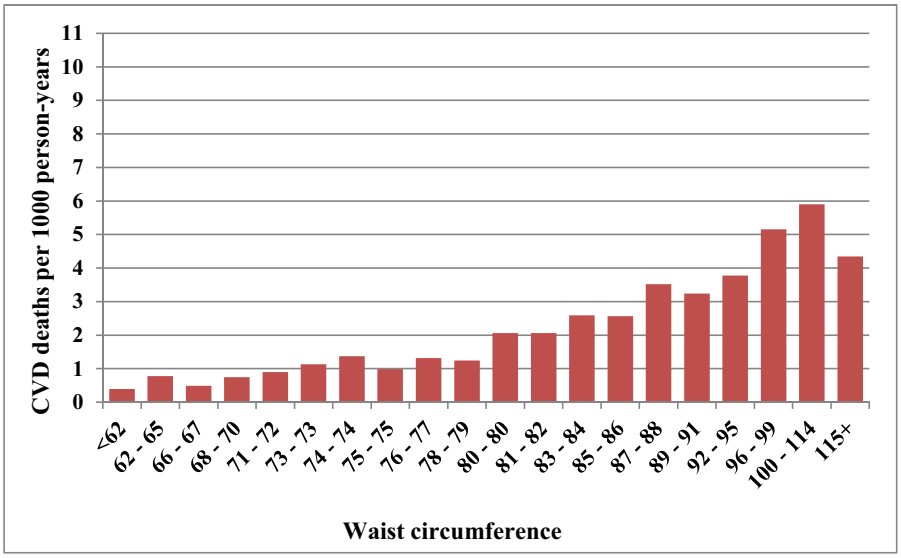

Figure H. CVD mortality per 1000 person-years among women depending on waist circumference.

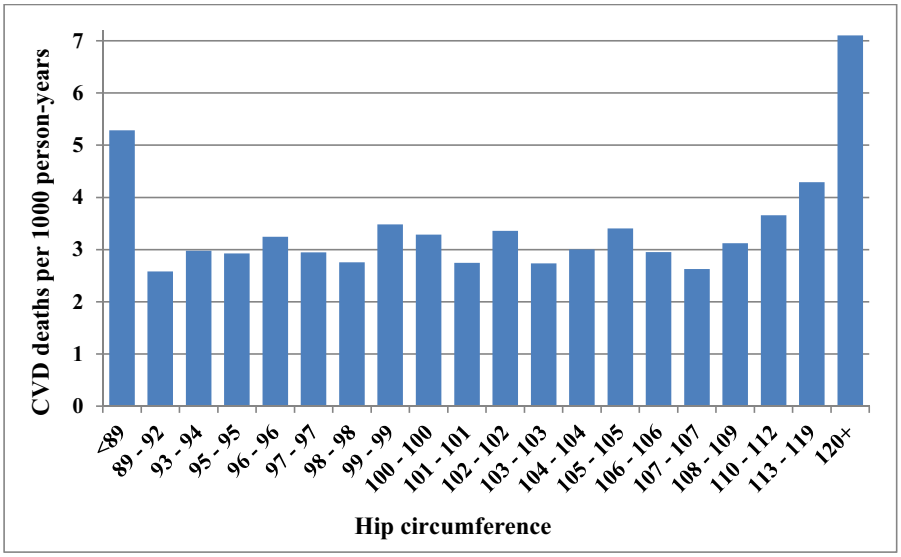

Figure I. CVD mortality per 1000 person-years among men depending on hip circumference.

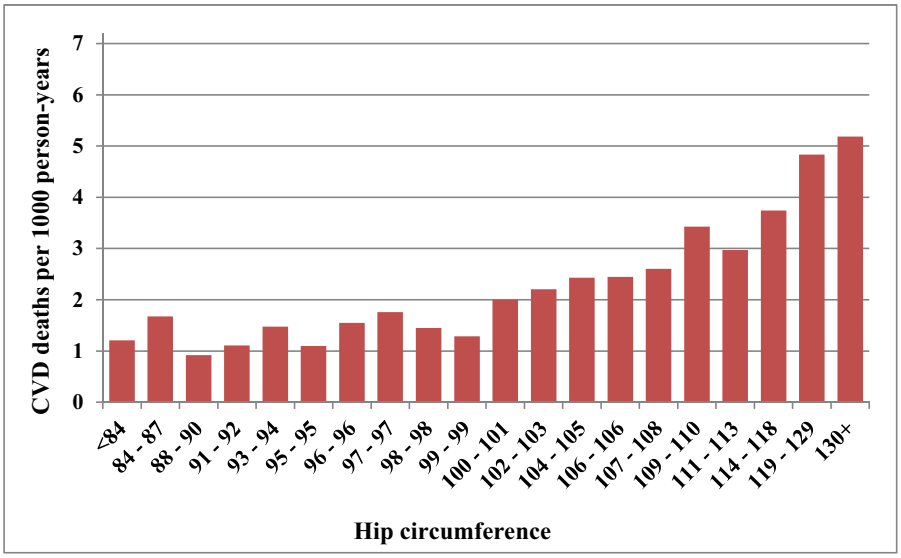

Figure J. CVD mortality per 1000 person-years among women depending on hip circumference.

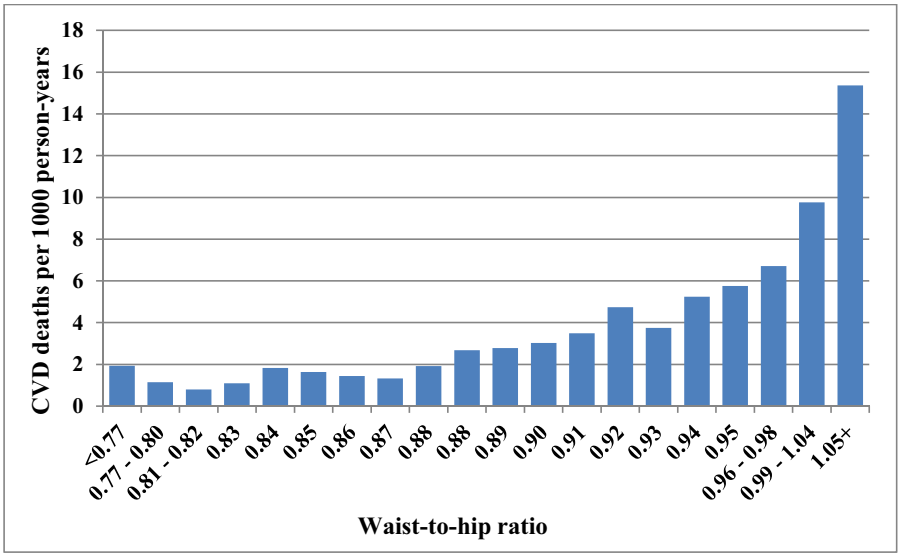

Figure K. CVD mortality per 1000 person-years among men depending on waist-to-hip ratio.

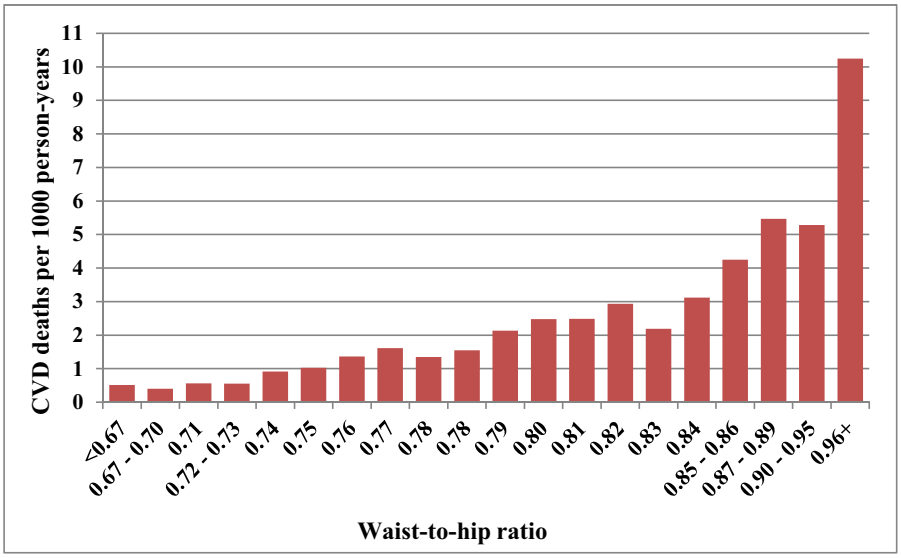

Figure L. CVD mortality per 1000 person-years among women depending on waist-to-hip ratio.

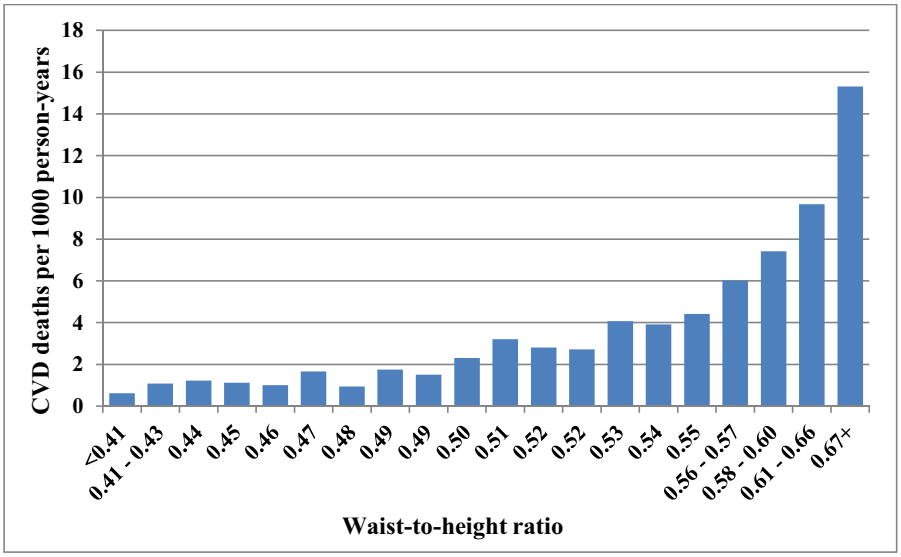

Figure M. CVD mortality per 1000 person-years among men depending on waist-to-height ratio.

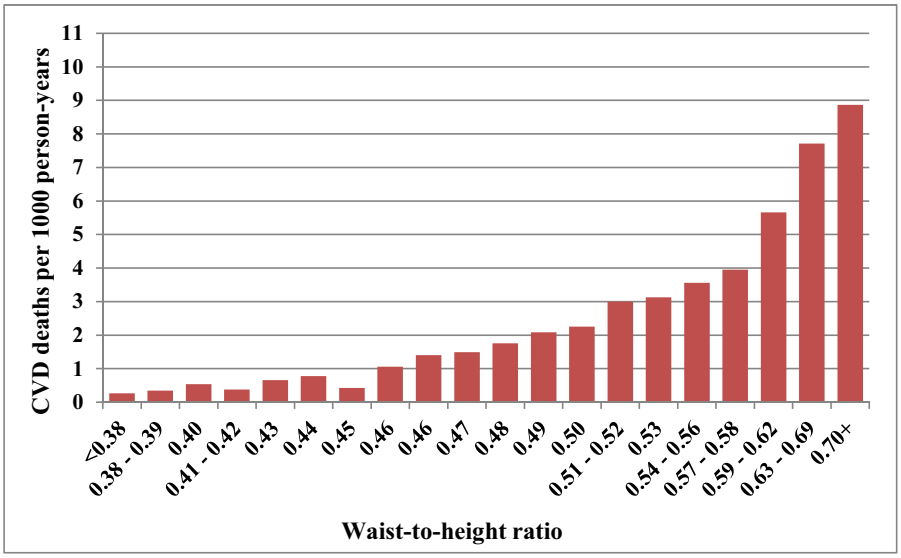

Figure N. CVD mortality per 1000 person-years among women depending on waist-to-height ratio.

Appendix III

Letter to the Editor

(Paper III)

NTNU
Norwegian University of
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Professor Andrew Miles
Editor-in-Chief
Journal of Evaluation in Clinical Practice
World Health Organisation Collaborating Centre for Public Health Education and Training
Imperial College, London
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Trondheim, November 15, 2011

Dear Editor,

the results presented in our paper (1) are in discordance with the mainstream view of the association between total cholesterol and mortality. However, our findings are in good accord with many previous studies, as discussed in the paper and also another, recent publication (2).

We hereby provide an additional Table A to document the effect of stratification by age. This helps explain, but does not alter, our previous conclusions. Within each age group, the age stratified mortality rate per 1000 personyears is similar across the different cholesterol levels.

For our analyses (1), we used attained age as our time-scale, rather than the time-on-study. This ensures that the estimated associations are adjusted for age, without age being included in the regression model as a covariate. Thus, fewer variables are needed to be specified, and potential proportional hazards violations between various age-categories are avoided. The method is widely used and has been described in detail elsewhere (3). We realize that the impact of using attained age could have been discussed more specifically in our paper.

As Professor Thelle et al. point out, the crude mortality rates are quite different from the age-adjusted ones. The age-stratified mortality rates for the four different cholesterol categories might have been presented in our paper to further clarify this discrepancy, since the paper's Figure 1 only includes two cholesterol categories.

Yours sincerely,

Halfdan Petursson, Johann A. Sigurdsson, Calle Bengtsson, Tom I. L. Nilsen, Linn Getz

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2. Hamer, M., Batty, G.D., Stamatakis, E., Kivimaki, M. (2011) Comparison of risk factors for fatal stroke and ischemic heart disease: A prospective follow up of the health survey for England. *Atherosclerosis*, Aug 22. doi:10.1016/j.atherosclerosis.2011.08.016 [Epub ahead of print]
3. Korn, E. L., Graubard, B. I., Midthune, D. (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *American Journal of Epidemiology*, 145, 72-80.

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Table A. Mortality rate (all causes) by age and total cholesterol (mmol/L) at baseline.

	Total cholesterol (mmol/L)											
	<5.0			5.0-5.9			6.0-6.9			≥7.0		
Age	N	Deaths	Rate*	N	Deaths	Rate	N	Deaths	Rate	N	Deaths	Rate
Men												
20-29	2 196	24	1.10	1 067	4	0.38	333	1	0.30	94	0	0.00
30-39	1 621	13	0.80	1 923	11	0.57	1 111	8	0.72	428	2	0.47
40-49	1 046	23	2.22	2 103	29	1.38	1 910	43	2.27	1 025	34	3.37
50-59	562	25	4.54	1 530	74	4.93	1 650	100	6.22	1 018	57	5.74
60-69	346	64	20.31	990	150	16.20	1 155	186	17.37	779	133	18.47
70-74	147	59	49.18	408	142	40.37	499	162	37.93	294	103	41.25
Women												
20-29	2 591	9	0.35	1 343	4	0.30	421	1	0.24	166	1	0.60
30-39	2 582	8	0.31	2 076	9	0.43	853	7	0.82	292	2	0.69
40-49	1 692	15	0.89	2 671	49	1.85	1 607	27	1.69	717	8	1.12
50-59	516	15	2.95	1 495	53	3.59	1 725	60	3.53	1 551	58	3.79
60-69	174	35	22.31	689	68	10.32	1 269	127	10.47	1 712	157	9.51
70-74	58	16	31.46	291	60	22.50	529	105	21.58	832	149	19.23

*Mortality rate per 1000 personyears.

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129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
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138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
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143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

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171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
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175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
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208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
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217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
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220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
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243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
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268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
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286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
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297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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