UiT The Arctic University of Norway

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Cardiovascular disease: risk assessment, total risk, and primary prevention in the general population

Insights from the population-based Tromsø Study

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Abbreviations

BMI	Body Mass Index
BP	Blood pressure
CHD	Coronary Heart Disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
GP	General Practitioner
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MI	Myocardial Infarction
mmHg	Millimetre of mercury
mmol/L	Millimole per litre
OR	Odds ratio
SBP	Systolic blood pressure
Total CVD risk	10-year risk of CVD
Tromsø6	The sixth survey of the population-based Tromsø Study
Tromsø7	The seventh survey of the population-based Tromsø Study
WHO	World Health Organization

List of papers

Paper I

Nilsen A, Hansen TA, Lappegård KT, Eggen AE, Løchen ML, Njølstad I, Wilsgaard T, Hopstock LA. Secular and longitudinal trends in cardiovascular risk in a general population using a national risk model: The Tromsø Study. *European Journal of Preventive Cardiology*. 2019;26(17):1852-1861. https://doi.org/10.1177/2047487319830806

Paper II

Nilsen A, Hansen TA, Lappegård KT, Eggen AE, Løchen ML, Selmer RM, Njølstad I, Wilsgaard T, Hopstock LA. Change in cardiovascular risk assessment tool and updated Norwegian guidelines for cardiovascular disease in primary prevention increase the population proportion at risk: The Tromsø Study 2015-2016. *OpenHeart.* 2021;8(2):e001777. https://doi.org/10.1136/openhrt-2021-001777

Paper III

Hagen NA, Ariansen I, Hanssen TA, Lappegård KT, Eggen AE, Løchen ML, Njølstad I, Wilsgaard T, Hopstock LA. Achievements of primary prevention targets in individuals with high risk of cardiovascular disease. An 8-year follow-up of the Tromsø Study. *European Heart Journal Open.* 2022;2(5):oeac061. https://doi.org/10.1093/ehjopen/oeac061

Summary

Cardiovascular disease (CVD) is a major cause of mortality and morbidity and an economic burden for society, calling for an active preventive approach. The risk factors for CVD are multifactorial, and the key risk factors include age, sex, family history, elevated cholesterol and blood pressure, smoking, diabetes, physical inactivity, unhealthy diet, and obesity. Several risk factors combined may lead to a high total CVD risk. Thus, primary prevention guidelines recommend using multivariable risk assessment prediction tools to identify individuals with a high total CVD risk to initiate measures through lifestyle modifications or medication to lower CVD risk.

The overall aims of this thesis were to study risk assessment of CVD and total CVD risk by the NORRISK 2 score, which estimates the 10-year risk of fatal and non-fatal myocardial infarction and stroke, and the primary prevention of CVD in a general population. We used data from the Tromsø Study, an ongoing population-based study consisting of repeated health surveys. The papers in this thesis used data from Tromsø6 (2007-2008) and Tromsø7 (2015-2016). In Paper 1, we observed a reduction in total CVD risk in a general population between Tromsø6 and Tromsø7 and a change in distribution from higher to lower risk categories between the surveys. Further, the main contributors of the risk factors included in the NORRISK 2 score to the total score were age, total cholesterol, blood pressure, and smoking, with some variation between sex and age groups. Furthermore, we found that total CVD risk increased during follow-up in the longitudinal analysis. However, when we set the age to baseline age (age held constant), the total CVD risk remained stable or decreased, confirming the contribution of age to the NORRISK 2 score and the effect of reduction in several modifiable risk factors. Paper 2 demonstrated how the NORRISK 2 score and the current national primary prevention guidelines increase the population proportion at risk by 3.4 percentage points compared to the former risk assessment tool NORRISK and the 2009 prevention guidelines. Finally, in Paper 3, we followed individuals with a high CVD risk between Tromsø6 and Tromsø7, finding several positive changes in CVD risk factors. However, less than 10% of the study sample achieved all treatment targets of lipids, blood pressure, and non-smoking. Further, we found that medication use was the strongest

characteristic associated with reaching treatment targets. Moreover, those with the highest risk of CVD have the lowest probability of achieving the treatment targets and thus reducing their risk of CVD.

In summary, we observed a reduction in total CVD risk and favourable changes in several risk factors in the general population over time, as well as an increase in the population proportion identified as high risk and eligible for intervention using NORRISK 2 score and the current primary prevention guidelines compared to the previous risk score and guidelines. An increased population proportion at risk could lead to a significant challenge for the primary health care system but is also an opportunity to prevent more high-risk individuals from developing CVD. We also found advantageous changes in several risk factors in those at high risk. However, the proportion reaching treatment targets is suboptimal, demonstrating the great potential for improvements in the primary prevention of CVD.

Sammendrag

Hjerte- og karsykdommer er en vanlig årsak til dødelighet, sykelighet og er en økonomisk belastning for samfunnet, og det kreves en aktiv forebyggende tilnærming. Risikofaktorene er multifaktorielle, og de viktigste risikofaktorene inkluderer alder, kjønn, familiehistorie, forhøyet kolesterol og blodtrykk, røyking, diabetes, fysisk inaktivitet, usunt kosthold og fedme. Nivået av en enkelt risikofaktor kan være lav, men effekten av flere risikofaktorer kan sammenlagt føre til en forhøyet risiko for hjerte- og karsykdommer. På bakgrunn av dette anbefaler retningslinjene for primærforebygging for hjerte- og karsykdommer at det brukes risikoskåringsverktøy for å identifisere individer med høy totalrisiko for å igangsette tiltak gjennom livsstils intervensjoner eller medisinsk behandling for å redusere risikoen for å utvikle hjerte- og karsykdommer.

Formålet med denne avhandlingen var å undersøke risikoskåring for hjerte- og karsykdommer ved hjelp av NORRISK 2 som estimerer 10-års risiko for akutt hjerteinfarkt eller hjerneslag, inkludert kardiovaskulær død, og videre studere primærforebygging av hjerte- og karsykdommer i befolkningen. Det ble benyttet data fra den befolkningsbaserte Tromsøundersøkelsen bestående av gjentatte og repeterte helseundersøkelser. Artiklene i denne avhandlingen er basert på data fra Tromsø6 (2007-2008) og Tromsø7 (2015-2016). I den første artikkelen ble det observert en reduksjon i totalrisiko for hjerte- og karsykdommer i befolkningen mellom Tromsø6 og Tromsø7, hvor færre ble identifisert til å være i høy risiko i Tromsø7 sammenlignet med Tromsø6. Blant risikofaktorene inkludert i NORRISK 2 skåren er det alder, total kolesterol, systolisk blodtrykk og daglig røyking som bidrar mest i skåren, med noen variasjoner mellom kjønn og aldersgrupper. I den longitudinelle analysen økte den totale risikoen i oppfølgingsperioden, men når aldersvariabelen ble holdt konstant forble den totale risikoen uendret eller lavere. Dette funnet bekrefter betydningen av alder i skåren, men som også belyser effekten av endringer i flere av de modifiserbare risikofaktorene. I den andre artikkelen ble det demonstrert hvordan NORRISK 2 skåren og de gjeldende nasjonale retningslinjene for primærforebygging øker andelen som blir beregnet som høy risiko for hjerte- og karsykdommer med 3.4 prosentpoeng sammenlignet med det tidligere skåringsverktøyet NORRISK og retningslinjene fra 2009. I den tredje artikkelen ble individer

med høy risiko for hjerte- og karsykdommer fulgt mellom Tromsø6 og Tromsø7 hvor det var flere positive endringer i risikofaktorer. Midlertidig så var det færre enn 10% som oppnådde alle behandlingsmålene for kolesterol, blodtrykk og røyking. Medisinbruk var den faktoren som var sterkest assosiert med måloppnåelse. Videre var det slik at de med høyest total risiko var de som hadde lavest sannsynlighet for nå behandlingsmålene og redusere sin risiko for hjerte- og karsykdom.

For å oppsummere, denne avhandlingen har demonstrert en reduksjon i totalrisiko for hjerte- og karsykdommer og flere positive endringer i flere risikofaktorer i befolkningen over tid. I tillegg ble det vist at NORRISK 2 skåren og de gjeldende retningslinjer for primærforebygging øker populasjonsandelen som blir beregnet som høy risiko sammenlignet med den forrige risikoskåren og de tilhørende retningslinjene. Dette er noe som fører til en større utfordring for helsevesenet, på den andre siden kan man forebygge at flere i høy risiko utvikler hjerte- og karsykdom. Videre, blant individer med høy risiko var det flere gunstige endringer i risikofaktorer over tid. Andelen som oppnår behandlingsmålene er ikke optimal, noe som viser at det foreligger et stort potensiale for forbedring i primærforebygging av hjerte- og karsykdommer.

1 Introduction

The main topic of this thesis is primary prevention and risk assessment of cardiovascular disease (CVD), and centres around the current Norwegian risk assessment tool NORRISK 2, which estimates the 10-year risk of fatal and non-fatal CVD (1). CVD is diseases of the circulatory system, which includes the heart and the blood vessels, where coronary heart disease (CHD) and cerebral stroke (stroke) are the two main types of diseases (2). Key risk factors for CVD are age, sex, smoking, hypertension, hypercholesterolemia, diabetes, obesity, and physical inactivity (2). Prevention of CVD focuses on identifying and managing the risk factors, and prevention strategies can be directed both at the populational and individual level (2). Strategies directed at the populational level can be where extensive changes in risk factors are made through different measures, such as tobacco control laws. At an individual level, a widely recognised approach is identifying high-risk individuals (3, 4). The level of a single CVD risk factor might be low, but the contribution of several risk factors simultaneously can lead to a high total CVD risk (5). Thus, primary prevention guidelines recommend using multivariable risk assessment prediction tools to estimate the risk of identifying individuals at high total risk of CVD and guide clinical decision-making on initiating or intensifying measures through lifestyle interventions or medication to lower CVD risk (6).

CVD is a leading cause of mortality worldwide, with an estimation of 17.9 million deaths in 2019, representing 32% of all global deaths (7). In Europe, 3.9 million deaths are yearly caused by CVD, which is 45% of all deaths in Europe, and CVD is thus a leading cause of mortality and a major cause of morbidity (8). Despite that CVD mortality is now decreasing in nearly all European countries (9), The World Health Organization (WHO) estimates that 80% of all premature CVD events in high-risk individuals is preventable (10). Surveillance of risk factors and diseases, such as CVD, can provide important information needed for policymakers to prioritise and establish health policies (11). Previous research with data from Norwegian population-based studies has demonstrated favourable changes in single risk factors such as blood pressure (12-14), cholesterol levels (15, 16), and smoking prevalence (17, 18) in the Norwegian population. However, studies of trends in total CVD risk are lacking.

The overall objective in the primary prevention of CVD is to prevent the manifestation or postpone the onset of disease (19, 20). The CVD prevention guidelines aim to provide health professionals with updated evidence in risk assessment and which measures to initiate to reduce risk (19-21). The European primary prevention guidelines have been updated at regular intervals since the first was presented in 1994 (19, 22-27). In Norway, the first multifactorial guideline was presented in 2009 (28), and included the first Norwegian risk assessment tool, the NORRISK score, which estimates the 10-year risk of fatal CVD (29). In 2017, the current Norwegian guideline was introduced (20). The updated guideline included the NORRISK 2 score, which included the estimation of both fatal and non-fatal CVD (1). The updates of the guidelines have led to new or revised risk assessment tools, new thresholds for defining individuals at high risk of CVD, and changed treatment targets for primary prevention. Modifications in the guidelines and changes in risk assessment tools have contributed to some debate, given that this could lead to a larger proportion of individuals being identified as high-risk. Hence, a more significant proportion needs lifestyle changes and potentially medication therapy (30, 31). Prevention of disease and health promotion is an essential task for the general practitioner (GP). The GP is a ground pillar in the healthcare system providing primary and preventive healthcare for the patient and working as a link between other parts of the healthcare system (32). Although NORRISK 2 and the updated prevention guidelines are tools that influence a GPs workload and everyday life in clinical practice that also affects many high-risk individuals, only a small amount of research on the Norwegian risk assessment tools and primary prevention guidelines has been performed after its implementation.

Primary prevention of CVD and management of cardiovascular risk factors are of interest to those working with public health issues related to the burden of CVD. Furthermore, this is an area affecting clinical practice. Therefore, the GP or other health personnel have to identify high-risk individuals and initiate measures to manage risk factors. Measures to reduce risk could include advice on smoking cessation, physical activity, and dietary lifestyle changes or the initiation of medication therapy (20). For the individual identified at high risk of CVD, this means addressing their habits and lifestyle and potentially being prescribed a lipid or blood pressure lowering medication to reduce their risk of CVD. In addition, the GP is recommended to initiate measures that aim to achieve the guideline-defined treatment targets for the high-risk individual (19-21).

Previously performed studies have demonstrated that individuals with a high risk of CVD do not reduce their risk as necessary (33-35), and studies on target achievement among those with hypercholesterolemia shown that the proportion who achieve treatment targets is suboptimal (36-38). The same applies to studies on target achievement among individuals with hypertension (39-41). The common conclusion of these studies is that there is still a need for improvements in the primary prevention of CVD. Despite the declining CVD mortality rates in Europe (9) and Norway (42), the burden of CVD is still vast for the society, healthcare workers, and individuals at high risk. Hence, CVD is one of the most demanding public health issues. Consequently, this leads to a need to focus on the primary prevention of CVD, monitor cardiovascular disease risk in the population, and for more research on this topic.

1.1 Cardiovascular disease

CVD is an umbrella term for several diseases of the circulatory system, and this thesis concerns descriptive epidemiology on the risk factors and the risk of fatal and non-fatal CVD of two groups of diseases in particular; CHD and ischaemic stroke (2, 7). CHD is the most common form of heart disease occurring when one or more of the coronary arteries are blocked or narrowed. CHD can cause angina pectoris or myocardial infarctions (MI) (2, 7). Stroke or cerebrovascular disease is an acute neurological injury leading to the sudden death of brain cells. A stroke can be caused by ischemia by occlusion of the arteries due to thrombosis, embolism, or systemic hypoperfusion (2, 7). Common to many of the CVDs is the underlying pathophysiology process known as atherosclerosis (43), where several risk factors contribute to the accumulation of this process. Atherosclerosis is a build-up of fibrofatty lesions called plaque in the artery wall, in which the arteries are stiffened and thickened, leading to impaired circulation and lack of oxygen supply to the heart muscle, brain, or extremities, which may cause an ischemic condition in the tissue (43, 44). Atherosclerosis is a chronic inflammatory condition, and the development is due to a gradual accumulation of lipids and fibrous components. Low-density lipoprotein (LDL) is an important factor in the process of atherosclerosis. The other risk factors such as elevated blood pressure, dyslipidaemia, diabetes, smoking, obesity, and unhealthy diet also contributes to the atherosclerosis process. (43, 44).

1.1.1 Epidemiology of cardiovascular disease in Norway

Mortality caused by CVD has declined in Norway since the peak in the 1970s (42). The declining mortality rates by CVD is a reflection of the decline in mortality from CHD and stroke. CVD has been the leading cause of death in Norway for several decades; however, today cancer is an almost as frequent cause of death as CVD (45). The number of new CVD cases is also declining in Norway. Between the years 2001 and 2014, the decline in the incidence of acute MI was 2.8% per year among women and 2.6% among men (46). In the Tromsø Study there was an overall 24% decrease in stroke incidence between 1995-2010 with some age, sex, and time variation (47). Improved screening and prevention, improved medical treatment including drug treatment and percutaneous intervention on the coronary arteries are some of the explanations of the decline in the morbidity and mortality of CVD (42, 48). In the Tromsø Study, advantageous changes in modifiable risk factors accounted for 66% of the decline in incident MI between 1994-2008, where a reduction in total cholesterol, blood pressure and smoking and less physical inactivity were the risk factors contributing most to the decline (48).

1.2 A historical throwback on risk factors, guidelines, and risk assessment scoring

This chapter includes a brief historical throwback on the discovery of the conventional CVD risk factors, primary prevention guidelines, and risk assessment tools for CVD. Further, an overview of the concept of risk assessment scoring and its role in primary prevention is introduced.

1.2.1 The history of the discovery of cardiovascular risk factors

Hypercholesterolemia, hypertension, smoking and diabetes are considered the four major conventional risk factors for CVD. The role of cholesterol in the pathogenesis of atherosclerosis was proposed in 1913 by the Russian experimental pathologist Nikolai Anitschkow (49, 50). His work is considered the first significant step in identifying

cholesterol as a risk factor for CVD. Anitschkow and one of his medical students, Chalatow fed rabbits purified cholesterol from egg yolks and dissolved it in sunflower oil. Within weeks their arteries started to show signs of lesions rich in “lipoids.” (50, 51). In the 1950s, John Gofman “the father of clinical lipidology” was responsible for a breakthrough in ultracentrifuge research in lipoproteins. Gofman revealed the association between cholesterol and MI, and that cholesterol contained LDL cholesterol, and observed that high levels of HDL was inversely associated with MI (49, 50, 52).

The first measurement of blood pressure were performed already in 1733 by Stephen Hales, a British physiologist and chemist (53). The invention of the cuff-made mercury sphygmomanometer in 1896 by doctor Scipione Riva-Rocci, and the discovery of the heart sounds by physician Nikolai Korotkoff was essential to define systolic and diastolic blood pressure (54, 55). This knowledge led to a focus on blood pressure, and in 1928, the term malignant hypertension was proposed by Keith et al. (56, 57)

The use of tobacco was common when Christopher Colombo arrived in North America in 1492, where tobacco was not only used for smoking, it was chewed, eaten, drunk like tea, smeared over the body to kill lice and parasites, and used as analgetic and antiseptics (58). Smoking was heavily marketed during the first world war, and advertising and massive campaigns contributed to the widespread of cigarette smoking (59).The major evidence in the modern history of the health effects of smoking came in the 1950s with the publication of four retrospective studies of smoking habits and lung cancer (58, 60, 61).

Thomas Willis an English physician born in 1621 was the first European to describe the sweetness of the urine in diabetes and attributed this to eating habits and psychological status (62, 63). Claude Bernhard, a French physiologist, is known for his contribution to the study of metabolism and diabetes, and in 1855 Bernhard isolated glycogen (64). In 1889 the two German physicians, Minkowski and von Meering, discovered the role of the pancreas in diabetes (65) this was an important finding leading the way for the work in the discovery of insulin. The Canadian researchers Banting, Best, Macleod, and Collip executed several experiments leading to the discovery, isolation, and structural classification of insulin. In 1922, the first experiment with insulin in humans were performed and found glucose levels to drop significantly (63, 65). The impact of hypercholesterolemia, hypertension, smoking and

diabetes on CVD risk has been studied extensively after their discovery, but gained severe momentum in research in the 1950s.

1.2.2 From concepts of risk factor to risk scoring and primary prevention guidelines

After World War 2, CHD was recognised as an epidemic when CVD had become the leading cause of death in western societies. In the United States, this led to the formation of the National Heart, Lung, and Blood Institute, which initiated the Framingham Heart Study in 1948 (66). This population-based cohort study on the consequences of CVD led to its initial publication in 1961 and introduced the concepts of risk factors for the development of CHD (67). Further, the knowledge gained from the cohort study led to the development of the first risk prediction tool: The Framingham Risk Score was developed and presented in 1976, the risk score which included a general cardiovascular endpoint; CHD, stroke, claudication and heart failure (68).

In America and Europe, different programs and recommendations in the management of cardiovascular risk factors were presented, but in the beginning, they were single risk factor centred (69). In Norway, the first guideline on hypertension was published in 1986 (70), and revised in 1993 by the Norwegian College of General Practitioners (NSAM) (71). Nationally there were large debates regarding the definition of hypertension and hypercholesterolemia, about guidelines in general, and when to initiate treatment. Much of the criticism came from the fact that many studies were initiated from drug companies and were therefore considered not objective or independent (71).

The first European primary prevention guidelines from the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension were presented in 1994 (22), and have been updated at regular intervals since then. In 1998, an updated version of the guidelines was introduced (23), which included the most broadly used risk score; the Framingham Risk Score for 10-year risk for coronary heart disease (72), and since then, several other risk scores have been developed.

1.3 The risk factors for cardiovascular disease

CVD is a multifactorial disease, and several risk factors can increase the risk of developing disease. A distinction is often made between non-modifiable and modifiable risk factors. Non-modifiable and modifiable risk factors act both together and independently (19, 73). Non-modifiable risk factors include age, sex, family history, and ethnicity, whereas modifiable risk factors include (but are not limited to) hypertension, dyslipidaemias, diabetes, smoking, excessive alcohol consumption, physical inactivity, unhealthy diet, and obesity (2, 73). Other risk factors are low socioeconomic status, psychological distress, and environmental factors such as air pollution. In this chapter, a selection of the risk factors will be described in more detail, while others will be mentioned only briefly.

1.3.1 Non-modifiable risk factors

Age and sex

Age is the most important determinant of cardiovascular health, and aging is associated with a decline in several physiological processes where the circulatory system is affected, leading to an increased risk of CVD (74). Age is an independent risk factor for CVD (75, 76). However, increasing age also contributes to increased exposure time to other CVD risk factors. Stroke is more likely to be the first manifestation of CVD in women (77, 78), whereas, in men, CHD is more common (78, 79). The risk of MI increases with age in both sexes. Studies have found that men overall have twice the risk of MI compared to women (80). On average, women have their first MI 6-10 years later than men (81). Studies have also found sex differences in risk of stroke, where the risk of stroke is higher in men than in women, but women experience more severe strokes (82). At age 55, the overall lifetime risk of CVD were 66.4% in women and 67.1% for men (78). The lifetime risk of first manifestations of CVD in women were 16.9% in women and 27.2% in men for CHD, and 29.8% and 22.8% for stroke, respectively (78). The risk factors for CVD contribute to the overall risk differently between women and men (81).

Family history

A family history of CHD is an independent risk factor for CVD (83). It has been questioned whether a family history of CHD is due to a genetic component or the shared lifestyle affecting modifiable risk factors. It is suggested that genes play an important role, but the underlying genetic mechanisms are not completely understood (84, 85).

Ethnicity

Different ethnic groups are disproportionally at higher risk of CVD, including both CHD and stroke (86). A systematic review found ethnic differences in several CVD risk factors, which could be due to both biological, social and environmental determinants (87). The prevalence of risk factors for CVD is found to explain to a large degree the difference in risk within ethnic groups, but cannot entirely explain the distinctions in CVD risk between different ethnic groups, and it is proposed that other explanations might exist (86).

1.3.2 Modifiable risk factors

Blood lipids

Dyslipidaemia occurs when there are abnormal levels of blood lipids. Total cholesterol is a measure of the total amount of cholesterol in the blood and includes LDL cholesterol (Low-Density Lipoprotein), HDL cholesterol (High-Density lipoproteins), and triglycerides. Elevated levels of LDL are associated with increased CVD risk, and in contrast, high HDL is inversely associated with CVD (88). Triglycerides' independent impact on CVD risk has been more debated and is considered more uncertain (89, 90). Total cholesterol is positively associated with CHD incidence and mortality in both sexes, and this association decreases with age (91). Overall, total cholesterol levels are similar among both sexes, but women have lower levels of LDL cholesterol and triglycerides, and higher levels of HDL cholesterol, hence; a more favourable lipid profile compared to men (92). One study found for every one mmol/L increment in total cholesterol, the risk of CHD increase by 20% in women and 24%

in men. The association between total cholesterol and stroke is generally weaker (93), but several studies have found an association between dyslipidaemia and stroke (91, 94, 95). Studies have demonstrated that a reduction in total cholesterol and LDL cholesterol is associated with a decrease in the incidence of CVD (91, 96, 97), where lowering LDL cholesterol by one mmol/L is associated with a 23% relative risk reduction of major vascular events (98).

Blood pressure and hypertension

Elevated blood pressure is a leading preventable cause of CVD morbidity and mortality and is a major global disease burden (99, 100). Hypertension is commonly defined as systolic blood pressure (SBP) 140 mmHg and/or diastolic blood pressure (DBP) 90 mmHg (101). Studies have indicated a continuous association between blood pressure and total mortality (102), and the risk of death from CHD or stroke increases linearly in both SBP and DBP, and a there is found to be a doubling in the risk of CHD and stroke with every 20 mmHg increase in SBP and 10 mmHg in DBP, starting from as low as SBP 115 mmHg and DBP 75 mmHg (19, 103) SBP and DBP are positively associated with CVD independently of age, but different age thresholds have been observed for when blood pressure starts to be associated (102). Men have higher blood pressure than women (104) but, during a life course, women experience a steeper increase in blood pressure in the third decade of life which continues throughout life (105). Overall, the prevalence of hypertension is similar among women and men, but at a younger age, the prevalence is higher among men, whereas the prevalence is highest among women at an older age (106, 107). Lowering systolic blood pressure is associated with a reduced risk of CVD, where the lowest risk is found between 120-124 mmHg (108).

Smoking

Smoking is a major health hazard and impacts all phases of the atherosclerotic phase (109). Many of the mechanisms involved are unknown, but smoking increases inflammation, thrombosis, and oxidation of LDL cholesterol and impacts both lipid profile and blood pressure levels. Both passive and active smoking predispose to cardiovascular events (109). There seems to be a dose-dependent relationship in smoking, where a smoker's risk of CVD,

increases with the number of cigarettes (110). The risk of CVD is highest among current and recent smokers compared to never smokers and those who stopped smoking in the more distant past (60). However, one study found current smokers to have a doubled risk of developing CVD compared to individuals who have never smoked, and the mortality from CVD is almost tripled in current smokers versus never smokers (111). The relative risk from current smoking is greater at younger ages, and the risk of CVD in smokers under 50 years is fivefold higher than in non-smokers (112). Studies have found sex differences in the smoking influence of CVD risk; Female smokers have a higher risk of CHD compared to male smokers (113), an increase which is significant after adjusting for other known risk factors (114). A sex difference is also present in the risk of stroke and stroke mortality, especially high in women at older ages (115, 116).

Diabetes

Diabetes is a chronic metabolic disease (117). In Type 1 diabetes, the pancreas produces little or no insulin leading to increased blood glucose levels. Type 2 diabetes is the most common diabetes type. The pathogenesis of type 2 diabetes is complex and is characterised by hyperglycaemia, relative insulin resistance and impaired secretion of insulin (118). Raised blood (hyperglycaemia) glucose levels over time can lead to damage to the blood vessels, the kidneys, nerves, and the heart (117). The risk of CVD in individuals with diabetes is about two-threefold compared to those without diabetes (119). Individuals with diabetes tend to also have higher systolic blood pressure, total cholesterol, BMI and waist circumference, and lower HDL cholesterol (120). There are also found sex differences in the risk of CVD, where women with diabetes have about 40% higher risk of CHD compared to men with diabetes (120) and a 27% higher risk of stroke when adjusting for other cardiovascular risk factors (121), consequently diabetes poses a greater relative risk for CVD in women than men.

Other modifiable risk factors

Several modifiable risk factors for CVD have over the years been identified, and several of these risk factors influence the risk of CVD directly but also indirectly by affecting blood pressure, lipids and diabetes (30). Obesity, defined by body mass index (BMI) $\geq$30 kg/m^2

(122), and abdominal obesity, defined by waist circumference of ≥88 cm in women and >102 cm in men (123) are linked to an increased risk of diabetes (124) and CVD (125). Physical inactivity are associated with increased CVD risk (30, 126-128). A healthy diet with lower amount of meat, more fish, fruit, and vegetables and food rich in fibres is associated with a lower risk of CVD, (19, 30, 129). Excessive intake of alcohol is associated with increased risk (130), Psychological distress is associated with increased CVD risk, but the association is largely explained by behavioural factors (131). Low socioeconomic status is associated with increased risk of CVD, and is to a large degree related to behavioural risk factors (132, 133).

1.4 Risk prediction tools in cardiovascular disease prevention

Assessment of total CVD risk is also referred to as global risk assessment, absolute risk assessment, or risk scoring and is emphasised in CVD primary prevention guidelines (6, 19, 20). The most common method is risk models that incorporate risk factors that calculate the total risk, often given as a 10-year risk in percent. However, other methods, like imaging modalities such as computed tomography (CT) with coronary calcium scoring and CT coronary angiography and ultrasound with measurements of the carotid-intima media thickness, have an increasing role in preventive cardiology (21). In addition, biomarkers in blood and urine have gained some attention (21). However, imaging and biomarkers will not be further presented in the following sections.

CVD primary prevention guidelines aim to work as a guide for clinicians to identify individuals at high risk and to initiate measures to reduce the risk of CVD through lifestyle modification or pharmacological therapy in those with highest risk of CVD (134). Already in the 1970s, when the first algorithm from the Framingham Heart Study was presented, the idea was to identify those at the highest risk of CVD who would benefit the most from preventive measures by estimating the combined effects of multiple risk factors (135). The justification for using risk charts and prediction tools to estimate an individual's total CVD risk is that traditionally a physician has qualitatively estimated an individual's risk by combining the patients' characteristics, clinical signs such as blood pressure, and laboratory tests. Hence, a physician's estimation relies on clinical judgment, previous experiences, personal beliefs, and

interpretation (6). Risk prediction tools are not developed to replace a physician's clinical judgment but to provide an objective risk estimate and to work as a guide to initiate, intensify, or discontinue preventive medication (6). The rationale for aiming to identify high-risk individuals is on the basis of observations that treatment of high-risk individuals induces a greater reduction in absolute risk (5, 6).

Studies on the predictive value of using the high-risk strategy have been questioned since it excludes individuals with low and moderate risk, who are found to ultimately make up for over 80% of all strokes and MIs (136, 137). Further, some reviews on total CVD risk scoring have been conducted. In 2006, Brindle et al (138) found no strong evidence supporting the aim to reduce CVD-related outcomes. However, they found then only four randomized controlled trials that had investigated the effectiveness of total CVD risk scoring. One systematic review of systematic reviews on the impact of total CVD risk assessment found no studies reporting the effectiveness of scoring on CVD-related outcomes and found little and low-quality evidence for small reductions in SBP, lipids, and increased odds for smoking cessation (139). A Cochrane review could not prove that CVD risk scoring reduces CVD events, but found that using risk scores may increase the prescription of preventive medication in high-risk individuals (140). A more recent review also supports these findings, but an equal feature of all the articles is that they summarise that there is generally poor evidence and that the studies have major limitations (141). Several prediction models have been developed and included in clinical guidelines over the last two decades, and one study found 125 papers describing the development of 363 different risk models (142). However, many models were used several times with alterations. This review observed a considerable variation in predicted outcomes and had a median of 7 predictors included in the models. For 27% of the models, both discrimination and calibration of the models were reported, and the majority were never externally validated. The authors recommend improving evidence in this field. Rather than developing new CVD risk prediction models, there should be more focus on external validation of different models and comparing head-to-head the existing models (142).

1.4.1 The Norwegian cardiovascular risk models

Risk models based on the American Framingham study were the foundation for the European prevention guidelines. However, studies found that the Framingham risk score overestimated the risk in European populations (143-146). The European SCORE project (Systematic Coronary Risk Evaluation) was developed on this basis (147). The SCORE model used mortality data based on European data, and the risk model was divided into a high-risk function and a low-risk function (147). When the SCORE model was presented, Norway was allocated the high-risk function. However, the Norwegian CVD mortality rates were rapidly declining and when comparing the high-risk and low-risk functions of the SCORE model in a general Norwegian population, the high-risk function overestimated risk among men. In contrast, the low-risk function underestimated risk among men. Furthermore, the high-risk and low-risk functions underestimated risk in young women and overestimated risk in older women (148). Moreover, another study found that the SCORE high-risk function overestimated CVD mortality in Norway (149). In addition, another study demonstrated how European guidelines for CVD primary prevention and the SCORE model could imply a doubling of the number of cardiovascular medications for primary prevention of CVD (150). Therefore, a model that was adjusted adequately to national levels before implementing the use of total CVD risk assessment in clinical practice were requested. Thus, a Norwegian risk score was warranted.

1.4.2 NORRISK

NORRISK is a national calibrated version of the European SCORE algorithm and estimates the 10-year risk of fatal CVD in individuals aged 40-69, and is based on age, sex, systolic blood pressure, serum total cholesterol and daily smoking habits (29). A three-step procedure was conducted in the development. Age and sex-specific national mortality rates from Statistics Norway 1993-2003 were used in the calibration. In addition, age and sex-specific mean risk factor levels were included with data from health surveys from five Norwegian counties between 2000-2003. The estimated risk factor level was compared with the observed values, and there was good agreement between the estimated and observed values (29).

In the adjustment procedure, the calculation was as follows:

$$w = \beta chol\ \ (cholesterol - \overline{cholesterol)} + \beta syst\ \ (systolic - \overline{systolic)} + \beta smoke\ (smoke - \overline{smoke)}$$

$$HR = e^{w}$$

The relative hazard rate for individuals with the specified risk factor level compared with individuals with a mean risk factor level.

For age (a) and sex (k) and given risk factor level, the calculation is: $S(10 \mid a, k = S0\ (10 \mid a,k))^{HR}$

The estimated 10-year mortality risk is $1 - S\ (10|a,k).$

Additional risk factors such as HbA1c levels and first-degree family member with a history of premature CHD can be used to recalculate risk with specific cut-offs. Age-specific thresholds are set to determine need of lifestyle advice and/or therapy with antihypertensives and/or lipid-lowering medication, where indication to initiate treatment is set to NORRISK score: 40-49 years score ≥1%, 50-59 years score ≥5%, 60-69 years score ≥10% (29).

1.4.3 NORRISK 2

The Norwegian health authorities decided to revise the national CVD prevention guidelines and required a prediction model for acute CVD events and not only for CVD mortality (1, 20). Thus, the NORRISK 2 estimates the 10-year risk of incident MI and stroke combined, including both non-fatal and fatal events of CHD and stroke in individuals aged 40-79 years. The variables included in the model are age, sex, systolic blood pressure, serum total cholesterol, daily smoking habits, a first-degree family member with a history of premature MI (before the age of 60 years), low serum HDL-cholesterol based on sex-specific cut-off values (1.0 mmol/L in men and 1.3 mmol/L in women) and use of antihypertensives (where current use increases the score) (1).

NORRISK 2 is based on data from the Cohort of Norway (CONOR) study and linked through the CVDNOR project (151), a database of CVD hospital discharge diagnoses and mortality in Norway from 1994-2009. The CONOR study included data from several regional health surveys in Norway (152). In the model development, CONOR surveys from 1994-1999 was

included (the fourth Tromsø Study, the second Nord-Trøndelag Health Study, and the Hordaland Health Study). In addition, CONOR surveys from 2000-2003 (The Oslo health Study, the fifth Tromsø Study, the Troms and Finnmark Health study) were included in the model validation. Participants attending both the fourth and fifth Tromsø Study were only included in the validation population (1).

For the development of NORRISK 2, participants aged 40–79 years, free of angina pectoris, MI, or stroke, were followed from 1994 to 2009 for the first occurrence of MI or stroke, which included either hospitalization (non-fatal cases) or deaths (fatal cases). In total, 31,445 men and 35,267 women were included in the model population, whereas 19,980 men and 19,309 women were included in the external validation population. The Fine and Gray regression model was used to estimate the 10-year risk, adjusting for competing risks, such as deaths from other causes (153). The NORRISK 2 model was validated by the area under the receiving operating characteristic (ROC) curves and calibration plots (predicted – observed cumulative risk within deciles of predicted risk).

The NORRISK 2 score calculation;

Cumulative incidence function at time t:

$$I(t|Z) = 1\text{-}\exp(-\exp(\beta^t Z) \int_0^t \overline{\lambda_0}(s)ds)$$

Z = vector of covariates, β^t = vector of regression coefficients.

$\int_0^t \overline{\lambda_0}(s)ds = \Lambda_0(t)$ = cumulative sub distribution baseline hazard

The estimated baseline cumulative sub-distribution hazard refers to age 40, total cholesterol 4.0 mmol/L, systolic BP 120 (the regression coefficient is for 10 mmHg), HDL> 1.0 mmol/L in men and >1.3 mmol/L in women, no family history of CHD and not on drug treatment for hypertension.

The calculation for men is as follows: *$w = 0.11447*Age -0.00043*Age^2 + 0.22283*$ Systolic BP+ 0.35625*Total cholesterol + 0.91727*Smoke-0.00896*Systolic BP*Age-0.00430*Systolic BP*Age-0.02051 *Smoke *Age+0.27824*BPmed+0.33162*lowHDL +0.29986*familyCHD_1 + 0.59692* familyCHD_2.*

The calculation for women is as follows: *w= 0.13037* Age -0.00066 *Age^2 + 0.25241 * Systolic BP + 0.07235* total cholesterol + 1.26781* Smoke -0.00500*S*Age- 0.02456*Smoke*Age+0.19200*BPmed+0.32377* lowHDL+0.25361* familyCHD_1 +0.54909* familyCHD_2*

hr=exp(w)

*risk=1-exp(-hr * 0.00526) in men; risk=1-exp(-hr* 0.00232) in women*

10-year risk as percentage: Risk percent= risk * 100

Selmer et al. (1) suggest age-specific thresholds in age groups 45-54, 55-64 and 65-74 years to determine whether an individual is at low, medium, or high risk of CVD (1). Additional risk factors (South Asian ethnicity risk*1.5, diagnosis of rheumatoid arthritis risk*1.4) can be used to recalculate the risk score, with specific cut-offs. Abdominal obesity, mental strain and stress are additional risk factors without a specific cut-off value.

1.4.4 Comparison of NORRISK 2 with other risk models

There is no gold standard in total CVD risk models, and perhaps the most crucial component before applying a model is recalibrating the model to fit the population since risk will be overestimated in populations where CVD is declining (21). Nonetheless, comparison of different risk models can be useful, as Damen et al. (142) emphasised. Thus, in Table 1 (page 18), an overview of a selection of CVD risk assessment tools is presented with the geographical region, prediction outcomes, and variables included in the risk score. The presentation of the risk models is not a comparison of validity, predictive value, or performance of the score. However, the chosen models are selected with the objective to show some selected scores with their contents.

In total, including the Norwegian risk assessment tools NORRISK 2 and NORRISK, the table presents 10 different risk models. The geographical areas of the risk scores are Norway, Worldwide, United States, Europe, and some specific countries such as Italy, Scotland, and United Kingdom. Globorisk (154) and SCORE (147) estimate the 10-year risk of fatal CVD, whereas Reynolds Risk Score (155-157), ASCVD (158, 159), SCORE2 (160, 161), CUORE

(162), ASSIGN (163, 164) and QRISK3 (165, 166) estimate a 10-year risk of CVD including both fatal and non-fatal events.

The variation in age included in the risk models differs. However, most of the risk score is in the age-group 40-70 years. All models include age, sex, systolic blood pressure, and smoking. HDL cholesterol is included in several of the scores but is defined differently. Further, the variables family history of CVD and use of antihypertensives varied. The majority of the included risk models in this overview had additional variables. Ethnicity and diabetes were variables in several risk scores, followed by rheumatoid arthritis.

The NORRISK model included the risk factors most common in other international risk models, such as systolic blood pressure, total cholesterol, smoking, age, and sex. In the development of the NORRISK 2 model, low HDL cholesterol and a family history of premature CHD were included (1). In addition, the use of antihypertensives as a variable was included in the model and increases the score; this is because patients treated for hypertension have a higher risk of a CVD event compared to untreated individuals with the same blood pressure level (1, 167). However, this is a variable not included in most risk models. Furthermore, Selmer et al. (1) aimed to include participants using statins to make corrections in the model, but this was not available in the data. A major strength in the NORRISK 2 score, in addition to the large sample size and the population-based design, is that the external validity model found the NORRISK 2 score fits well in the Norwegian general population without known CVD (1). Furthermore, a study with data from Oslo Ischemia Study found that the NORRISK 2 performed well to predict CVD among men (168). In addition, a version of the NORRISK 2 model that included South-Asian ethnicity and diabetes has improved predictions of CVD in South-Asians substantially (169).

Table 1: Comparison of a selection of CVD risk assessment models

Risk model	Geographical region	Prediction Outcome	Age	Sex	SBP, TC, Smoking	Low HDL cholesterol	Family history	Use AHT	Other variables
NORRISK 2	Norway	10-year CVD risk	45-74	Yes	Yes	Yes	Yes	Yes	South-Asian ethnicity Rheumatoid arthritis
NORRISK	Norway	10-year risk fatal CVD	40-69	Yes	Yes	No	No	No	Family history Hba1c
Globorisk	Worldwide	10-year CVD risk	40-74	Yes	Yes	No	No	No	Country Body Mass Index
Reynolds Risk Score	United States	10-year CVD risk	<80	Yes	Yes	mmol/L	Yes	No	High Sensitivity CRP
ASCVD	United States	10-year CVD risk	40-79	Yes	Yes	mg/dL	No	Yes	Ethnicity Diastolic blood pressure Diabetes
SCORE	Europe (low/high risk regions)	10-year risk fatal CVD	40-65	Yes	Yes	No	No	No	
SCORE2	Europe (low/high risk regions)	10-year CVD risk	40-69	Yes	Yes	mmol/L	No	No	LDL-cholesterol SCORE-OP (older persons >70 years)
CUORE	Italy	10-year CVD risk	35-69	Yes	Yes	mg/DL	No	Yes	Diabetes
ASSIGN	Scotland	10-year CVD risk	25-90	Yes	Yes	mmol/L	Yes	No	Rheumatoid arthritis Diabetes
QRISK3	United Kingdom	10-year CVD risk	25-84	Yes	Yes TC/HDL ratio	TC/HDL ratio	Yes	Yes	Ethnicity Diabetes Chronic kidney disease (stage 3-5) Atrial fibrillation Migraine Rheumatoid arthritis Systemic lupus erythematosus (SLE) Severe mental illness Use of atypical antipsychotic medication Use of regular steroid tablets Erectile dysfunction Body Mass Index

1.5 Primary prevention in clinical practice

1.5.1 Primary prevention guidelines

The guidelines provide health professionals with summarised, updated evidence and clinical, practical recommendations and advice on assessing risk, treatment, and preventing CVD (19, 20). Still, as highlighted in the Norwegian and European guidelines, the treatment of patients should be individually tailored, and the health care professional should manage the overall assessment and decisions.

The Norwegian CVD primary prevention guidelines have graded recommendations: a strong recommendation, a recommendation, and a weak recommendation (20). In the European guidelines (19), the recommendations are classified by numbers from 1-3, where class 1 is a recommended treatment or procedure, class 2 is conflicting evidence with variations of recommendations ranging from should be considered too may be considered, and class 3, the treatment or procedure is not recommended. In addition, in the European guidelines, the level of evidence A-C is included. In the Norwegian guidelines a total CVD risk assessment is graded as a strong recommendation (20). However, in the European guidelines (19) total CVD risk assessment is graded class 1 in individuals with any major risk factor, with an evidence level C, whereas systematic or opportunistic total CVD risk assessment in the general population in men >40 years and women >50 years is a class 2b recommendation (may be considered) with a C level of evidence (19) .

Individuals with a high total CVD risk estimated by NORRISK 2 score should receive non-medical interventions such as advice on lifestyle advice for 3-12 months and treatment with medications if the non-medical interventions do not result in sufficient improvement in risk factor levels (20). Whether an individual should be initiated with medical treatment directly is assessed by the levels of the risk factors and the total CVD risk score. Furthermore, according to the guidelines, individuals with elevated values on single risk factors; SBP ≥160 mmHg or DBP ≥100 mmHg, total cholesterol ≥7 mmol/L or LDL-cholesterol ≥5 mmol/L (not in women over 50), or people with diabetes with BP >140/90 or LDL >2.5 mmol/L should be considered for medical treatment regardless of their total CVD risk (20).

Furthermore, in the guidelines (19, 20) and the ESC handbook of preventive cardiology (21), a strong recommendation is to offer follow-up care to re-assess total CVD risk to determine whether further interventions are needed. The national guideline treatment targets in primary prevention 2017 guidelines are as follows: BP <140/90 mmHg (<135/85 if diabetes), total cholesterol <5 mmol/L, LDL cholesterol <3 mmol/L (<2.5 if diabetes) and non-smoking (20).

1.5.2 Non-medical interventions

The risk of CVD relates to a large degree to modifiable risk factors. Thus, risk factor management is a key element in the primary prevention of CVD. Lifestyle changes can influence cardiovascular risk directly or through lipids, blood pressure, or plasma glucose levels (30). Smoking cessation is potentially the most effective non-medical intervention to reduce an individual's risk of CVD (19, 170). Smoking cessation is associated with lower CVD morbidity and mortality (30, 170). The impact of smoking cessation happens rapidly after quitting smoking, and the risk of CVD can be 39% lower within five years after cessation (171). Thus, in consultation between a health professional and an individual who smokes, the importance of smoking cessation is a focus area in risk factor management. Improving lipid profiles in high-risk individuals can reduce CVD risk. Studies have demonstrated that a reduction in total cholesterol and LDL cholesterol is associated with a decrease in the incidence of CVD (91, 96, 97), where lowering LDL cholesterol by one mmol/L is associated with a 23% relative risk reduction of major events (98). Lowering systolic blood pressure is associated with a reduced risk of CVD, where the lowest risk is found between 120-124 mmHg (108). However, the use of medical treatment to improve lipid profile and blood pressure levels is necessary for some high-risk individuals (19, 20). In both the Norwegian and European prevention guidelines, physical activity and reducing sedentary behaviour are recommended, and reviews of the literature have found that physical activity reduces the risk of CVD (30, 126-128). A healthy diet is considered a cornerstone of CVD prevention (19). However, diet advice is in the national guidelines graded as a weak recommendation based on the poor evidence level of studies and the challenges in performing studies on diet and CVD risk (20). The recommendations for a healthy diet are based on the Mediterranean diet, which is associated with a lower risk of CVD (129). Some of the characteristics of this diet are less animal-based food patterns with lower amounts of meat,

more fish, <5 grams of salt per day, more fruit, vegetables, and food rich in fibre (19, 30, 129). Replacing saturated fats with unsaturated fats is essential to improve lipid profile, and reduced salt intake is especially important among individuals with hypertension (19). Research on alcohol intake and the risk of CVD has been divergent, but excessive intake is associated with increased risk (130), and an alcohol consumption <100 g week is recommended (19). Individuals that are overweight or obese should initiate measures to improve lipid profile, blood pressure levels, and plasma glucose levels to reduce the risk of CVD (19, 30, 172). The European guidelines emphasize a diet that can be managed over time to reduce CVD risk. Many studies have shown that a healthy diet, smoking cessation, maintaining a healthy weight, and regular physical activity reduces the risk of CVD. However, incorporation of lifestyle changes is found difficult to achieve at an individual level (134, 172, 173).

1.5.3 Interventions with medication therapy

Treatment with medications is recommended for individuals with high total CVD risk with significantly increased values or unsatisfactory results from lifestyle changes in blood pressure and/or cholesterol levels (19-21, 30). Antithrombotic treatment in primary prevention is controversial, as it is associated with reduced risk of CVD but is also associated with increased risk of major bleeding (174), Thus, antithrombotic therapy is not recommended in the national guidelines (20). Treatment with medication to achieve glycaemic control in patients with diabetes is not presented here. In the following section, a brief introduction of lipid-lowering and blood pressure lowering medication is presented.

Lipid-lowering medication

The Norwegian guidelines (20) advise primary prevention treatment with statins to improve lipid profile to individuals aged 45-74 years with high total CVD risk with total cholesterol 5,0-7,0 mmol/l (and LDL-cholesterol 3,0-5,0 mmol/l) and individuals <75 years in individuals with total cholesterol levels >7,0 mmol/l and LDL-cholesterol >5,0 mmol/l. In individuals with diabetes, statins should be initiated in LDL-cholesterol >2.5 mmol/L. Statins reduce the

LDL cholesterol levels by reducing the cholesterol production in the liver, resulting in increased LDL receptor expression in liver cells leading to increased uptake of the LDL by the liver (21, 30, 175). Statins can also increase HDL cholesterol levels, reduce triglycerides, and may reduce inflammation in the artery walls (21, 176, 177). Therefore, statins are the first choice of medical treatment, and the recommendation is to titrate up to the highest tolerable dose to achieve cholesterol treatment targets (19, 20). After the initiation of statins, a control of lipid levels is recommended after 6-12 weeks and after one year to ensure adherence and achievement of treatment targets (20). If the statin treatment is not tolerated or lipid levels remain significantly high other medications can be considered, such as fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g., ezetimibe), or PCSK9 inhibitors (19, 20). Treatment with statins reduces both fatal and non-fatal CVD endpoints and all-cause mortality (175, 178, 179).

Blood pressure lowering medication

The national guidelines recommend treatment with medication among individuals with elevated blood pressure, individuals with high total CVD risk or elevated values on single risk factors: SBP ≥160 mmHg or DBP ≥100 mmHg, or people with diabetes with BP >140/90 mmHg, or other risk conditions such as kidney disease (20). However, the national guidelines underscore the importance of non-medical interventions to lower blood pressure levels before medical treatment in individuals with mild hypertension (SBP 140-159, DBP 90-99 mmHg) and reassess in 3-12 months. The treatment target is to lower BP to <140/90 mmHg (<135/85 if diabetes), without introducing major side effects (20). Monotherapy is often insufficient to treat hypertension. The recommendation is to initiate treatment with two antihypertensive agents (19, 20, 180, 181) and titrate treatment to ensure BP is lowered sufficiently and if the treatment is tolerable for the patient. There are several different groups of antihypertensive agents shown effective in preventing CVD; angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and thiazide or thiazide-like diuretics (19, 182). After initiating blood pressure-lowering medication, the follow-up should be frequent until the levels are stabilised, and then 1-2 times per year (20). The use of antihypertensive medications to lower blood pressure found that a 10 mmHg reduction in systolic blood pressure by using antihypertensive drugs reduces the risk of CVD by 20% and gives a 13% reduction in all-cause mortality (183).

1.5.4 Shared decision making and individually tailored treatment

Shared decision-making (SDM) is essential in patient-centred care, focusing on the patient's view, experience, and needs (184). In a clinical setting, various interventions, treatments, and options can be reasonable, and where patients arrive at crossroads with several options, patient involvement in decision-making adds important value (184). SDM does not mean that the individual is abandoned in the decision but that the clinician should recognize the patient's autonomy (185). Clinicians and patients working together can produce the best outcome for the patient. SDM is the opposite of clinicians making decisions on behalf of the patient (184, 185). An important step in SDM is providing information and investigating the patient's existing knowledge. Thus, the first task of SDM is to ensure that individuals can make well-informed decisions. Further, the clinician needs to explore the patient reaction to the information and provide reasonable options, discuss these options with the patient, and then decide and support the patient's choice (185). The importance of individually tailored treatment is highlighted in the Norwegian and European prevention guidelines (19, 20), which refer to non-medical inventions and medical interventions. When communicating the risk status and proposed treatment, the clinician should include the benefits and the potential disadvantages and, additionally, identify the patient's potential barriers that can affect the patient's ability to make lifestyle changes, such as cognitive and emotional factors, comorbidities, socioeconomic status, and educational level (19, 21). Furthermore, the clinician needs to identify the individuals' thoughts, attitudes, and willingness to change behaviour. Motivational interview, goal setting, and providing feedback are useful tools when treatment is initiated. Investigating the likelihood of the patient adhering to the treatment is essential in patients where treatment with medications is initiated (19-21). Non-adherence to primary prevention medication is a challenge (186), and there is an association between non-adherence and CVD events in patients prescribed blood pressure-lowering medications (187) and statins (188). Therefore, it is recommended that clinicians use SDM when communicating CVD risk to patients and that clinicians routinely follow up with patients in the discussion about their CVD risk and the measures initiated to ensure adherence and patient's experience and preferences (189).

1.6 Rationale for the thesis

Primary prevention of CVD aims to prevent or delay the onset of disease, and the primary prevention guidelines contribute to a compilation of the evidence on how to prevent and manage risk for CVD. Assessing risk in clinical practice is recommended to identify those at the highest risk by using a total CVD risk assessment tool. Surveillance of disease and risk factors provides information about the populations' health. Norwegian population-based surveys have shown declining trends in cardiovascular risk factors, but studies of trends in total CVD risk in the Norwegian population are lacking. The different total CVD risk assessment tools and thresholds to identify high-risk individuals have changed over time. Despite the impact of change in risk factor level and risk factor thresholds, Norwegian risk assessment tools and guidelines has been scarcely studied. The burden of CVD is one of the most demanding public health issues, and most premature CVD`s are preventable. However, previously performed studies in high-risk individuals have demonstrated that most do not reduce their risk and do not achieve the guideline-defined treatment targets. However, many of these studies are cross-sectional patient studies. To our knowledge, no previously performed study has used a total CVD risk assessment tool and guidelines to identify high-risk individuals from a population-based study and followed over a long period individuals free from CVD but with a high risk of CVD, who do not experience a CVD during follow up.

Assessing trends in total CVD risk in the general population, exploring the Norwegian assessment tools and prevention guidelines, and following a cohort of individuals with a high risk of CVD may provide valuable insights about the risk and primary prevention of CVD in Norway.

2 Aims of the thesis

The overall aim of this thesis is to contribute to new knowledge of primary prevention of CVD and cardiovascular risk assessment. The objective is to provide new insights into CVD risk and risk assessment by exploring aspects of the Norwegian national CVD risk assessment tool NORRISK 2 applied on a Norwegian general population. More specifically, the research questions addressed in the three papers are:

Paper I:

- What are the secular and longitudinal trends in cardiovascular risk profile using the risk assessment tool NORRISK 2 score in a general population?
- What is the relative contribution of each single risk factor included in the NORRISK 2 score, and how does this impact the total score in NORRISK 2?

Paper II:

- How does the NORRISK 2 score and the 2017 guidelines change the population proportion at high risk of CVD and eligible for primary prevention, compared with NORRISK and the 2009 guidelines?
- To what extent do the risk scores and guidelines overlap regarding who is identified as eligible for primary prevention?

Paper III:

- Among individuals with high risk of CVD, to what extent do CVD risk factors and medication use change over time?
- Do individuals at high risk of CVD achieve the national guideline-defined treatment targets and what characteristics are associated with achieving treatment targets in the primary prevention of CVD?

3 Material and methods

3.1 The Tromsø Study

The Tromsø Study is an ongoing, longitudinal population-based cohort study consisting of repeated health surveys conducted in the Tromsø municipality (190). The city of Tromsø is the largest urban area in Northern Norway and the Tromsø municipality is the eighth-largest municipality in Norway, with approximately 75.000 inhabitants. The University of Tromsø initiated the Tromsø study in 1974, then referred to as the "Tromsø Heart Study," and aimed to investigate the high mortality rate of cardiovascular disease among men in Northern Norway and develop methods to prevent CVD (190). Since then, the study has expanded to cover many conditions and purposes. Since the initiation of the Tromsø Study, seven surveys have been conducted: Tromsø1 (1974), Tromsø2 (1979-1980), Tromsø3 (1986-1987), Tromsø4 (1994-1995), Tromsø5 (2001), Tromsø6 (2007-2008) and Tromsø7 (2015-2016) (190). Tromsø8 is planned to be conducted in 2024-2025. The data collection includes a vast amount of data on health, including questionnaires, biological samples and clinical examinations. From Tromsø4 and onwards, the surveys included a first visit (all invited) and a second visit (pre-defined selected samples).

Table 2: Overview of the Tromsø Study.

Survey	Year	Participants	Age	Attendance
Tromsø1	1974	6595*	20-49	74%
Tromsø2	1979-80	16,621	20-54	78%
Tromsø3	1986-87	21,826	12-67	75%
Tromsø4	1994-95	27,158	25-97	72%
Tromsø5	2001-02	8130	30-89	79%
Tromsø6	2007-08	12,984	30-87	66%
Tromsø7	2015-16	21,083	40-104	65%

*Men only

The studies included in this thesis are based on data from Tromsø6 and Tromsø7 (first visits). We used several study designs: a cross-sectional design (data collected at a single time point), repeated cross-sectional design and longitudinal designs (prospective cohort). Both cross-sectional and longitudinal designs are considered observational studies (191).

3.1.1 Tromsø6

Tromsø6 (192, 193) was conducted during 2007-2008. In Tromsø6, four groups were invited; all residents aged 40-42 years and 60-97 years (n=12,578), a 10% random sample aged 30-39 (n=1056) and a 40% random sample aged 43-59 (n=5787), and previous participants that attended the second visit of Tromsø4 in 1994-1995 (n=7965), if not already included in the three other groups (n=341) (a total of N=19,762 invited). A total of 12,984 women and men participated, i.e., an attendance of 65.7% of the invited.

Table 3: Attendance in Tromsø6 according to age and sex. The Tromsø Study 2007-2008.

	Women			Men		
Age	**Invited**	**Participated**	**Attendance**	**Invited**	**Participated**	**Attendance**
30-39	541	297	54.9%	544	212	38.9%
40-49	2969	1913	56.8%	2988	1663	55.7%
50-59	1705	1289	75.6%	1702	1147	67.4%
60-69	2635	2108	80.0%	2702	1995	73.8%
70-79	1456	988	67.9%	1197	841	70.3%
80-89	831	335	40.3%	492	196	39.8%
Total	10137	6930	68.4%	9625	6054	62.9%

All invited participants received a personal invitation by mail including an invitation letter, an information brochure about the study, and a 4-page questionnaire two weeks before a suggested appointment for the first visit. The questionnaire (Q1) covered topics about general health such as diseases, use of health services, use of medication, alcohol, tobacco, physical activity level, and diet. On the first visit at the examination site, the participants received an additional (Q2) and more comprehensive questionnaire (28 pages) to complete at the examination site or to bring home and send in return with a pre-stamped and addressed

envelope. During the first visit, several examinations took place, such as anthropometric measurements, blood pressure- and pulse measurements, pain sensitivity tests, and sampling of blood, urine, hair, nose & throat swabs. The second visit was performed in a pre-defined subsample of the total invited sample (attendance n=7307), and the data collection included additional biological sampling, physical function tests, cognitive tests, 12 lead ECG, echocardiography, carotid artery ultrasonography, echocardiography, lung function tests, eye examinations, and DXA scans (193).

3.1.2 Tromsø7

Tromsø7 (194, 195) was conducted during 2015-2016. In Tromsø7, all inhabitants 40 years or older were invited to participate (a total of N= 32,591 invited). A total of 21,083 women and men participated, i.e., an attendance of 65% of the invited.

Table 4: Attendance in Tromsø7 according to age and sex. The Tromsø Study 2015-2016.

	Women			Men		
Age	**Invited**	**Participated**	**Attendance**	**Invited**	**Participated**	**Attendance**
40-49	5195	3378	65.0%	5562	3054	54.9%
50-59	4534	3245	71.6%	4327	2790	64.5%
60-69	3586	2677	74.7%	3543	2502	70.6%
70-79	2001	1361	68.0%	1897	1315	69.3%
80-89	981	389	39.7%	639	325	50.9%
≥90	242	24	9.9%	84	23	27.4%
Total	16539	11074	67.0%	16052	10009	62.4%

All invited participants received a personal invitation by mail including an invitation letter, an information brochure and a 4-page questionnaire (Q1) in paper format. The invitation letter included a username and password for completion of questionnaires online. Online questionnaires included the Q1 questionnaire more comprehensive questionnaire (Q2) and the graphical index of pain (GRIP) questionnaire (thus, Q1 could be completed on paper or online). Participants could complete the questionnaires before attendance, but also had the opportunity to answer the questionnaires at the examination site during the first visit. During the first visit, several examinations took place, such as anthropometric measurements, blood pressure- and pulse measurements, pain sensitivity tests, sampling of blood, nasal and throat

swabs, and dental examination (in a subsample). The second visit was from a pre-defined subsample of the total invited sample (attendance n=8346), and the data collection included additional biological sampling, 12-lead ECG, cognitive tests, carotid artery ultrasonography, echocardiography, lung function tests, eye examinations, physical function tests, auscultation of the heart and lungs, accelerometery and DXA scans (194).

3.1.3 Clinical examinations and blood samples

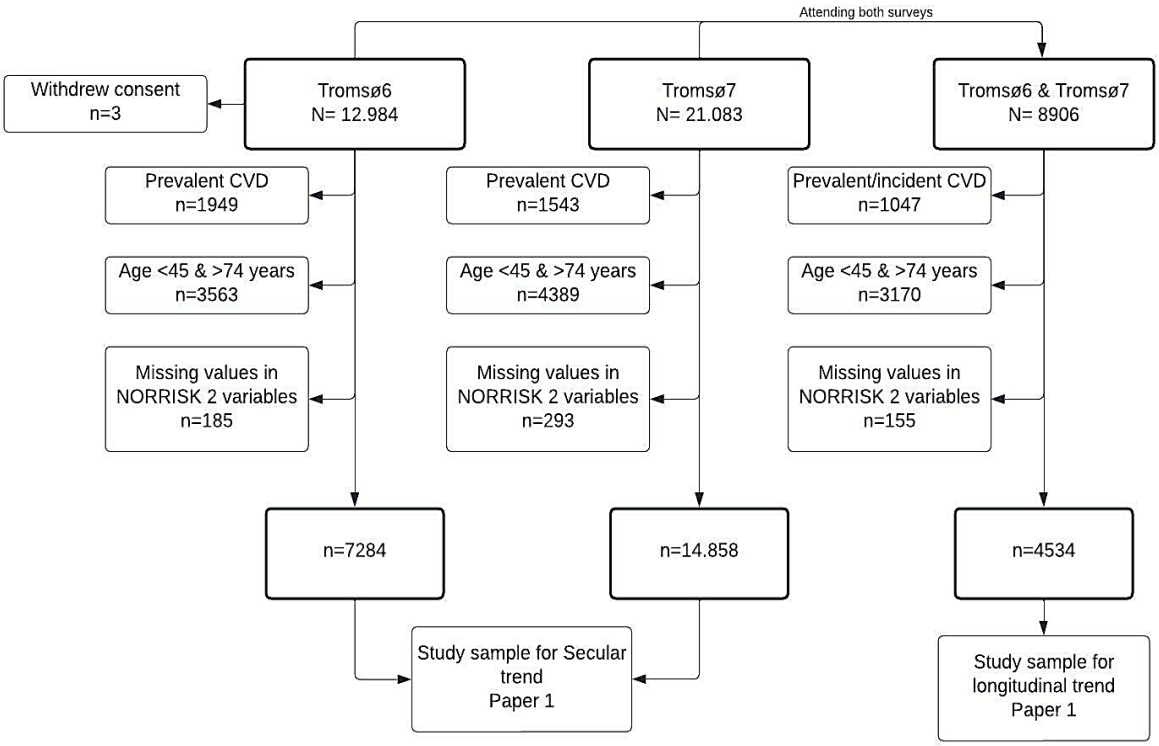
Both surveys had trained personnel that performed all clinical measurements and blood sampling using similar procedures. Blood pressure was measured on the participant's right upper arm with a properly sized cuff based on arm circumference (by a Dinamap pro care 300 monitor, GE Healthcare, Norway). Blood pressure was measured three times at one-min intervals after two minutes seated rest, and the mean of the two final readings was used in the analysis. Non-fasting venous blood samples were collected with a brief venous stasis applied to the upper arm released before venipuncture, with the participant sitting. The samples were analysed for cholesterol, LDL and HDL cholesterol within 48 hours (with Roche diagnostics, Mannheim, Germany) at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø. Weight and height were measured with light clothing and no shoes to the nearest 0.1 kilograms (kg) and 0.1 centimetres (cm) using the Jenix DS102 height and weight scale (Dong Sahn Jenix, Seoul, Korea). Waist and hip circumference were measured to the nearest 0.1 cm with a Seca measurement tape at the level of the umbilicus and the greater trochanter (193, 195, 196).

3.2 Study samples

3.2.1 Paper I

We included participants attending Tromsø6 (N=12,984) and/or Tromsø7 (N=21,083) to investigate secular trends, and participants attending both surveys (N=8906), to study longitudinal trends. After exclusion of participants with prevalent CVD, aged <45 and >74 years, with missing values included in the NORRISK 2 score variables and those that had withdrawn their consent, the final sample included n=7284 participants from Tromsø6, n=14,858 from Tromsø7, and n=4534 attending both surveys.

Figure 1: Flowchart of the study population Paper I

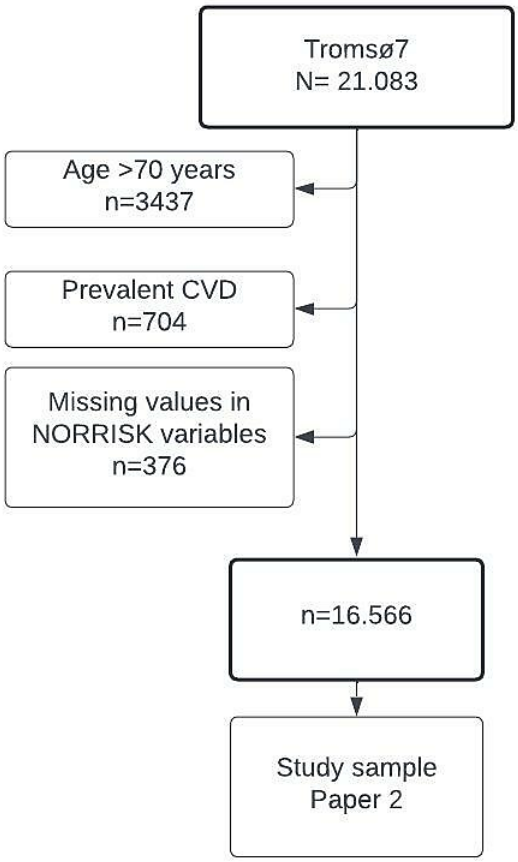


Note: In the published paper there is a typographical error in the flowchart, where the number of participants <45 years should be n=2813, instead of n=750. The statistical analysis has been re-performed to ensure that the total n=7284 is correct, and that this is in fact a typographical error. An erratum will be sent to the journal.

3.2.2 Paper II

We included participants attending Tromsø7 (N=21,083). After exclusion of participants ≥70 years, those with prevalent CVD, and participants with missing values in the NORRISK scores variables, the final sample included 16,566 participants for analysis.

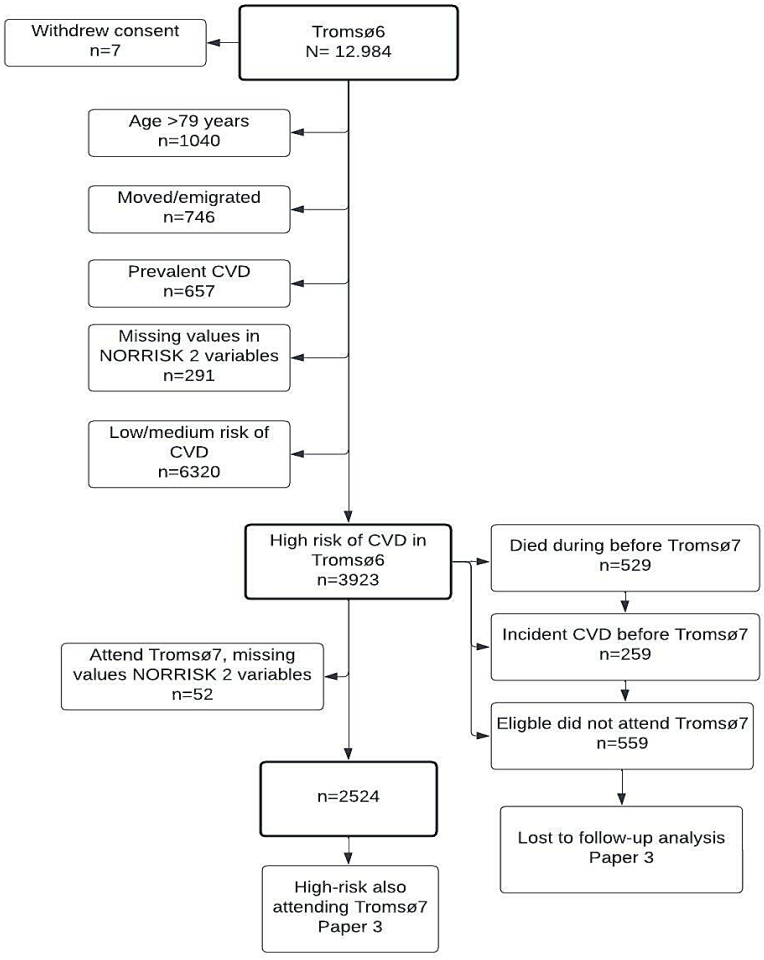
Figure 2: Flowchart of the study population Paper II



3.2.3 Paper III

We included participants aged 40-79 years attending Tromsø6, and excluded participants who emigrated (out of Norway) or moved (out of the municipality) after Tromsø6 and before Tromsø7, with prevalent CVD, and missing variables in NORRISK 2 variables. Participants calculated as low/medium risk of CVD (by NORRISK 2) were excluded. Participants that died after Tromsø6 and before Tromsø7, or had an incident CVD between the two surveys, or who were eligible but did not re-attend Tromsø7 were included for supplementary analysis. The final study sample for the main analysis was n=2524 participants with high risk of CVD by; NORRISK 2 score, elevated values in single risk factors from the 2017 primary prevention guidelines, or individuals treated with antihypertensives or lipid-lowering drugs with levels above treatment targets in Tromsø6 who re-attended in Tromsø7.

Figure 3: Flowchart of the study population Paper III



3.3 Variables

Demographics

A focus on differences by *age* and *sex* were included in all papers. In Paper I, analysis was stratified by sex, and by age-groups 45-54, 55-64, and 65-74 years, and birth cohorts in participants between 45-74 years at baseline (born 1941-1961) to study longitudinal trends. In Paper II, analysis was stratified by sex and by age groups 40-49, 50-59, 60-69 years. In Paper III, analysis was stratified by sex, we presented mean age in the study population, and the proportion <60 and ≥60 years, age-adjusted cardiovascular risk factors, and age and sex-adjusted variables associated with reaching treatment targets in primary prevention. *Education* was collected from questionnaire data, found to have good validity in the Tromsø Study (197) with the question "What is the highest level of education you have completed*"*. In Tromsø6 the answer alternatives were *"*Primary/secondary school, modern secondary school," "Technical school, vocational school, 1-2 years senior high school", "High school diploma," "College/university less than four years and "College and university four years or more". In Tromsø7, the answer alternatives were "Primary/partly secondary education (Up to 10 years of schooling)", "Upper secondary education: (a minimum of 3 years), "Tertiary education, short: College/university less than four years", and "Tertiary education long; College/university four years or more". In Paper I, education was not included in the analysis. In paper II, we categorised the educational variable into four categories: Primary school, High school, College university <four years, and College/university ≥four years to describe the study population. In Paper III, we dichotomised education into: "Lower education" (primary school, technical school/vocational school/1-2 years senior high school and high school diploma) and "Higher education" (college/university <four years and ≥ four years). We used education to describe the study population and the association of education with reaching treatment targets (Paper III). *Psychological distress* was calculated by using the Hopkins Symptom Checklist 10 (HSCL-10), a commonly used and validated instrument (198) that was included in the questionnaire, a tool designed to measure symptoms of depression and anxiety consisting of 10 questions with four response categories ranging from 1 "No complaint," 2" Little complaint," 3 "Pretty much" and 4 "Very much." The score is summarised based on all items, and a mean score of ≥1.85 was categorised as psychological distress or no distress in accordance with Strand et al (198). The ten questions included are: During the last week, have you: "Experienced sudden fear without apparent reason," Felt afraid or anxious,"

"Experienced faintness or dizziness, "Felt tense or upset," "Easily blamed yourself," "Had sleeping problems," "Felt depressed or sad", "Felt useless, worthless", «Felt that everything is a struggle" and "Felt hopelessness with regard to the future. «We presented the proportion with psychological distress and its association with reaching treatment targets (Paper III).
Self-reported health is a phenomenon a holistic reflection of a person's disease burden as well as mental and social condition, and a widely used measure of self-reported health is the first item in the well-known SF-36 instrument (199). This was included in the questionnaire phrased as "How do you, in general, consider your own health to be," with the answer alternatives "Very bad," Bad," "Neither good nor bad," "Good" and "Excellent". We dichotomised self-reported health into: "Poor health" (very bad, bad and neither good nor bad) and "Good/very good health" (good and excellent). We used self-reported health to describe the study population and the association of reaching treatment targets (Paper III).
Marital status was included from questionnaires with the response alternatives "Single", "Widow/widower," "Divorced," "Separated" and "Married/registered partner". We dichotomised marital status into: "Single" (Single, widow, widower, divorced and separated) and "Married/partner" (married or registered partner). We used marital status to describe the study population and the association with reaching treatment targets (Paper III).

CVD cases

CVD cases (participants with a previous history of or incidence of MI and/or stroke) were excluded in all three papers. CVD cases were recorded and validated from study entry until 31 December 2014 by the Tromsø Study CVD endpoint registry. Due to a lack of validated endpoints after 2014 and among participants attending Tromsø7 only, we also used self-reported data on MI or stroke with the question "Have you had a heart attack?" and "Have you had a stroke," with the answer alternatives "Yes" and "No". In Paper III, we aimed to discriminate between previous MI and/or stroke at baseline and incident MI and/or stroke during follow-up. Thus, we used the date at the CVD event to identify participants with incident CVD after participation in Tromsø6 (2007-2008). CVD events after their participation date were considered an incident CVD event. To identify participants with incident CVD events after 2014, we included "Age at first heart attack" and "Age at first stroke" from the Tromsø7 questionnaire. We compared an individual's age at participation in Tromsø7 with age at the CVD event. If an individual reported their age at their first CVD

event to be a maximum of two years less than their age at participation, it would be considered an incident CVD event. For example, an individual aged 55 years at participation in Tromsø7, who reported 54 or 53 years on the variable age at a first heart attack or stroke, would be considered an incident event.

Total CVD risk

We used the NORRISK 2 score as a measure for *total CVD risk* in all three papers, valid in a general population without known CVD (1). In Paper I, we presented the mean NORRISK 2 score and the proportion at low, medium, and high risk. In Paper II, we calculated the population proportion identified as high risk by NORRISK 2 score and in combination with single risk factors. In Paper III, we used NORRISK 2 score to identify the study sample, study the change in NORRISK 2 score between two time periods, and study its association with reaching treatment targets. The original *NORRISK score,* found to fit in a Norwegian population (29) was used in Paper II to calculate the proportion of high-risk individuals by the original NORRISK score and in combination with single risk factors from the 2009 guidelines. We used the additional risk factors HbA1c levels, and a first-degree family member with a history of premature CHD was used to recalculate NORRISK risk with specific cut-offs.

Cardiovascular risk factors

We used information on *total cholesterol* in all three papers. We presented mean values (Paper I-III), together with *LDL-cholesterol.* These variables were used to identify participants at high risk of CVD (Paper II-III) and to calculate the proportion reaching treatment targets for lipids and the association with baseline lipid levels on reaching treatment targets (Paper III). *HDL cholesterol* was categorised as low HDL, with the cut-offs <1.3 mmol/L in women and < 1.0 mmol/L in men. We presented the proportion with low HDL (Paper I and III) and mean levels (Paper II). *Blood pressure* was presented with means (Paper I-III), to identify participants as high risk (Paper II-III) and to calculate the proportion reaching the blood pressure treatment targets and the association with baseline blood pressure levels with reaching treatment targets (Paper III). *Smoking status* (Paper I-III) was collected by questionnaires with the question "Do you/did you smoke daily" with the answer

alternatives "Yes now," "Yes, previously," or "Never". Smoking was dichotomised into: “Smoker” (“Yes now”) and “Non-smoker” (“Yes, previously” and “Never”). *Family history of premature CHD* was collected from questionnaires with the question "Have any family members had an acute myocardial infarction before the age of 60 years" With the answer alternatives: “Parents”, “Children”, and/or “Siblings”. In Tromsø7, the alternatives were “Mother”, “Father”, “Children”, “Siblings, or “None”. The variable was constructed to numeric and then categorised into one family member with premature CHD and two or more relatives with premature CHD. Family history of CHD is included in the NORRISK 2 model (Paper I-III) and was used to re-calculate the original NORRISK score (Paper II). *Diabetes status* was collected by questionnaires with the question "Do you have or have you had diabetes″ In Tromsø6 the answer alternatives was: “Yes” and “No”. In Tromsø7 the answer alternatives were: “Yes”, “Yes, previously” and “No”. Diabetes was dichotomised into “Diabetes” and “No diabetes” where “No” and “Yes previously” was set to “No diabetes” and “Yes” to “Diabetes”. The prevalence of diabetes was used to describe study characteristics (Paper II-III) and to identify individuals eligible for primary prevention (Paper II-III) and the association with diabetes status and reaching treatment targets (Paper III). *HbA1c* (glycated haemoglobin) was used to describe participants' characteristics (Paper II) and as an additional risk factor to recalculate risk the original NORRISK (Paper II). *Obesity* was defined by the use of measurements of body mass index (BMI) and waist circumference (WC) General (BMI) and abdominal (waist circumference) obesity was categorised with cut-offs in accordance with WHO (122, 123). BMI was categorised as “Normal” BMI <25 kg/m^2, “Overweight”; BMI 25-29.9 kg/m^2, and “Obese” BMI ≥30 kg/m^2. Waist circumference was categorised as obesity with ≥102 cm for men and ≥88 cm for women. We presented the proportion with normal, overweight and obesity and abdominal obesity (Paper II). In Paper III, BMI was dichotomised to “Normal/overweight” and “Obesity”, and we studied the change in the proportion with obesity and abdominal obesity in the study sample and the association of general and abdominal obesity with reaching treatment targets (Paper III). *Physical activity level* was collected from questionnaires using the Saltin and Grimby leisure time physical activity questionnaire (200) with the question "Enter exercise and physical exertion in leisure time; if your activity varies much, then give an average, the question refers only to the last twelve months”, with the answer alternatives "Reading, watching tv or other sedentary activity," "Walking, cycling, or other forms of exercise at least 4 hours a week (including walking, or cycling to the place of work, Sunday walking, etc.", "Participation in recreational sports, heavy gardening (note duration of activity at least 4 hours a week",

"Participation in hard training or sports competitions, regularly several times a week". The variable was dichotomised into “Sedentary” ("reading, watching tv or other sedentary activity") or “Active (all others answer alternatives). We presented the proportion of the study sample with sedentary physical activity levels (Paper II-III), change in activity level and studied the association of activity level with reaching treatment targets (Paper III).

Medication use

Information about *medication use* was collected from questionnaires with the question “Do you use, or have you used blood pressure-lowering drugs*”* and “Do you use, or have you used cholesterol-lowering drugs*”,* with the answer alternatives “Never used”, “Previously” and “Currently”. We dichotomised the variable into “User” and “Non-user”, where “Never used and “previously were categorised as “Non user” and “Currently” as “User”. Information about medication use was combined with data from a self-reported written list of brand names of regularly used medications included as an open list in the questionnaire. This list was Anatomical Therapeutic Control (ATC) coded. We included blood pressure-lowering drugs ATC C02, C03, C07, C08, and C09, and for lipid-lowering drugs C10. We presented the proportion of use of antihypertensives (Paper I-III) and lipid-lowering drugs (Paper II-III), change in medication use, characteristics of users and non-users of medication and the association between medication use and the association with medication use on reaching treatment targets (Paper III).

Table 5: Overview of the variables included in Paper I-III

Variables	Paper I	Paper II	Paper III
Demographics			
Age	Continuous Cat: 45-54, 55-64, 65-74 Birth cohorts: 1941-42, 1943-52, 1953-62	Continuous Cat: 40-49, 50-59, 60-69	Continuous
Sex	Women, Men	Women, Men	Women, Men
Education	-	Cat: Primary, secondary, tertiary <4 years, tertiary ≥4 years	Cat: Primary/secondary, Tertiary education
Marital status	-	-	Cat: Married/partner
Self-reported health	-	-	Cat: Good/very good
Psychological distress	-	-	Cat: Yes/No
CVD cases	Excluded	Excluded	Excluded
Cardiovascular risk			
NORRISK 2 score	Continuous Cat: Low risk, medium risk, high risk	Continuous Cat: High risk	Continuous Cat: High risk
NORRISK score	-	Cat: High risk	-
Total cholesterol	Continuous	Continuous High risk: ≥8 mmol/L High risk: ≥7 mmol/L	Continuous High risk: >7 mmol/L Uncontrolled dyslipidaemia: treated & TC>5
LDL cholesterol	-	Continuous High risk: ≥5 mmol/L High risk ≥2.5 mmol/L if diabetes	Continuous High risk >5 mmol/L Diabetes >2.5 mmol/L Uncontrolled dyslipidaemia: treated & LDL>3
HDL-cholesterol	Cat: low HDL	Continuous	Cat: Low HDL
Systolic BP	Continuous	Continuous High risk: ≥160 mmHg High risk ≥140 mmHg	Continuous High risk : >140mmHg High risk : >140mmHg if diabetes Uncontrolled hypertension: AHT with BP >140
Diastolic BP	-	Continuous High risk: ≥100 mmHg High risk: ≥90 mmHg	Continuous High risk >90 mmHg High risk >90 mmHg if diabetes Uncontrolled hypertension: AHT & BP >90
Family history of CHD	Cat: 1 relative, ≥2 relatives	-	-
Daily smoking	Yes/No	Yes/No	Yes/No
Diabetes	-	Yes/No	Yes/No
HbA1c	-	Continuous	-
Body mass Index	-	Cat: normal, overweight, obesity	Cat: Obesity
Abdominal obesity	-	Cat: Yes/No	Cat: Yes/No
Physical activity level	-	Cat: Sedentary	Cat: Sedentary
Medication use			
Antihypertensives	Yes/No	Yes/No	Yes/No
Lipid-lowering drugs	-	Yes/No	Yes/No
Treatment targets	-	-	
Blood pressure	-	-	<140/90 mmHg <135/85 if diabetes
Total cholesterol	-	-	<5 mmol/L
LDL-cholesterol	-	-	<3 mmol/L <2.5 mmol/L if diabetes
Non-smoking	-	-	Yes

Cat = category

3.4 Statistical analysis

3.4.1 Paper I

In Paper I, we used descriptive statistics to examine cardiovascular risk, risk categories, and single risk factors by sex, age groups, and survey for secular trends, and to present changes in cardiovascular risk and single risk factors by birth cohorts and sex for longitudinal trends. Means and standard deviations (SD) were presented for continuous variables and percentages and numbers for categorical variables. We used a t-test and chi-square test to assess time, sex- and age group differences. To calculate how each single risk factor included in the NORRISK 2 score contributed to the total score and the overall explained variation of the model, we used the Shapley value technique. The Shapley Value was originally used in gaming theory to determine the contribution of each player in a coalition or a cooperative game (201), and the decomposition technique were further developed by Shorrocks (202). As presented by Kolker (201); A group of k cooperating members is a coalition, s. The members form the grand coalition S that consists of all n participants, k<=n. Each non-empty coalition has a value V(s), which the value of this coalition. The Shapley value provides a 'fair' share in the sense that all members are compensated proportionally to their merit, i.e., proportionally to their marginal contributions, V(s)-V(s-k). These contributions are then averaged over all possible different combinations in which the coalition can be formed. Thus, the Shapley value, Shk for each participant k is calculated as

$$Sh_k = \sum_{S \subset n} \frac{(s-1)!(n-s)!}{n!}[V(s) - V(s-k)],$$

s is the number of participants in coalition S; summation is performed over all possible coalitions, which participant k joins; (s-1)! is the number of arrangements for participants before joining s; (n-s)! is the number of arrangements for participants after joining s; and n! is the total number of all possible coalitions. Thus, the Shapley value is computed by calculating the average marginal contribution that participant k brings to a coalition (group) s if this participant joins any coalition, and all coalitions for this participant k are formed in random order. Thus, the Shapley Value assesses the contribution of the coefficients of determination

in a regression model, a measure of the overall goodness of fit. We performed the analysis using the command *rego* in Stata 15 developed by Huettner and Sunder (203). Traditionally, in a regression model the coefficients provide information about the correlation and the significance between the variables. However, the regression model does not rank the explanatory variables in order of importance, and it is not possible to quantify the actual contribution of each variable to explain dependent variable (204). The Shapley Value decomposition (202) calculates the exact contribution of the explanatory variables of a regression to its R-square (R^2), and in the *rego* command the contribution from all the explanatory variables sums up to 100%.

We used the Shapley Value decomposition to assess how each variable included in the NORRISK 2 score contributed to the total score in both Tromsø6 and Tromsø7 (secular trend)

$$rego\ Y_{NORRISK\ 2\ score} = \beta_{age} + \beta_{age2} + \beta_{sex} + \beta_{smoke} + \beta_{systolic\ BP} + \beta_{BP\ medication} + \beta_{total\ cholesterol} + \beta_{low\ HDL\ cholesterol} + \beta_{one\ family\ CHD} + \beta_{two\ family\ CHD.}$$

In addition, we used the Shapley Value decomposition to assess the relative importance of change in each risk factor to the change in total risk between Tromsø6 and Tromsø7 in birth cohorts (longitudinal trends).

$$rego\ Y_{Change\ in\ NORRISK\ 2\ between\ Tromsø6\ and\ Tromsø7} = \beta_{sex} + \beta_{Change\ in\ smoke} + \beta_{Change\ in\ systolic\ BP} + \beta_{Change\ in\ BP\ medication\ use} + \beta_{change\ in\ total\ cholesterol} + \beta_{change\ in\ low\ HDL\ cholesterol} + \beta_{change\ in\ one\ family\ CHD} + \beta_{change\ in\ two\ family\ CHD.}$$

Statistical analyses were performed using STATA version 15 (StataCorp. 14, College Station, TX, USA, (StataCorp LP).

3.4.2 Paper II

In the second paper, we used descriptive statistics to present the study population's characteristics, the proportion of participants eligible for primary prevention intervention defined by the NORRISK score and single risk factors from the 2009 guidelines, and the NORRISK 2 score and the 2017 guideline. Means and standard deviations (SD) were presented for continuous variables and percentages and numbers for categorical variables. To compare sex differences, we used t-tests for continuous variables and chi-square tests for categorical variables, and the McNemar test for pairwise data, comparing the difference in a proportion defined by high risk in women and men in risk scores. Results were considered statistically significant when a p-value less than 5% was attained. To visualise the overlap of high-risk participants defined by NORRISK and NORRISK 2 scores, as well as risk score with additional risk factors from the concurrent guidelines. Area proportional Venn diagrams were presented using the command "pvenn" in STATA." All the statistical analyses were performed using STATA version 15 (StataCorp. 15, College Station, TX, USA, (StataCorp LP).

3.4.3 Paper III

In Paper III, we presented the means and proportions of the study population's baseline characteristics. Further, we compared the study sample at high risk with participants at high risk of CVD that was lost to follow-up, and then we used regression models with the margins command. Regression models with the margins command were also used to present age-adjusted characteristics among users and non-users of primary prevention at second screening, stratified by sex, and to assess the difference between the two groups. We calculated the proportion of the study population that achieved treatment targets for primary prevention, and we used multivariable regression with odds ratios (OR) to identify variables associated with treatment target achievement adjusted for age and sex in one model, and age, sex, education, and current medication use in the second model. Results were considered statistically significant with p-values <5%. All analyses were performed using STATA version 16 (StataCorp. 2019, Stata Statistical Software: College Station, TX, StataCorp LLC).

3.5 Ethics and participant feedback

The Tromsø Study was performed in accordance with the principles of the Helsinki Declaration and the Health Research Act. Tromsø6 was approved by the Data Inspectorate of Norway (Datatilsynet) and the Regional Committee of Medical and Health Research Ethics, North Norway (REC north) (reference 121/2006). Tromsø7 was approved by the Data Inspectorate of Norway and REC North (reference 2014/940). All participants gave written informed consent, and participants were informed that they can withdraw their consent at any time. Data from participants that had withdrawn their consent was not included in the analyses. This PhD project was approved by REC North (reference 1778/2015).

The Tromsø Study uses a feedback system for action and communication of pathological findings in participants. As described in the method papers of Tromsø6 (193) and Tromsø7 (195) the pre-defined thresholds values and consecutive response (immediately at examination, by phone, or through letters) was developed in collaboration with clinical specialists. Within 2-4 weeks days after participation, all participants received information containing screening values of blood pressure, height, weight, and serum high-density lipoprotein, total cholesterol and Hba1c. Participants with values above pre-defined thresholds levels were recommended to contact their own primary physician for a follow-up. This information was not automatically transferred to the participant's GP, thus relied on the participant's own initiative for follow-up. Participants with abnormal results from other examinations received additional letters with specific recommendations. A small number of participants was referred directly to the hospital due to findings from the clinical examinations or were contacted by phone due to abnormal laboratory findings (193, 195).

4 Results – summary of papers

4.1 Paper I: Secular and longitudinal trends in cardiovascular risk in a general population using a national risk model: The Tromsø Study

In paper I, a total of 7284 participants from Tromsø6 (2007-2008) and 14,858 from Tromsø7 (2015-2016) free from CVD, aged 45-74 and with valid values on variables included in the NORRISK 2 score was included for analyses on secular trend. For longitudinal trends, a total of 4534 participants attending both Tromsø6 and Tromsø7, free from CVD, born between 1941-1962 and with valid values on NORRISK 2 variables was included. Analyses were stratified by age and sex.

The analyses for secular trend showed that the distribution in risk categories moved from higher to lower risk categories between the surveys. In both surveys mean NORRISK 2 was higher among men than women. Between the two surveys there was a decrease in systolic blood pressure, total cholesterol, and smoking for both sexes while the use of antihypertensives increased, NORRISK 2 score decreased for both sexes (but men had a greater decline). The main contributors to the total NORRISK 2 score measured by Shapley value (% R^2) was age, systolic blood pressure and smoking. We found some age and sex differences in the contribution of risk factors, where in both surveys total cholesterol explained more of the variation among the youngest age-groups and more for men than women, whereas daily smoking explained more of the variation in the youngest age-groups and more for women than men. Systolic blood pressure, low HDL cholesterol and family history of CHD explained more of the variation in the oldest age groups, and with minor sex differences.

In the longitudinal follow-up of we found that for both sexes and all birth cohorts NORRISK 2 score increased, and the increase was larger among men. However, when we used baseline age in the NORRISK 2 calculations there was a decrease in NORRISK 2 score. Overall, the use of antihypertensive drugs and family history of CHD increased, and daily smoking decreased during follow up. Total cholesterol decreased between the two study periods, except for the youngest women. The change in the proportion with low HDL cholesterol and mean systolic blood pressure varied between sexes and birth cohorts. Overall, change in daily

smoking, systolic blood pressure and use of antihypertensives was the main contributors to explain the total variation (%R^2) in change in NORRISK 2 score during follow-up.

4.2 Paper II: Change in cardiovascular risk assessment tool and updated Norwegian guidelines for cardiovascular disease in primary prevention increases the population proportion at risk. The Tromsø Study 2015-2016.

In paper II, a total of 16,566 participants from Tromsø7 free from CVD, aged 40-69 years and with valid values variables included in the NORRISK scores were included. Mean age was 53 years for both women and men. When comparing the sexes, we found that men had higher mean LDL cholesterol, blood pressure, prevalence of obesity, self-reported diabetes, sedentary physical activity level, lower education and a higher proportion was users of lipid-lowering drugs and antihypertensives. Women compared to men had higher mean HDL cholesterol, prevalence of daily smoking and abdominal obesity.

The total proportion at high risk defined by risk score only was 12.0% using NORRISK and 9.8% for NORRISK 2. When NORRISK was calculated without additional risk factors (HbA1c and family history) the proportion at high risk was 8.6%. Among women, both risk scores defined a higher proportion as high risk in the oldest age groups, whereas among men this was only found by NORRISK 2, but not NORRISK where men aged 40-49 and 60-69 years had a higher proportion at high risk compared to men aged 50-59 years. When including risk factors from the Norwegian primary prevention guidelines the proportion eligible for intervention increased by 3.4 percentage points, where the proportion was 15.5% in NORRISK 1 combined with the 2009 guidelines, and 18.9% in NORRISK 2 combined with the 2017 guidelines.

Overall, participants defined as being at low risk by risk score were to a greater extent identified as eligible for intervention by single risk factors when using the 2017 guidelines compared to the 2009 guidelines. This was due to change in the cut-off value for serum total cholesterol and the introduction of a specified value for LDL cholesterol, and diabetes specific thresholds. Among individuals identified as high risk by risk score only, NORRISK identified in total 12.0% (2.2% of women and 23.3% of men) as high risk, while NORRISK 2 identified in total 9.8% (2.4% of women and 18.3% of men) as high risk. The overlapping proportion identified as high risk in both risk scores was in total 5.4% (0.9% of women and 10.7% of men). Combining NORRISK and the 2009 guidelines, 15.5% in total (6.8% women

and 25.6% men) was identified as eligible for intervention, while in NORRISK 2 and the 2017 guidelines the proportion was 18.9% in total (9.8 % women and 29.4% men). Overall, the overlapping proportion of 10.7 %, (5.1% women and 17.3% men) was identified as eligible for intervention in both risk scores with their respective guidelines.

4.3 Paper III: Achievements of primary prevention targets in individuals with high risk of cardiovascular disease. An 8-year follow-up of the Tromsø Study.

In paper 3, a total of 2524 participants with a high risk of CVD aged 40-79, free from CVD, with valid values in the NORRISK 2 score attending both Tromsø6 and Tromsø7 were included to study the change in risk factors and achievement of treatment targets in primary prevention. The mean baseline age was 61 years, and women were 2.7 years older than men at baseline. To compare the study sample with individuals at high risk who were excluded or did not re-attending Tromsø7, we found those not included were older, had higher mean total CVD risk, a larger proportion had diabetes, low HDL cholesterol, were daily smokers, lower physical activity level and lower educational level. All CVD risk factors except for total CVD risk and obesity improved during follow-up. When comparing sexes, change in risk factors was similar among the sexes, except for a greater change in SBP among women compared to men. The proportion using blood pressure-lowering drugs and/or lipid-lowering drugs increased during follow-up from 48 % to 71 %. Second screening medication users differed in characteristics at both time points. Users were older, a larger proportion were women, had a higher educational level, reported poorer self-reported distress and more psychological distress, and had less favourable levels at baseline except for total CVD risk and lipid levels, and a lower proportion were smokers. During follow-up, total CVD risk increased less in medication users. SBP and LDL cholesterol decreased in medication users and increased in non-users. Total cholesterol and DBP decreased in both users and non-users.

Overall, 31% achieved the treatment target for total cholesterol, 27% for LDL cholesterol, and 24% achieved both lipid targets. About 40% achieved the treatment targets for blood pressure, 85% the non-smoking target, and 10% achieved all treatment targets combined. Higher levels of total CVD risk, lipid, and baseline BP levels were associated with lower odds of achieving treatment targets. Medication use was the characteristic with the strongest association of achieving treatment targets in lipids, smoking cessation and all targets combined.

5 Discussion of methodology

5.1 Study design

In Paper I, the aim was to study secular and longitudinal trends in CVD risk profile. A definition of a secular trend, which is changes over a long period of time (205), where it is not required to follow the same participants; thus, it was suitable to use repeated cross-sectional data from both Tromsø6 and Tromsø7 for this study. In addition, the use of a longitudinal design allowed us to describe the change in CVD risk profile over time with repeated measurements in the same individuals. Furthermore, to study how the change in each risk factor included in the NORRISK 2 score influenced the change in total CVD risk between birth cohorts and sex between the two surveys. In Paper II, the aim was to compare the current risk assessment tool NORRISK 2 and primary prevention guidelines from 2017 with the previous and original tool; NORRISK and the guideline from 2009 to estimate the population proportion identified as high-risk CVD, thus eligible for intervention. In this study, we used data from Tromsø7 with a cross-sectional design. A weakness in cross-sectional designs is that they cannot be used to show the directions of associations. However, it is suited to provide insights into the prevalence of risk factors and diseases and multiple outcomes and exposures (191, 206). Thus, it allowed us to answer the aim of the study. In addition, it was important to use the most recent survey since population characteristics, and prevalence of risk factors are changing over time. In Paper III, we aimed to follow individuals with high risk of CVD over a period of time. Thus, using a longitudinal prospective cohort allowed us to follow the same individuals and change in CVD risk and medication use, investigate differences between users and non-users of medication between the surveys, and calculate the proportion of individuals reaching treatment targets and characteristics associated with reaching targets. In addition, this study design allowed us to study how characteristics at baseline in Tromsø6 influenced the achievements of treatment targets in primary prevention at the second screening in Tromsø7.

5.2 Internal validity

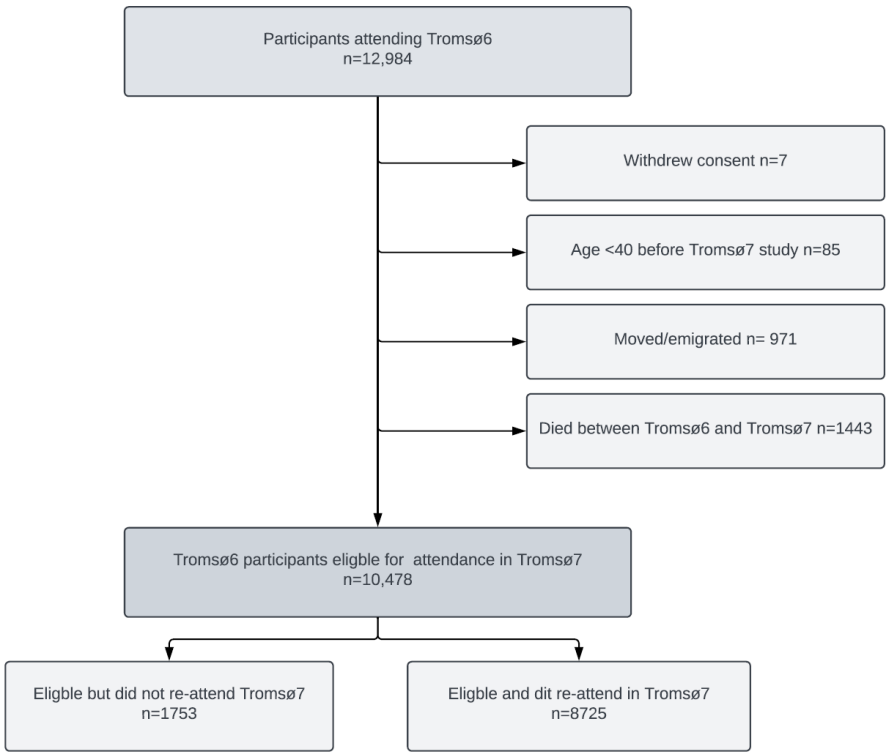
In epidemiological studies, there are two main types of error; random and systematic error (191). Errors in epidemiological research can be challenging to avoid, and how these potential errors have been handled impacts the validity of a study. Internal validity refers to the degree a study is influenced by errors and how these potentially impact the trustworthiness of the results. Whereas, external validity refers to the generalisability of the results to other populations (205). Another term for systematic error is bias, they are often classified into three broad categories; selection bias, information bias and confounding (191). These biases together with statistical considerations will be discussed in the following sections. External validity will be further discussed in chapter 5.3.

5.2.1 Selection bias

Selection bias is a distortion in the measure of the association occurring when the sample selection does not accurately reflect the target population (206). Potential selection bias in this thesis could be related to sampling and choice of the study population, and non-response bias which refers to when non-responders (non-attendees) differ from responders (attendees) (207). The Tromsø Study is a population-based study, where both whole birth cohorts and random samples of the population were invited (190). Participation in the Tromsø Study is voluntarily, and there is risk of selection bias, considered to be the major potential bias in this thesis. Although the total number of participants and (more importantly for the risk of selection bias) the proportion of invited attending the Tromsø Study is high, the general trend in declining attendance in health surveys in Norway (208) and in international studies is also observed in The Tromsø Study (209-211). In Tromsø6, the overall attendance was 66% and in Tromsø7 65%. In this study, we included participants within the age-range 40-80 years, specifically for each paper:45-74 in Paper I, 40-69 in Paper II, and 40-80 in Paper III, which also is the age groups with highest proportion of attendance in both surveys (see Table 3 and Table 4 in the material and methods section). This lowers the risk of participation proportion induced selection bias in this thesis.

Differences between attendees and non-attendees may lead to selection bias. Participants attending population studies tend to be different from non-attendees, with more favourable health status in those participating (208, 212). However, non-response bias is difficult to quantify due to limited information. Analyses on morbidity and mortality among non-participants in the Tromsø Study have previously been precluded due to legal restrictions by the Norwegian Data Inspectorate (196). A publication from the Norwegian population-based HUNT study showed no clear evidence of bias in the association and causal studies due to non-attenders (208). Nonetheless, non-participants in the HUNT study had a higher prevalence of several chronic diseases, and lower socioeconomic status had lower socioeconomic status and higher prevalence of chronic diseases compared with those attending the study (208), also found in other studies (209, 212). In the Tromsø Study, several participants have participated in more than one survey; thus, there is the risk that those attending the study are healthier than non-attendees. To provide some insights, we have performed age and sex adjusted regression analysis to compare participants who attended Tromsø6 eligible for re-attendance in Tromsø7 to compare demographics and risk factors.

Figure 4: Flowchart of participants attending Tromsø6 eligible for attendance in Tromsø7



A total of n=10,478 participants in Tromsø6 were eligible to re-attend in Tromsø7. Of these n=8725 attended, and n=1753 did not attend. In Tromsø7, a total of 32,591 were invited; in total, 21,083 participated, and as shown in Figure 4, a large proportion participants (41%) had previously participated in Tromsø6. It is generally a strength to be able to follow participants over time. However, this could introduce selection bias if taking part in the Tromsø Study is believed to influence health awareness, attitudes and behaviour change. In addition, as described in the method section, participants received standardised feedback of several CVD risk factors. Those with values above pre-defined thresholds in blood pressure, cholesterol, and blood sugar levels in Tromsø6 were recommended to contact their GP for further examination.

Table 6: Demographics and cardiovascular risk factors in participants attending Tromsø6 2007-2008, stratified by participants eligible for invitation to Tromsø7 but lost to follow-up (non-re-attenders) and participants attending both Tromsø6 and Tromsø7 (re-attenders).

	Eligible to attend Tromsø7. Lost to follow-up n=1753	Attenders Tromsø6 and Tromsø7 n=8725	p
Demographics			
Age[1], mean	56.9 (13.2)	55.9 (11.3)	<0.001
Age ≥60 years[1], %	48.0 (842)	45.0 (3923)	<0.05
Women[2], %	57.3 (1004)	53.5 (4669)	<0.05
Higher education[3,4] ,%	31.3 (548)	40.9 (3569)	<0.001
Married/partner[3], %	51.9 (909)	63.0 (5496)	<0.001
Self-reported good/very good health[3], %	60.9 (1068)	70.5 (6151)	<0.001
Psychological distress[3], %	14.0 (245)	9.9 (864)	<0.001
Cardiovascular risk factors			
NORRISK 2 score[2]	7.4 (7.2)	6.3 (6.0)	<0.001
Diabetes[2], %	6.2 (109)	3.8 (331)	<0.001
Total cholesterol mmol/L[2]	5.6 (1.1)	5.6 (1.1)	0.745
LDL-cholesterol mmol/L[2]	3.6 (0.9)	3.5 (0.9)	0.566
Low HDL-cholesterol[2,4]	16.7 (293)	13.7 (1195)	<0.05
Systolic blood pressure mmHg[2]	137.2 (24.4)	133.9 (21.8)	<0.001
Diastolic blood pressure mmHg[2]	78.5 (10.9)	77.6 (10.5)	<0.05
Daily smoking[2], %	28.7 (503)	17.9 (1561)	<0.001
General obesity [2,5] %	23.7 (415)	19.7 (1719)	<0.001
Abdominal obesity[2,6] %	54.8 (961)	50.7 (4423)	<0.05
Sedentary activity level[2], %	25.4 (445)	17.7 (1544)	<0.001

Numbers are means (standard deviations) or proportions (numbers). P= difference between individuals lost to follow-up and attenders Tromsø6 and Tromsø7.

[1] Adjusted for sex, [2] Adjusted for age [3] Adjusted for age and sex [4] Higher education: College/university < & ≥ 4 years [5]. Low HDL cholesterol <1.3 mmol/L women, <1.0 mmol/L men [6] Body mass index ≥30 kg/m^2 [7] Waist circumference men ≥102 cm, women ≥88 cm.

Tromsø6 participants that did not re-attend in Tromsø7 differed from those participating in both surveys (Table 6). Participants that attended both surveys had lower mean age, and a lower proportion was ≥60 years; a larger proportion had higher education, was married/partner, reported good/very good health, and a lower proportion had psychological distress. In addition, most cardiovascular risk factors were more favorable among re-attenders than among non-re-attenders, except for total and LDL cholesterol levels.

Since the first survey in the Tromsø Study, 45,473 people have participated in one or more of the seven surveys, 18,510 have participated three or more times (190), and participants in Tromsø6 and Tromsø7 consist of both first-time attenders and individuals that have participated in previous surveys. Potential bias due to differences in attendees versus non-attenders is difficult to avoid but is a subject to consider when interpreting the results. In the three papers included in this thesis, there is reason to believe that the observed secular and longitudinal trends in risk factors levels were more favorable than in the total population (Paper I), that a lower population proportion is calculated to be at high risk and eligible for primary prevention (Paper II), and a more healthy cohort of high-risk individuals is followed (Paper III) than in the total population. In Paper I, we studied both secular and longitudinal trends in cardiovascular risk profile, In the longitudinal analysis, we included all participants attending both Tromsø6 and Tromsø7, except those with prevalent or incident CVD during follow-up. Thus, we included all eligible participants motivated and/or healthy enough to attend both surveys, which could influence prevalence of CVD risk factors. For instance, the proportion of women aged 45-54 years being daily smokers was 28.8% in Tromsø6, while the proportion in the same age group was 25.2% in women also attending Tromsø7; in men, this was 21.4% versus 18.3% respectively. Thus, the findings of favourable changes over time in total cardiovascular risk profile and single risk factors could in part be due to survivor bias, which is a form of selection bias (206). Survivor bias is also a potential limitation in Paper III, where we followed high-risk individuals between Tromsø6 and Tromsø7. One way to address this potential selection bias is to compare differences between those who are lost to follow-up with re-attenders (206). Hence, we compared demographics and risk factor levels in re-attenders with those lost to follow-up due to incident CVD, death, or eligible but did not re-attend Tromsø7, and found those lost to follow-up to be older, have higher total CVD risk and a larger proportion had lower educational level. Consequently, when interpreting the results, this could lead to an overoptimistic interpretation of the change of CVD risk factors and the proportion reaching treatment targets.

5.2.2 Information bias and misclassification

Information bias arises if there is a systematic difference in the definition, collection, recall, recording, analysis, or interpretation of study data (191, 213). Epidemiological research, including population-based studies such as the Tromsø Study, includes self-reported measures from interviews and questionnaires and objective measures. Hence, there are several different types of information biases potentially affecting the internal validity of this thesis (206, 207). These errors in measurements can lead to misclassification, which means that an value or individual is put wrongfully into a category (205). Misclassification can be categorised into differential, and non-differential. Non-differential misclassification occurs when the probability of individuals being misclassified is similar across all groups in the study. Differential misclassification occurs when the probability of being misclassified differs between groups in a study (205, 206).

Error in self-reported data measurements

Self-report bias is a measurement error that arises when there is a deviation between the self-reported and the actual values of a measure (214, 215), and can occur in different contexts, both at random or systematically; for instance, if responders do not comprehend the question, do not correctly remember an event, or selectively choose to modify information (216). Several self-reported measures have been used in this thesis. Thus, presented below is a selection of these variables and the potential implications of errors. CVD cases were intended to be excluded in all three papers. Due to the lack of validated endpoints in the Tromsø Study CVD end point registry after 2014, we used self-reported data on the history of MI or stroke Therefore, we had to rely on a participant's ability to report an event correctly. The variable self-reported family history of premature MI is included in calculating the NORRISK 2 score (1) total CVD risk. Information bias could occur if a participant does not comprehend what an MI is (phrased in the questionnaire as “hjerteinfarkt” in Norwegian, where the common medical term and lay people term is the same) or incorrectly remember whether a family member had experienced a MI before the age of 60 years, and can introduce bias and erroneous mean total CVD risk, which further could lead to misclassification of risk category low, medium, high (Paper I), the proportion identified as high risk of CVD (Paper II) and an

erroneous study sample (Paper III). Selective response and social desirability are potential errors in this study. Study participants usually better recall some events, such as diseases and factors recognised as risk factors by the individual. However, unhealthy behaviour is more often underreported and healthy behaviours more often overreported. Social desirability responding can lead to reporting incorrect information, omitting information, or altering the magnitude of the reported information (214-216). Self-reported variables included in this thesis prone to selective response and social desirability bias are smoking status and physical activity level. Suppose many smokers report to be a non-smoker and thereby misclassified; this would lead to a lower mean total CVD risk and a lower proportion identified as high risk of CVD (Paper I-III). In that case, this could also lead to a larger proportion achieving the non-smoking primary prevention target, and an incorrect estimate of the OR of daily smoking association with achieving treatment targets (Paper III). Despite that we have used several variables that are self-reported, we do believe that the potential misclassification unlikely is differential.

Errors in objective measures

Information bias could also arise in measurement errors in objectively measured variables included in this thesis; blood pressure, blood samples, height, weight, and waist circumference. For example, suppose blood samples were performed inaccurately with prolonged venostasis. In that case, this can increase the concentration of total cholesterol and HDL cholesterol (not triglycerides and LDL cholesterol in the referred study) (217); this could influence the mean level of the variable but also the prevalence of low HDL cholesterol. Since total and HDL cholesterol are variables included in the NORRISK 2 calculations, this could affect the proportion at high risk. Another example is if technicians differ in how they consider proper cuff size before measuring the blood pressure, which is important for correct measurement and a valid blood pressure result (218). Another kind of information bias is apprehension bias. This is a bias occurring when a study participant responds differently due to being observed (219). Blood pressure is a measurement prone to apprehension bias. White-Coat hypertension is a well-known example of this (220), potentially leading to an overestimation of participants being calculated as high risk of CVD (Paper I-III), elevated mean blood pressure levels (Paper I-III), and underestimated proportion reaching treatment targets (Paper III). Overall, the potential measurement errors are likely to go in both directions

in the participants attending the Tromsø Study; it is likely non-differential. The errors could lead to uncertainty of the results and thereby threaten the internal validity of this thesis. However, to minimise the risk of measurement error the Tromsø Study have included standardised procedures for all performed measurements, and the technicians are trained personnel. Thus, measures are taken to limit risk of measurement error. Nevertheless, measurements error could still occur.

Misclassification by choice of definition of high-risk of CVD

Another potential misclassification is the choices made regarding how to define participants as high-risk of CVD, and arises when a study participants is categorised into an incorrect category (221). In Paper I, we used NORRISK 2 score to present the proportion with a low, medium, and high risk of CVD and present secular and longitudinal trends. However, as demonstrated in Paper II, including individuals with low risk, but elevated values on single risk factors, and further, re-calculating total CVD risk with and without additional risk factors impact the total proportion identified as high risk. In Paper III, we followed high-risk individuals of CVD identified by NORRISK 2, the 2017 guidelines or individuals with treated but uncontrolled hypertension or dyslipidaemia. One could argue that those treated but with controlled hypertension or dyslipidaemia also are at high risk of CVD and could be included in the study population. The same applies to those with diabetes, which is a well-known risk factor for CVD (222, 223). If we included all participants using antihypertensives, lipid-lowering drugs, or those with diabetes, we would get a larger study sample to study, but this could also lead to a more favourable result in the proportion reaching targets in primary prevention, whereas the chosen study sample could lead to a lower proportion reaching target than it actually is in a real-world setting, this supports that the choice of definition of high-risk individuals could lead to misclassification.

Handling of missing data

Information bias can also be introduced depending on the handling of missing data (213). Whether missing data will create a significant bias largely depends on its magnitude or the

pattern of missingness (224). Missing can be classified into missing completely at random, missing at random, and missing not at random (205). Missing completely at random means that the missing data is independent of the observed and unobserved data (205). Missing at random is when data is missing systematically related to the observed but not the observed data (205), meaning that the missingness is to do with the study subject but can be predicted from other information about the person. Missing not at random is when data is systematically missing related to the unobserved data, and the missingness is related to events or factors not measured by the researcher (205). Analysing datasets with missing data can be handled by imputation or by excluding participants with missing data (206, 225). In this study, since total CVD risk calculations are performed in all three papers, participants with missing values included in total CVD risk calculations were excluded. In Paper I, the proportion missing values in NORRISK 2 variables was for secular trend analysis 1.8% and also 1.8% in Tromsø7. In the longitudinal analysis, 3.3% had missing values in variables in the NORRISK 2 variables. In Paper II, the proportion of missing variables in the NORRISK calculations was 2.2%. In Paper III, the proportion with missing variables was 2.8%, and among those identified as high risk in Tromsø6 who not was lost to follow-up the proportion with missing variables was 2.0%. Excluding participants could induce bias if the participants with missing data were different from those with complete data; it also leaves us with a smaller study population and could lower the statistical power. However, the proportion of participants with missing data/values is overall low and should not reduce the validity of the study to a great extent.

5.2.3 Confounding

In epidemiological studies one aim is to study associations (191) between an independent variable and a dependent variable. Confounding occurs when the association of the variables under study is influenced by other one or several other variables (205). Confounders should be controlled for to attain valid results (206, 207) and could be handled in the design of a study or in the statistical analysis by stratification or adjustment (206). Age and sex were considered potential confounders in our study. In Paper I, we stratified by 10-year age groups for the secular trend analysis and by birth cohorts for the longitudinal analysis, and all analysis was presented separately for women and men. In this paper, we studied the

contribution of each variable included in the NORRISK 2 score by using linear regression and the Shapley Value technique, and we studied the relative importance of change in each variable and how this impacted change in the NORRISK 2 score. A limitation here is that there are several other potential explanations and confounders that we did not control for that also could impact change in risk factors and thereby change in NORRISK 2 score, however, the aim was study change in risk factors included in the score, and not to establish predictors or causality, and was therefore considered appropriate. In Paper II, age and sex as confounders were also handled by stratification. We did not adjust for other potential confounders since the main aim was only to describe and estimate the difference in the proportion of high-risk individuals by comparing risk assessment tools and primary prevention guidelines. In Paper III, we handled confounders by stratification and adjustment using regression models. We presented age-adjusted characteristics of medication users versus non-users overall and stratified by sex, and when analysing variables associated with reaching the treatment target, we adjusted for age and sex in one model and for age, sex, education, and current treatment with primary prevention medication in model two. There is, however, always a potential of not including all possible confounders, and some confounders could be unmeasured and therefore not accounted for. However, in this paper the aim was to describe the associations with a selection of risk factors and characteristics associated with achieving treatment targets without the aim to establish causal pathways or identify predictors.

5.2.4 Statistical considerations

Decisions made about the research design, statistical methods, and tests performed may impact the validity of statistical conclusions. Type 1 error is defined as *"The error of wrongly rejecting a test hypothesis; e.g., in null testing, declaring that a difference exists when it does not*" (205, p. 99). The probability of making a type I error depends on the alpha level (206) a two-tailed p-value of <0.05 was considered statistically significant in the papers included in this thesis, meaning that the probability of type 1 error in a single test was 5%. To reduce the risk of a type I error, the p-value could be lowered. However, this increases the risk of a type II error. A type II error is *"The error of failing to reject a false test hypothesis; e.g., in null testing, declaring that a difference does not exist when in fact it does"* (205, p. 99), meaning

that a conclusion is that there is no a significant finding when there actually is. To reduce the risk of a type II error, large sample size will increase power and leads to smaller standard errors (206). In all three papers, we performed several statistics tests, and when doing several tests, there is an increased risk of a type I error (206, 207), and small differences between groups may be statistically significant simply because of the large sample size, and may not be biological or clinically meaningful; interpreting results should therefore not only be done by relying on p-values from statistical tests. Thus, we chose to perform the statistical tests when appropriate and to answer the research questions. In Paper I, we tested for a difference between sexes but chose not to test for each single risk factor to avoid random significant findings. In Paper I, we used the Shapley Value decomposition to study the contribution of each single risk factor included in the NORRISK 2 score to the total score. The Shapley Value method is primarily used in gaming theory and economics (202). Although considered a stable method in other research areas (201, 202), the little use in health research leads to the need for more research on the suitability of the method. A limitation is that highly correlated data can lead to inclusive results and the Shapley Value can be misinterpreted (226). A study of the method in strategy research concluded that the Shapley Value approach provides more accurate measures of effect importance compared to an ANOVA approach, Hierarchical Linear Modelling (HLM), and Variance Component Analysis (VCA) (227). The method's strength is that the values are always positive and treats all factors in a symmetric manner, and the ability to rank the variables in order of importance (201, 204, 226). In Paper II, we presented characteristics of study participants overall, by sex and age groups. In this study, the study sample included over 16,000 participants. An example where we found a significant association by statistical tests that may not be clinically meaningful is that the LDL cholesterol was 3.6 mmol/L among women and 3.7 mmol/L among men, and by using a t-test, a p-value <0.001 was found. However, in a clinical setting, this may not be relevant, and due to this, we did not perform the statistical test on all variables included in this paper. In Paper III, we had a smaller study sample, and in the regression analysis of characteristics associated with reaching the treatment target, the OR and 95% confidence interval (CI) could imply that there was not an association in some characteristics of reaching the target. For instance, the educational level which is known in other studies to be associated with more favourable risk factor levels, was not associated with reaching treatment targets (except for non-smoking) in Paper III, with a p-value >0.05, meaning that it was not statistically significant, but it could still be relevant in a clinical setting. Judging whether a difference is clinically relevant is evaluated on the basis of expert knowledge in the field. The level of statistical significance

and the large sample size in this study increases the chances of finding a true difference in statistical tests, and we consider that there is a good balance in the probabilities of committing a type I and type II error. Further, in this study, we have used both simple descriptive statistics and slightly more sophisticated analysis, but we consider our statistical approaches to be suitable for the aims presented in the three papers.

5.2.5 Summary of internal validity

We acknowledge that there are some weaknesses and potential biases in our study. Selection bias could occur concerning the study population and non-response bias since individuals attending health surveys differ from non-attendees; this could lead to an erroneous distribution of low, medium, and high risk of CVD (Paper I), a lower estimated population proportion at risk (Paper II) and a lower study sample and more favourable changes in risk factors and proportion reaching treatment targets (Paper III), compared to if all invited participants attended the survey. In addition, information bias from measurement error of the self-reported variables, the objective measures, and the handling of missing data could lead to misclassification. However, these errors and information biases are likely random and can lead to misclassification in either direction. Thus, an equally erroneous distribution of misclassified participants. Not proper handling of potential confounders could also influence the results. However, we have adjusted and stratified for the two main potential confounders, age and sex. Confounding could lead to misclassification, which could influence the estimates and results of the papers included in this thesis. To minimise the risk of errors, the Tromsø Study has included standard operating procedures for all measures performed. The technicians at the clinical examinations were trained to follow protocols, and the questions in the self-administered questionnaires were thoughtfully selected. The choices made in this study were thought out, and measures were to limit the risk. Despite these limitations and measures taken, we believe that this thesis's internal validity was not compromised. Nonetheless, there is always a potential that errors might still occur.

5.3 External validity

External validity refers to whether the results from the study sample can be generalised to populations that did not participate in the study. In order to achieve external validity, the study is dependent on internal validity (206, 207). This thesis used a nationally calibrated risk assessment tool and the national primary prevention guidelines, which differ from other countries. Therefore, directly comparing different risk assessment tools or proportions at high risk is challenging. A threat to external validity is the representativeness of the study participants. The Tromsø Study is based on data from registered inhabitants living Tromsø municipality which include the seventh-largest Norwegian city Tromsø. Tromsø municipality include both urban (80%) and rural (20%) settled inhabitants. Tromsø has a university and a university hospital. With relatively few immigrants, a limitation in generalisability concerns ethnic diversity since the vast majority of the participants are Caucasian subjects. Residents in Tromsø are mainly employed in tertiary (trade, health service, education, public administration) and a lesser proportion in secondary and primary industry (195, 196). Numbers from Statistics Norway (228) show considerable variation in educational levels in the Norwegian population; for example, In 2016, among individuals aged 40-66 years, the proportion with higher education was 35.0% in Norway, 28.0% in the Østfold county and 50.2% in Oslo county. In the seventh Tromsø Study, the proportion with higher education in individuals aged 40-69 years was 51.8% (195). Thus, the educational level in the Tromsø Study may not represent the Norwegian population. Statistics Norway conducts regular living conditions survey with interviews of randomized population samples, covering data on self-rated health, disease prevalence, and disability. In the 2015 survey (229), the total proportion of daily smokers was 10% among those 67 years and older , and 12% when restricting to Northern Norway. In comparison, in the study sample of Paper II (Tromsø7 conducted in 2015-2016), 14.5% were smokers. Attendance is declining in the Tromsø Study, with 66% attendance in Tromsø6 (2007-2008) (193) and 65% attendance in Tromsø7 (2015-2016) (195) compared to the earliest surveys with close to 80% attendance (190). However, the attendance is slightly higher than the comparable population-based study in Trøndelag, the HUNT study. Here, the attendance has also declined over time, HUNT4 (2017-2019) had an attendance of 54% compared to 89%% in HUNT1 (1984-1986) (230). The declining attendance in epidemiological surveys and research studies is also found internationally (209, 210) and the attendance proportion in The Tromsø Study is considered fair. However, about 35% of the

invited did not attend, which is can increase the risk of selection as described above. Nonetheless, in the papers included in this thesis, we used participants aged 45-74 (Paper I), 46-69 (Paper II), and 40-79 (Paper III), which is the age-groups with the highest attendance in the Tromsø Study (see Table 3 and Table 4 in the materials and methods section). As discussed in chapter 5.2.1 Selection bias, attenders are believed to be healthier and have a more favourable risk factor profile compared to non-attenders (208). The Tromsø Study is considered to be representative of a Northern European urban Caucasian population (193). Although we acknowledge the potential limitations, we believe that our results are generalisable for the general population aged 40-80 years and potentially other Northern European populations.

6 Discussion of main results

The overall aim of this thesis was to provide new knowledge on total CVD risk assessment and primary prevention of CVD in a general population. The results of the three papers included in this thesis are already discussed in detail in the papers. However, to provide a broader understanding, our results will be discussed from several perspectives.

6.1 The NORRISK 2 model

This thesis centres around the NORRISK 2 score, the current national total CVD risk assessment tool implemented in clinical practice. The NORRISK 2 score identifies high-risk individuals and guides clinicians in initiating measures to reduce CVD risk by providing non-medical interventions such as lifestyle modification or in combination with medical interventions such as lipid-lowering drugs and/or antihypertensives (1, 6, 20). Although this thesis has focused on NORRISK 2, we cannot contribute with a clear answer to whether NORRISK 2 is the gold standard in total CVD risk assessment since this is beyond the scope of the thesis. However, with a throwback into the history of total CVD risk assessment, and findings from other studies discussed with results from the papers included in this thesis, we can still provide some insights. The idea of the first and most broadly used CVD risk assessment tool from the American Framingham study was brilliant – to integrate several well-known risk factors to identify individuals with a high risk of CVD (68). However, the Framingham risk score overestimated the risk in European populations (143-146), leading to the European SCORE's development (147). However, SCORE also overestimated the Norwegian population's risk and was considered unsuitable for national conditions (148-150). Hence, a national assessment tool was warranted before including total CVD risk assessment tools in clinical guidelines. The NORRISK score (29) was a nationally calibrated variant of the SCORE model using national risk data and was implemented in the 2009 guidelines. Ever since the 1970s, there has been a substantial decline in CVD mortality and morbidity in Norway (42), and between 2001 and 2014, the reduction in the incidence of acute MI was 2.8% per year among women and 2.6% among men (46). In the Tromsø Study, there was an overall 24% decrease in stroke incidence between 1995-2010 (47). Studies have also shown positive changes in blood pressure (12-14), cholesterol levels (15, 16) and smoking

prevalence (17, 18) and Paper I in this thesis demonstrated the general population's decline in total CVD risk between 2007 and 2016. Furthermore, another publication from the Tromsø Study showed that the positive changes in modifiable risk factors accounted for a substantial part of the observed decline in incident MI (48). Despite the positive changes in CVD incidence, mortality, and risk factor levels, it was requested by the Norwegian Health Authorities (1) that when the CVD guidelines were to be revised, a model should include both fatal and non-fatal CVD events, leading to the development of the NORRISK 2 score.

There is a large selection of total CVD risk models, and in a review by Damen et al., (142) over 300 different models were identified. In addition, as demonstrated in Table 1 (page 18) in this thesis, there is a considerable variation in which variables are included in various total CVD risk assessment tools. Hence, one could argue that there is no clear evidence for a gold standard of risk models. Age, sex, total cholesterol, smoking, and systolic blood pressure are the most traditionally used variables. In addition, various additional risk factors are included in different models to re-calculate risks, such as a family history of premature CHD, diabetes, and rheumatoid arthritis. The NORRISK 2 model included, in addition to the traditional risk factors, low HDL cholesterol, and a family history of premature CHD. In contrast, family history in the original NORRISK was an additional risk factor and not included in the standard model (1, 29). In contrast to most risk scores, in the NORRISK 2 model the use of antihypertensives was included and where use increases the score (1). The rationale behind this choice is that patients treated for hypertension have a higher risk of CVD than individuals with the same blood pressure level not treated with antihypertensives (167) so the idea is scientifically justified. When the NORRISK 2 model was presented with the updated primary prevention guidelines, this led to some debate where clinicians raised questions about the scientific rationale for these changes and were critical about the potentially increasing workload and overtreatment of healthy individuals. Interestingly, in Paper II, we did not find a large increase in the population proportion eligible for primary prevention intervention by NORRISK 2 score compared to the original NORRISK score. The main reason for the increased population proportion at risk was lowering the threshold in total cholesterol and defined levels for LDL-cholesterol. In Paper II, we also re-calculated the NORRISK score without the additional risk factors HbA1c and family history of CHD, leading to a lower proportion of high risk than the NORRISK 2 score. However, perhaps the most important explanation why we did not observe a larger population proportion at risk in NORRISK 2 compared to NORRISK is because NORRISK 2 is calibrated using newer data on morbidity,

mortality, and risk factor levels. Another interesting finding in Paper II was the overlap between risk scores demonstrated by Venn diagrams. By risk score only, a total of n=898 would be considered eligible for intervention by both risk scores, while the total number was n=1987 by NORRISK and n=1621 by NORRISK 2. In other words, NORRISK 2 is not just an extension of the original NORRISK, the different models identify different subjects. However, the risk score is different as they measure different endpoints and are thus not directly comparable.

During the last decades, several publications have emphasised the impact of the conventional risk factors and these are included in many of the total CVD risk models. In our study sample of high-risk individuals in Paper III, the study sample had higher mean total CVD risk than the general population in Paper I and Paper II, higher cholesterol levels and blood pressure, and a more significant proportion were smokers. Close to 30% were obese, about 60% had abdominal obesity, and about 20% had a sedentary physical activity level compared to 14% in the Tromsø7 general population presented in Paper II. Obesity and sedentary physical activity level are associated with an increased risk of CVD (124, 125, 127, 128), however these risk factors are not included in most total CVD risk models. There was scientific rationale behind the inclusion of the use of antihypertensive in the NORRISK 2 model, so one could question why several other risk factors have not been included. However, as discussed in the review by Damen et.al (142), creating new models and adding more variables is possibly not the solution. However, a focus should instead be on improving existing models. The external validity of the NORRISK 2 model found that it suited the general population (1), and a study from Oslo Ischemia Study found that NORRISK 2 performed satisfactorily (168). A version of the NORRISK 2 model that included South-Asian ethnicity improved the CVD predictions in South Asians (169). Adding more well-known risk factors to total CVD risk models may improve the predictive value of the models. However, this could also lead to a less user-friendly tool for clinicians. Total CVD risk models will not perform well if they do not fit the population (21, 142). Hence, the fact that the NORRISK 2 model used newer data on risk factor levels and mortality data in the model development is perhaps the most essential factor.

6.2 Secular changes in cardiovascular risk

The level of a single CVD risk factor might be low, but the contribution of several risk factors can lead to a high total CVD risk (5). Thus, in Paper I, we used the current national risk assessment tool NORRISK 2, which estimates the 10-year risk of fatal and non-fatal MI or stroke (1), to investigate secular and longitudinal trends in total CVD risk between Tromsø6 (2007-2008) and Tromsø7 (2015-2016). To better understand the NORRISK 2 score, we used The Shapley Value technique to "deconstruct" the NORRISK 2 score to investigate how each risk factor contributed to the score.

In Paper I, we observed a significant decline in total CVD risk between the two time periods in both women and men aged 45-74 years, resulting in a reduction in the proportion at high risk of CVD from 8.4% among women in Tromsø6 to 4.7% in Tromsø7, whereas the proportion at high risk changed from 33.4% to 25.5% among men. Furthermore, we found advantageous changes in the modifiable risk factors total cholesterol, blood pressure, and daily smoking, which are the main contributors to the mean NORRISK 2 score, with some differences between women and men. Few other studies have applied a risk assessment tool to study trends in CVD risk in a general population. However, some studies from Europe and the US have also demonstrated a decline in total CVD risk and a lower proportion at high risk of CVD (231-234)

The reduction in total CVD risk can be a reflection of the favourable changes in blood lipids, blood pressure, and smoking. Overall, there has been a decrease in total cholesterol in most parts of the world, but there has been an increase in the east and southeast Asia. The decrease in cholesterol has been most prominent in high-income western regions (235, 236), also demonstrated by findings from the Tromsø Study (15). The use of lipid-lowering drugs has increased substantially both globally and nationally. From 2008 to 2018, the global use of lipid-lowering drugs increased yearly by 4.13%, but with significant differences between countries (237). Also, in Norway, the use of lipid-lowering drugs has increased over time (15). This can explain a large proportion of the decrease in cholesterol levels. However, there is also a decrease among individuals not treated with medication, which can be explained by the favourable trends with decrease in the consumption of trans fatty acids or other unhealthy lifestyles such as physical inactivity and smoking (238-240).

Divergent changes in blood pressure are found at a global level (241). However, there has been a decline in blood pressure in the last decades in Norway, as demonstrated by the HUNT study in HUNT1-HUNT3 1984-2008 (12) and the Tromsø Study during Tromsø2-Tromsø6 1979-2008 (13). A continued decrease in blood pressure was demonstrated in Paper I, where systolic blood pressure further decreased between Tromsø6 and Tromsø7 for all ages and both sexes. Furthermore, the use of antihypertensives has increased worldwide (242) as well as in Norway (12, 13). However, the use of antihypertensive medication remained stable or were lower in Tromsø7 compared to Tromsø6, except among men in the oldest age group.

The prevalence of smoking in high-income countries was overall 17.6% among women and 26.9% among men in 2019, with an overall percentage change from 1990 to 2019 by -28.8% in women and -32.2% among men (243, 244). Norway was one of the first countries to introduce a comprehensive tobacco control law, resulting in a significant decline in smoking prevalence (17, 18, 245), also observed in the Tromsø Study with findings in the first paper of this thesis, as well as by Løvsletten et al who demonstrated a 22 percentage point reduction between 1994 and 2016 (246).

Despite the favourable changes in total CVD risk in the general population, we observed an increased proportion with a family history of premature CHD between 2007-2016 in both sexes and all ages, with the exception of women in the youngest age group. Several factors could explain this finding. The incidence of acute MI in Norway has decreased considerably (42). Thus, our results, with an increasing proportion of family members with premature CHD, are somewhat contradictory. However, there has been a significant decrease in mortality from MIs, and the mortality rate from MIs has shifted to higher age groups in the population. Half of all deaths occur after the age of 83 among men and after 89 years among women (42), meaning that a larger proportion individuals survive an acute MI. Hence, our finding of an increasing proportion with a family history should not be interpreted as an increasing trend in incident MIs at a young age, but rather that it may be due to increasing survival in the population. Furthermore, one should remember that this question is prone to information bias. Answering with certainty about the age of a relative with a heart attack of a specific age can be challenging. In addition, a large proportion of those who participated in Tromsø7 also participated in Tromsø6, which can lead to increased awareness of this question, which means that they are more prepared to answer this question when attending the Tromsø7 study. Since family history is part of the NORRISK 2 algorithm, one could also think that this finding might mask some of the decreases in total CVD risk. However, as the

Shapley Value regression showed, family history contributes less to the overall score than the other variables included in the score.

The favourable changes in total CVD risk and the risk factors have been of great importance for the declining incidence of CVD in Norway (48, 247), demonstrating the importance to continue a focus on modifiable risk factors.

6.3 Longitudinal changes in cardiovascular risk

In Paper 1, we also examined the longitudinal change in total CVD risk, risk factors, and how the change in the risk factors contributed to the change in total CVD risk over time. However, age is an independent and major risk factor for CVD development (75, 76), and the increase in total CVD risk over time in both sexes and all age groups was expected. This finding was also shown in a study using data from the Whitehall II longitudinal, prospective cohort study finding increased total CVD risk over time by the SCORE and ASCVD risk calculation (248). However, in our study at a single risk factor level, several factors remained stable over time, decreased, or slightly increased, similar to the findings from the Whitehall II prospective cohort. Thus, we analysed the change in total CVD risk by keeping the age variable constant (using baseline age), resulting in a stable or reduced total CVD risk. This finding demonstrated two important aspects; the contribution of age in calculating total CVD risk and the effect of reduction in modifiable risk factors on total CVD risk. In a clinical setting, the rationale for the general practitioner (GP) to use a total CVD risk assessment is to objectively calculate the total CVD risk to identify those at the highest risk of CVD to initiate measures (6). Therefore, something important to reflect upon is that if the GP estimates total CVD risk over time in a clinical setting, the risk will increase merely due to the impact of age, and the favorable changes in single risk factors might be camouflaged. Thus, one could argue that calculating total CVD risk alone should not be performed without reflecting upon change in the risk factors included in the score. Similar to the analysis of secular trends, total cholesterol, SBP and daily smoking were the main contributors to change in NORRISK 2 score over time, together with the use of antihypertensive medication.

6.4 Population proportion at risk of cardiovascular disease

CVD prevention is a central mission from a public health perspective, although resource-demanding (20). Thus, a highly adopted approach is the "high-risk" strategy, where the aim is to identify those at the highest risk of CVD to initiate measures to reduce CVD risk. In 2017, the updated primary prevention guidelines were presented with the new risk assessment tool NORRISK 2 and changed thresholds of cholesterol levels in the guidelines (1, 20). Although in line with the highly adopted high-risk strategy, the idea was brilliant in nature, but the NORRISK 2 score and the updated primary prevention guidelines met some resistance;

"New guidelines create tens of thousands of patients; The new professional guidelines for gestational diabetes and the prevention of cardiovascular disease, respectively, pose a serious threat to the quality of the health service - and should be withdrawn" Hjörleifsson S, Meland E, Mildestvedt T. (249, paragraph 1).

"The intention to prevent cardiovascular disease and birth complications is commendable, but the price is high. It will cost hundreds of man-years to identify patients and give them treatment. The authorities have not given signals to add new resources for this purpose, but have not explained which other tasks are to be downgraded. In addition, the actual screening, disease diagnosis, and treatment will entail inconveniences for those who are exposed to this" Hjörleifsson S, Meland E, Mildestvedt T. (249, paragraph 3).

Therefore, in Paper II, we aimed to compare NORRISK and the 2009 primary prevention guideline with the NORRISK 2 score and the current guideline from 2017 to estimate the population proportion identified as high risk of CVD among individuals aged 40-69 years. Overall, the current guideline and NORRISK 2 score increased the population proportion at risk by 3.4 percentage points. One of the main findings was that the proportion identified as high risk by NORRISK 2 score alone was 9.8% versus 12.0% by NORRISK. However, when the NORRISK score was calculated without the additional risk factors of family history of CVD, the proportion identified by NORRISK was 8.6%. However, a direct comparison of risk assessment tools must be made with caution since they are fundamentally different. It is

highlighted that risk assessment tools should be calibrated (6). One study found that not modelling the secular trend in risk factors and CVD incidence can cause over-prediction, concluding that risk scores should be based on current national data (250). Furthermore, the change in threshold in total cholesterol from ≥8 mmol/L to ≥7 mmol/L and the specified threshold in LDL cholesterol of ≥5 mmol/L were the main factors increasing the population proportion at risk of CVD. The NORRISK 2 score and the current national guidelines would cause almost 70.000 more individuals aged 40-69 years to be eligible for primary prevention. The use of total CVD risk assessment and the increased proportion demonstrated in Paper II and the impact could be viewed from several perspectives; the increased population proportion will affect the individual identified as high risk, the primary health care workers, and the system, this will be discussed further in the next sections.

6.5 High risk of CVD - implications for the individual

The papers included in this thesis have not provided any directly updated knowledge about the primary prevention of CVD from the patient's perspective. It is nevertheless highly relevant to reflect upon, given the focus of the thesis, since many results could affect the individual at high risk of CVD. From the patient's perspective, an increased population proportion at risk means more individuals informed about being at risk of CVD, more individuals in need of lifestyle modifications, and a more significant proportion of individuals eligible for medication therapy interventions such as lipid-lowering and antihypertensive medications. There is a saying, "*It is better to prevent than to treat*". In many cases, it is undoubtedly best to prevent than to treat. However, being at high risk of CVD does not equal 100% certainty that a CVD will occur in the future. Thus, the measures to reduce risk have to be acceptable regarding consequences for the individual involved. Shared-decision making is considered an important area in patient-centred care (184, 185) and highly relevant in the primary prevention of CVD. The clinician and the individual must work together to produce the best outcome of the measures initiated. Therefore, it is recommended that clinicians use SDM when communicating CVD risk to their patients (189). The effect of being informed about being at high risk of CVD is not something to take lightly. One qualitative study among

individuals with high cholesterol levels informed about their risk of CVD led to anxiety and self-centredness (251). A qualitative study by Farrimond et al. (252) of individuals' experiences of being identified as high risk of CVD found that the identification as high-risk came as a shock for many, particularly among those who considered themselves reasonably healthy. Moreover, some of the study participants, the concretised percentage, raised concerns about risk factors and lifestyles in their minds. In contrast, others found their GPs message about being at high risk of CVD to be more confirmatory (252). Furthermore, a study from the UK examining the patient's perspective of being identified as high-risk also found divergent reactions from the patients; participants reported that being informed about being at risk felt problematic. One participant reported that he "nearly died" when he received a letter about being at high risk of a stroke or an attack (253). In addition, some participants reported that being informed led to a decision to change their behaviour, while others did not agree to be at high risk and did not plan any measures to reduce their risk (253). Lifestyle changes are a cornerstone for reducing risk (19), but adherence to lifestyle changes remains challenging (172). A study of participants at high risk of CVD participating in a lifestyle counselling program in Sweden reported several barriers to lifestyle changes, such as bad weather (to be physically active), stress, and lack of time. Another barrier was that the participants were asymptomatic and did not feel sick (254). In a study by Jarbøl et al. (255), a sample of Danish inhabitants aged 40-60 years was invited to a survey and asked to imagine being diagnosed with an increased risk of heart disease; the majority preferred the idea of lifestyle changes compared to medical treatment, but also expressed doubts about maintaining the changed lifestyle over time.

Among high-risk individuals, where lifestyle modifications are insufficient to significantly reduce blood pressure or cholesterol levels toward the defined treatment targets for primary prevention, treatment with medication could be the next step (19, 20). Whether the health personnel recommend lifestyle changes before medication therapy must be assessed individually. However, according to the guidelines (19, 20), medication therapy should be initiated if the lifestyle measures have not produced the desired effect and immediately if the levels are exceptionally high. An increased population proportion at risk means a larger proportion potentially being treated with medications to lower cholesterol and/or blood pressure levels. In statins, the first choice of medication therapy to lower cholesterol levels (19, 20), severe side effects are rare, the most common is myopathy, but increased liver values can occur, especially in high doses (256, 257). In addition, more common subjective

symptoms and troubles are gastrointestinal trouble, muscle and joint aches, and tiredness (175). However, many individuals tolerate statins when they believe they are receiving a placebo (257). Nevertheless, symptoms that trouble the patient must be taken seriously. In treatment with antihypertensive medication, although generally well tolerated, side effects such as dizziness, drowsiness, light-headedness, or tiredness can occur (258). The side effects usually subside after a few weeks when the body has adapted to the lower blood pressure (258). A meta-analysis of randomized trials found that most types of antihypertensive agents significantly increased the risk of an individual discontinuing the treatment due to side effects compared to those side effects in individuals taking a placebo experienced (259). Some side effects result from lowering blood pressure, usually, if the blood pressure lowering is rapid, and therefore can be caused by any antihypertensive agent (258, 259). To summarize, treatment with medication therapy with lipid-lowering drugs and antihypertensives is generally well tolerated, but it can still cause problems for the individual. Despite the vast number of publications that have shown significant effect on risk reduction with lipid-lowering and antihypertensive medication, the individual's views, experiences, and needs have to be an area of focus in the choice of measures to reduce risk in primary prevention of CVD as described in shared decision-making (184, 185) .

6.6 Increased population at high risk of CVD – implications for the healthcare service

The favourable developments in mean total CVD risk and modifiable risk factors presented in Paper I could indicate that these changes would entail a lower proportion of individuals at risk of CVD and thus in need of primary prevention interventions. I.e., a lower proportion of individuals for the primary GP to initiate measures to reduce CVD risk. Nevertheless, as demonstrated in Paper II, the different risk models and thresholds in single cardiovascular risk factors defined in the primary prevention guidelines play an essential role in defining an individual at high risk of CVD. In Norway, there are about 2.1 million individuals aged 40-69 years (260). Thus, NORRISK and the 2009 guidelines identify 15.5% at high risk and eligible for intervention, approximately 320 000 individuals. Moreover, 18.9% at high risk of CVD by NORRISK 2 and the guidelines result in a roughly 396,000 individuals eligible for primary

prevention. Therefore, a 3.4 percentage point increase in population proportion at risk is a substantial increase in workload for the healthcare service. On one side, this could mean that about 70.000 more individuals could reduce their CVD risk, but this also means that the health personnel have to spend precious time during the workday to initiate measures to reduce CVD risk in apparently healthy individuals. It is important to reflect upon this because 70.000 more individuals mean not only one more consultation. It means a consultation to identify an individual at risk, attempting to initiate lifestyle modifications such as encouraging smoking cessation and counselling in diet and physical activity (19-21). In addition, follow-up consultations to evaluate the effect of these modifications. In high-risk individuals where medication therapy are initiated, the up-titrating can take time; if an individual experiences side effects, this also requires follow-up. Thus, the results from Paper II implies a considerable increment in workload for health personnel in health care services, and one could understand the reactions from some GPs when the NORRISK 2 model and the new guidelines were presented in 2017 (249).

In Norway, another critical factor that should not be ignored is the current "primary GP crisis", covered in media for some time (261). Due to this, many individuals are currently without a primary GP and more are at risk of being without a primary GP in the near future according to a report from Oslo Economics (262). Studies have demonstrated that in Europe and Norway GPs experience an increasing workload that influences the GP's work satisfaction and professional recruitment (263-265). The current situation with the increased workload, and the influence on work satisfaction and recruitment are worrisome as the GP plays an essential role in primary care (264). A recently published paper where the study sample was created by linking individuals ID-number with information from four nationwide registries demonstrated that having a primary GP that follows an individual for an extended period is associated with reduced acute hospital admissions and mortality (266). Furthermore, in the beforementioned qualitative study of GPs in Norway (265) GPs expressed their worries about being able to provide health care services expected from the population. Moreover, GPs were worried that time pressure affected how they interacted with the patients and increased their tendency to take resource-demanding shortcuts in medical investigations. Another interesting finding was that GPs experienced that preventive care was given less priority due to lack of time (265). Primary prevention of CVD aims to prevent or delay the onset of CVDs and the effort put into primary prevention can result in fewer individuals with CVD (19). On the other hand, individuals who experience CVD are at risk of complications such as heart

failure (267) and atrial fibrillation (268), which also could lead to a higher workload health personnel and the healthcare service. Hence, a greater proportion eligible for primary prevention increases the workload for the health care service, but not preventing CVD could also result in more multimorbid patients that require substantial resources.

Another factor to reflect upon is whether clinicians find risk assessment tool and primary prevention guidelines useful in clinical practice. A European study of physicians mainly working as GPs found the use of total CVD risk assessment was high, but among the 30% not using total CVD risk assessment, time constraints and the perception of it being useful were the main reasons for not using the tools (269). One study exploring the attitudes of both patients and GPs towards medication for CVD primary prevention (270) found both GPs and patients would rather try lifestyle changes before initiating medication to reduce CVD risk. Many patients expressed concerns about taking medication. However, many patients said that they would only accept treatment if they were at the highest risk levels, but at the same time, many stated that they also would do what the doctor recommended (270). In addition, some of the patients in this study were critical of the justification of initiating medication and did not want to trust the doctor blindly. Concerns from the GPs on medication were about the side effects and the value of preventive medication (270). Risk assessment tools to identify those at risk and reduced thresholds to initiate measures also increase the proportion eligible for medical treatment to lower lipid levels and blood pressure levels. A larger proportion of prescribed medication could also produce a more considerable number of patients with poor compliance and adherence to medical treatment. One qualitative study of GPs' views on cardiovascular risk and patient compliance (271) found various strategies to manage patient compliance. Some accepted the patient's decision, while others actively tried to improve compliance. Many GPs felt irritated and frustrated about the time wasted on consultations with patients not complying with the prescribed treatment (271). These examples demonstrate some of the complexity and importance of acknowledging that the increased population proportion at risk will affect the patient identified as high risk and who needs to make changes in their lives, the GP, and the primary health care system.

6.7 High-risk individuals do not achieve treatment targets, and potential explanations of why

The first European multifactorial guidelines in the primary prevention of CVD were presented in 1994 (22) and have been updated at regular intervals since then, and in 2009 the first national guideline was presented (28). The aim of these guidelines was then, and still is, to summarise the considerable amount of research in the field and provide recommendations and work as a guide for the health care professional to identify those at high risk of CVD and how to start preventive measures (30). Even though total CVD risk assessment and identification of high-risk individuals is a matter of clinical practice, the third paper included in this thesis sought to follow individuals with a high risk of CVD over a period of time to study the change in risk factors, medication use, target achievement and characteristics associated with attaining the targets. In Paper I, we found improvements in several modifiable risk factors at secular and longitudinal trends, in line with findings among high-risk individuals in the same period as presented in Paper III. However, as expected, total CVD risk and most modifiable risk factors was significantly more elevated in the high-risk cohort compared with the general population. Between 2007 and 2016, high-risk individuals increased their total CVD risk, but several modifiable risk factors improved, which can be explained by the impact of age on the NORRISK 2 score demonstrated in Paper I. High-risk individuals improved lipids, blood pressure levels, smoking, and physical activity levels, while the proportion with general and abdominal obesity aggravated. Despite several beneficial changes in risk factor levels, the proportion who achieved the guideline-defined treatment targets was about 30% for lipids, 40% reached the BP target, and 10% achieved all targets combined. These findings add to the series of other studies that have shown that the proportion of achieving treatment targets in the primary prevention of CVD is suboptimal (33-35, 272, 273). However, a direct comparison with other studies must be made with caution since these are mainly cross-sectional studies where the study sample includes participants due to their patient status. Nevertheless, a strength of these studies is that the participants are identified as at high risk of CVD. Thus, one knows that measures to reduce CVD risk are initiated. In contrast, in Paper III, we used total CVD risk assessment and guidelines to identify high-risk individuals in a general population. Thus, we are studying participants who may not even know they are at high risk and where no measures to reduce risk are initiated. On the other hand, 48% of the study sample was already treated with antihypertensives and/or lipid-lowering medication. Furthermore, individuals with elevated values in blood pressure or lipids attending Tromsø6

would receive a letter after participating with encouragement to see their primary GP due to elevated values. Thus, a substantial proportion of the study sample in Paper III is potentially identified as a high risk after participation in Tromsø6. A strength in this paper is the long follow-up period. Still, many factors that we cannot take into account can influence an individual.

Except for the non-smoking target, a low proportion of our study sample achieved the guideline-defined treatment targets of lipids and blood pressure. However, we identified several characteristics associated with achieving treatment targets, where medication use was the strongest overall. In addition, individuals treated with medications at the second screening experience more favourable lipids and blood pressure improvements. When to initiate treatment and the thresholds for treatment targets are debated, and adverse effects of medication can occur (31), but our study demonstrated the impact of medication use. Nevertheless, this must not be interpreted as all individuals should be treated with medications. Potentially, among those individuals where treatment with medication is initiated, other non-medical interventions are initiated as well. However, these are factors we cannot include in our analysis. We have included treatment with lipid-lowering drugs and antihypertensives in general, but not included any adjustments regarding dosage and types of medications, which can influence the change in lipids (274) and blood pressure (181) and thus the probability of achieving treatment targets. In Paper III , our analysis also showed that the baseline levels of medication users compared to non-users at the second screening differed; non-users were younger, and a more significant proportion had higher education and lower blood pressure. In contrast, the non-users had higher total CVD risk and lipid levels, and a more significant proportion were daily smokers. In addition, a lower proportion had general and abdominal obesity than users, and this could be interpreted as if this was in a clinical setting; potentially, the GP would focus on smoking cessation since smoking is a major CVD risk factor and one of the most important to reduce (171, 275). This finding can explain why using antihypertensives was associated with achieving the non-smoking target; possibly in individuals that smoke, the GP starts with medications earlier than among non-smokers. In addition, the GP initiates medical treatment in individuals with combined risk factors such as general and abdominal obesity and other characteristics such as psychological distress, which can potentially reduce the probability of successful lifestyle modifications.

We found that between baseline and second screening, the use of primary prevention medication increased to 70% (Paper III). Using data from a population-based study, it is impossible to conclude whether this is optimal or suboptimal use. Our findings, with 30% of the high-risk study sample not using primary prevention medication and the low proportion reaching treatment targets in primary prevention, contribute to highlighting the great potential in primary prevention of CVD. As mentioned previously, this does not mean that all should be treated with medication. However, the primary prevention guidelines and the developers of NORRISK 2 aim to identify individuals at the highest risk of CVD and initiate interventions to reduce risk. For many, that could result in the need for medication therapy in combination with non-medical interventions. Potential explanations for not reaching treatment targets can be "clinical inertia" (276), described as the failure of clinicians to initiate or intensify therapy when therapeutic targets are not reached, low dose prescriptions, not up-titrating doses, or poor patient adherence. However, the term "clinical inertia" is negatively charged, bordering on arrogance. Because it is unlikely that the health personnel makes choices that are in conflict with the patient or the patient's best interests, there could also be barriers within the healthcare system to following up on high-risk individuals (269). We cannot provide analysis, tables, or figures to show the complexity of each individual at high risk of CVD. Moreover, there could be important reasons for the health personnel not to start treatment with medications in clinical practice. For example, one study found that if patients had comorbidities such as diabetes or mental illness, the doctor could delay the prescription of medication to minimise the stress for the patient and that the doctor was concerned that the patients with multiple treatments could introduce more complexity and reduce adherence (277). However, European and national guidelines highlight that treatment to reduce CVD risk should be individually tailored (19, 20). Shared-decision making is a crucial element in primary prevention. Thus, although we found an overall low proportion that achieved guideline-defined treatment targets, this does not necessarily match the individually set treatment targets. In the meeting between health personnel the patient, the health personnel has to identify the patient's needs and attitudes towards changing behaviour, and investigate the likelihood that a patient will adhere to the medication therapy (19-21). Furthermore, it is not the case that only achieving treatment goals matters regarding risk reduction. In Paper III, we found positive changes in several risk factors. Individuals with the highest blood pressure and lipids values would experience a substantial risk reduction despite exceeding the defined targets.

6.8 Primary prevention of CVD - what to do next?

The high-risk strategy is well-known and highly adopted in the primary prevention of CVD. However, in the field of prevention, one cannot avoid Rose's (3, 4) conclusion that the high-risk strategy is only needed if the underlying cause of the disease is unknown and not able to control. A vast amount of research has identified the causes and risk factors associated with CVD. Hence, from Roses' point of view, there is no need for a high-risk strategy in the primary prevention of CVD. But then, one must remember there could be risk factors not yet discovered, or that more research contributes to more understanding of the already known risk factors. The most beneficial to the population's health is the shifting of the distribution of risk factors overall. Emberson et al., (278) concluded that the most effective is to initiate measures at a populational level compared to a high-risk strategy. Even though the incidence of CVD is declining, and the survival of an acute CVD event is high (42) the burden of developing a CVD is high with the risk of complications such as heart failure (267) and atrial fibrillation (268). Furthermore, individuals surviving a CVD event report lower health-related quality of life than the general population (279, 280). Thus, preventing CVD is important for the individual. In contrast with the study by Emberson et al., (278), Cooney et al. (281) compared the population strategy with the high-risk strategy and found that both strategies matter in risk reduction. For example, a reduction of 0.5 mmol/L in LDL cholesterol can significantly reduce the risk for the population, whereas a 0.5 mmol/L reduction is perhaps not enough for an individual with elevated values to substantially reduce the risk for CVD. In Paper I, we demonstrated several positive changes in risk factors in a general population. In contrast, in Paper III, we found that most high-risk individuals do not achieve the guideline-defined treatment targets. The main objective and purpose of CVD risk assessment is not to increase the population proportion at risk as such but to identify the right individuals to keep the balance between overtreatment and undertreatment (6). Do the findings in Paper III mean that primary prevention in clinical practice does not work? No. As demonstrated in Paper II, the total CVD risk assessment tool and thresholds in single risk factors influence who is calculated as being a high-risk individual. In addition, the increased workload on health personnel in the healthcare services (265) and primary healthcare services requires innovation. One finding from a review of doctors experiences of primary prevention was that GPs wanted more interdisciplinary cooperation (277). A systematic review of the usefulness of interventions to improve risk factors found that multifactorial interventions can reduce risk and is especially effective among those at high risk of CVD (282). One study from Sweden

used a lifestyle program focusing on lifestyle habits that reduced the 10-year risk by 14% within a year among high-risk individuals (283). However, interventions that last longer and seem more effective usually are not feasible in clinical practice (282). Total CVD risk assessment and initiating preventive measures is one of many other tasks in a GPs and other health personnel workday, and in the beforementioned review of GPs' experiences of CVD prevention (277), many of the GPs felt frustrated about the pressure to calculate total CVD risk assessment and follow-up these individuals due to lack of finances and resources. The responsibility to prevent CVD cannot be attributed alone to clinical practice. There is still a need to improve total CVD risk assessment tools that identify those at the absolute highest risk and implement valuable tools and guidelines in clinical practice. Thus, the population and high-risk strategy have to complement each other.

7 Conclusion and future perspectives

This thesis has studied total CVD risk assessment by the NORRISK 2 score and the primary prevention of CVD in a general population using data from a large Norwegian population-based study.

To conclude, we found a reduction in total CVD risk in a general population between Tromsø6 (2007-2008) and Tromsø7 (2015-2016) and a change in distribution from higher to lower risk categories between the surveys. Furthermore, we demonstrated the contribution of the risk factors included in the NORRISK 2 score, where age, total cholesterol, blood pressure, and smoking are the main contributors to the score. We also showed how the contribution of these risk factors varied by sex and age group. Another important finding was the reduction in several modifiable risk factors in the longitudinal analysis; the total CVD risk increased during follow-up; although by calculating NORRISK 2 using baseline age, we demonstrated that total CVD remained stable or decreased during follow-up, proving the contribution of age in the score and simultaneously the effect of reduction in modifiable risk factors on total CVD risk. Moreover, we showed how the NORRISK 2 score and the current primary prevention guidelines increase the population proportion at risk of CVD compared to the original NORRSISK score and the 2009 primary prevention guidelines. However, the main reason for the increased population proportion at risk was not mainly the NORRISK 2 score but the reduction in threshold in total cholesterol from ≥8 mmol/L to ≥7 mmol/L and the defined threshold in LDL cholesterol at ≥5 mmol/L to identify those at high risk of CVD who has a low total CVD risk by NORRISK 2 score. Moreover, this thesis has demonstrated the great potential for improvements in the primary prevention of CVD. Despite several advantageous changes in risk factors among individuals with a high risk of CVD, less than 10% achieved the targets of lipids, blood pressure, and non-smoking, where medication use was the strongest characteristic associated with achieving treatment targets. Furthermore, higher baseline total CVD risk, lipid levels, and blood pressure levels are associated with reduced odds of reaching targets, meaning those with the highest risk of CVD have the lowest probability of achieving treatment targets and reducing their risk of CVD.

In the future, there are several potential studies and perspectives to consider. Tromsø8 is planned to be completed in 2024-2025. Hence, it would be possible and interesting to study secular and longitudinal trends with an additional time-point measurement to study whether the positive reduction in mean total CVD risk and distribution from higher to lower risk categories continues. Furthermore, studying the NORRISK 2 score's performance and ability to predict a CVD event would be useful, and study whether using newer secular trend data on risk factors would improve the estimates and the prediction of the NORRISK 2 score. In line with other studies, we also demonstrated a low proportion of high-risk individuals achieving treatment targets and the potential for improvements in the primary prevention of CVD. Thus, investigating to which extent the GPs use the NORRISK 2 score and how the use of NORRISK 2 influences decision-making in primary care could be relevant. In addition, we have demonstrated several characteristics at an individual level associated with treatment target achievement. However, exploring and identifying barriers and success factors associated with achieving targets both at an individual level and in the primary health care system can contribute valuable knowledge beneficial to improving the primary prevention of CVD.

8 Final thoughts and reflections

Since I qualified as a nurse in 2010, I have found the field of cardiology fascinating. Most of my experience as a nurse is from care of the patient in the acute phase after experiencing an MI, of patients being hospitalised after a CVD event, and of patients living with the complications of MI such as heart failure or arrhythmias. I also worked with the educational program after an acute MI. Meeting with these patients, I became interested in the primary prevention of CVD. Many patients expressed that they could not believe that a MI could happen to them, as they had been treated with antihypertensives and lipid-lowering medications for a long time. Many of the patients had not realised that they were at high risk of CVD. I have reflected about the work conducted and how this can contribute to the clinical field. My contribution to the area of preventive cardiology in Norway is unlikely to win Nobel Prize, but a small contribution is still a contribution. In this thesis, we have demonstrated favourable changes in cardiovascular risk in the population. Furthermore, we have shown that the choice of a risk assessment tool and the thresholds to identify individuals at risk of CVD play an essential role, for the health care service, the health personnel and for the patient. In addition, despite several positive changes in risk factors control in high-risk individuals, a large proportion do not achieve the guidelines-defined treatment targets. Thus, there is a need for innovative thinking and policy efforts to introduce innovative tools health, and guidelines in clinical practice, to improve the primary prevention of CVD in Norway.

References

1. Selmer R, Igland J, Ariansen I, Tverdal A, Njolstad I, Furu K, et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. Eur J Prev Cardiol. 2017;24(7):773-82.
2. Wong DN, Fan, Wenjun Epidemiology and prevention of cardiovascular disease In: Roger Detels QAK, Fran Baum, Liming, Alastair H Leyland, editor. Textbook of Global Public Health 7ed: Oxford University press 2021.
3. Rose GA, Khaw K-T, Marmot M. Rose's strategy of preventive medicine: the complete original text: Oxford University Press; 2008.
4. Rose G. High-Risk and Population Strategies of Prevention: Ethical Considerations. Annals of Medicine. 1989;21(6):409-13.
5. Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: do they differ? Do they make a difference? Can we see the future? Circulation. 2010;122(3):300-10.
6. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). Eur J Prev Cardiol. 2019;26(14):1534-44.
7. World Health Organization (WHO). Cardiovascular diseases 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
8. European Society of Cardiology (ESC). About Cardiovascular Disease in ESC Member Countries 2019 [Available from: https://www.escardio.org/The-ESC/Press-Office/Fact-sheets
9. Townsend N, Kazakiewicz D, Lucy Wright F, Timmis A, Huculeci R, Torbica A, et al. Epidemiology of cardiovascular disease in Europe. Nat Rev Cardiol. 2022;19(2):133-43.
10. World Health Organization (WHO). The challenge of cardiovascular disease - quick statistics 2022 [Available from: https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics.
11. Wetterhall S, Pappaioanou M, Thacker S, Eaker E, Churchill R. The role of public health surveillance: information for effective action in public health. MMWR Morbidity and Mortality Weekly Report. 1992;41:207-18.
12. Holmen J, Holmen TL, Tverdal A, Holmen OL, Sund ER, Midthjell K. Blood pressure changes during 22-year of follow-up in large general population - the HUNT Study, Norway. BMC cardiovascular disorders. 2016;16:94-.
13. Hopstock LA, Bønaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Løchen ML, et al. Longitudinal and Secular Trends in Blood Pressure Among Women and Men in Birth Cohorts Born Between 1905 and 1977: The Tromsø Study 1979 to 2008. Hypertension. 2015;66(3):496-501.
14. Norwegian Instituite of Public Health. Blood pressure level (Indicator 11) 2018 [updated 16.02.2021. Available from: https://www.fhi.no/en/op/Indicators-for-NCD/blood-pressure/blodtrykksniva-indikator-11/.
15. Hopstock LA, Bønaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Løchen ML, et al. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromsø Study 1979-2016. BMJ Open. 2017;7(8):e015001.
16. Norwegian Institute of Public Health.. Total cholesterol level (Indicator 17) 2018 [updated 19.08.2021. Available from: https://www.fhi.no/en/op/Indicators-for-NCD/cholesterol/kolesterolniva-indikator-17/.
17. Health Directory of Norway (Helsedirektoratet). Tobacco Control in Norway Oslo: Helsedirektoratet 2018 [updated 25.02.2021. Available from: https://www.helsedirektoratet.no/english/tobacco-control-in-norway#referere.
18. Gartner CE, Lund KE, Barendregt JJ, Mohamed Nor N, Hassan H, Vedøy TF, et al. Projecting the future smoking prevalence in Norway. European Journal of Public Health. 2016;27(1):139-44.

19. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2022;29(1):5-115.
20. The Health Directory of Norway. Retningslinjer forebygging av hjerte- og karsykdommer. 2017 [Available from: https://www.helsedirektoratet.no/retningslinjer/forebygging-av-hjerte-og-karsykdom.
21. Jennings CS, Jennings C, Graham I, Gielen S. The ESC handbook of preventive cardiology: Putting prevention into practice: Oxford University Press; 2016.
22. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J. 1994;15(10):1300-31.
23. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Atherosclerosis. 1998;140(2):199-270.
24. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). Atherosclerosis. 2004;173(2):381-91.
25. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. †European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). European Heart Journal. 2007;28(19):2375-414.
26. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701.
27. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal. 2016;37(29):2315-81.
28. The Health Directory of Norway. Retningslinjer for individuell primærforebygging av hjerte- og karsykdommer. Oslo, Norway; 2009.
29. Selmer R, Lindman AS, Tverdal A, Pedersen JI, Njolstad I, Veierod MB. [Model for estimation of cardiovascular risk in Norway]. Tidsskr Nor Laegeforen. 2008;128(3):286-90.
30. Stewart J, Addy K, Campbell S, Wilkinson P. Primary prevention of cardiovascular disease: Updated review of contemporary guidance and literature. JRSM Cardiovasc Dis. 2020;9:2048004020949326.
31. Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. How Low to Go With Glucose, Cholesterol, and Blood Pressure in Primary Prevention of CVD. Journal of the American College of Cardiology. 2017;70(17):2171-85.
32. Brotons C, Björkelund C, Bulc M, Ciurana R, Godycki-Cwirko M, Jurgova E, et al. Prevention and health promotion in clinical practice: the views of general practitioners in Europe. Preventive Medicine. 2005;40(5):595-601.
33. Banegas JR, Lopez-Garcia E, Dallongeville J, Guallar E, Halcox JP, Borghi C, et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J. 2011;32(17):2143-52.
34. Kotseva K, De Bacquer D, De Backer G, Rydén L, Jennings C, Gyberg V, et al. Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to

Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. European Journal of Preventive Cardiology. 2020;23(18):2007-18.
35. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, et al. Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. Eur J Prev Cardiol. 2021;28(4):370-9.
36. Barrios V, Soronen J, Carter AM, Anastassopoulou A. Lipid management across Europe in the real-world setting: a rapid evidence review. Current Medical Research and Opinion. 2021;37(12):2049-59.
37. Bruckert E, Parhofer KG, Gonzalez-Juanatey JR, Nordestgaard B, Arca M, Giovas P, et al. Proportion of High-Risk/Very High-Risk Patients in Europe with Low-Density Lipoprotein Cholesterol at Target According to European Guidelines: A Systematic Review. Advances in Therapy. 2020;37(5):1724-36.
38. Mitchell S, Roso S, Samuel M, Pladevall-Vila M. Unmet need in the hyperlipidaemia population with high risk of cardiovascular disease: a targeted literature review of observational studies. BMC Cardiovascular Disorders. 2016;16(1):74.
39. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, Awareness, Treatment, and Control of Hypertension in Rural and Urban Communities in High-, Middle-, and Low-Income Countries. JAMA. 2013;310(9):959-68.
40. Dorans KS, Mills KT, Liu Y, He J. Trends in Prevalence and Control of Hypertension According to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline. Journal of the American Heart Association. 2018;7(11):e008888.
41. Borghi C, Tubach F, De Backer G, Dallongeville J, Guallar E, Medina J, et al. Lack of control of hypertension in primary cardiovascular disease prevention in Europe: Results from the EURIKA study. International Journal of Cardiology. 2016;218:83-8.
42. Norwegian Institute of Public Health. Cardiovascular disease in Norway 2020 [Available from: https://www.fhi.no/en/op/hin/health-disease/cardiovascular-disease-in-norway---/.
43. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
44. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56.
45. Norwegian Institute of Public Health. Tall fra dødsårsaksregisteret for 2020 2021 [Available from: https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/tall-fra-dodsarsaksregisteret-for-2020/.
46. Sulo G, Igland J, Vollset SE, Ebbing M, Egeland GM, Ariansen I, et al. Trends in incident acute myocardial infarction in Norway: An updated analysis to 2014 using national data from the CVDNOR project. European Journal of Preventive Cardiology. 2020;25(10):1031-9.
47. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Carlsson M, Mathiesen EB. Time Trends in Incidence and Case Fatality of Ischemic Stroke. Stroke. 2015;46(5):1173-9.
48. Mannsverk J, Wilsgaard T, Mathiesen EB, Lochen ML, Rasmussen K, Thelle DS, et al. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation. 2016;133(1):74-81.
49. Kuijpers MJCP. History in medicine: The story of cholesterol, lipids and cardiology 2021 19.04.2022 [cited 2022; 19(9). Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-19/history-in-medicine-the-story-of-cholesterol-lipids-and-cardiology.
50. Steinberg D. In celebration of the 100th anniversary of the lipid hypothesis of atherosclerosis. J Lipid Res. 2013;54(11):2946-9.
51. Classics in arteriosclerosis research: On experimental cholesterin steatosis and its significance in the origin of some pathological processes by N. Anitschkow and S. Chalatow, translated by Mary Z. Pelias, 1913. Arteriosclerosis. 1983;3(2):178-82.
52. Gofman JW, Lindgren F. The role of lipids and lipoproteins in atherosclerosis. Science. 1950;111(2877):166-71.
53. Booth J. A Short History of Blood Pressure Measurement. Proceedings of the Royal Society of Medicine. 1977;70(11):793-9.
54. Moser M. Evolution of the treatment of hypertension from the 1940s to JNC V. Am J Hypertens. 1997;10(3):2S-8S.

55. Moser M. Historical Perspectives on the Management of Hypertension. The Journal of Clinical Hypertension. 2006;8(s8):15-20.
56. Keith NM. Some different types of essential hypertension : their course and prognosis. Am J Med Sci. 1974;268:336-45.
57. Keith NM, Wagner HP, Kernohan JW. The syndrome of malignant hypertension. Archives of Internal Medicine. 1928;41(2):141-88.
58. Musk AW, DE Klerk NH. History of tobacco and health. Respirology. 2003;8(3):286-90.
59. Little B. When Cigarette Companies Used Doctors to Push Smoking 2018 [updated 11.09.2019; cited 2022. Available from: https://www.history.com/news/cigarette-ads-doctors-smoking-endorsement.
60. Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study C. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet. 2013;381(9861):133-41.
61. Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease …; 2014.
62. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23(4):373-8.
63. Karamanou M, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus: The main contributors. World J Diabetes. 2016;7(1):1-7.
64. Jörgens V, Grüsser M. Happy birthday, Claude Bernard. Diabetes. 2013;62(7):2181-2.
65. Lewis GF, Brubaker PL. The discovery of insulin revisited: lessons for the modern era. The Journal of Clinical Investigation. 2021;131(1).
66. Leening MJG, Ikram MA. Primary prevention of cardiovascular disease: The past, present, and future of blood pressure- and cholesterol-lowering treatments. PLoS Med. 2018;15(3):e1002539.
67. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J, 3rd. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55:33-50.
68. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol. 1976;38(1):46-51.
69. American Heart Association (AHA). History of the American Heart Association: Our Lifesaving History 2018 [Available from: https://www.heart.org/-/media/Files/About-Us/History/History-of-the-American-Heart-Association.pdf.
70. Holmen J. Tema: Hypertensjon ; er heller ikke blodtrykket som det var før? . Utposten 1986(15):102-3.
71. Holmen J. Høyt blodtrykk: handlingsprogram - og hva så? Utposten 1994;3.
72. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.
73. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020;395(10226):795-808.
74. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res. 2012;110(8):1097-108.
75. Dhingra R, Vasan RS. Age as a risk factor. Med Clin North Am. 2012;96(1):87-91.
76. Sniderman AD, Furberg CD. Age as a modifiable risk factor for cardiovascular disease. The Lancet. 2008;371(9623):1547-9.
77. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender Differences in Stroke Incidence and Poststroke Disability in the Framingham Heart Study. Stroke. 2009;40(4):1032-7.
78. Leening MJG, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. BMJ. 2014;349:g5992-g.
79. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. The Lancet. 1999;353(9147):89-92.

80. Albrektsen G, Heuch I, Lochen ML, Thelle DS, Wilsgaard T, Njolstad I, et al. Lifelong Gender Gap in Risk of Incident Myocardial Infarction: The Tromso Study. JAMA Intern Med. 2016;176(11):1673-9.
81. Appelman Y, van Rijn BB, ten Haaf ME, Boersma E, Peters SAE. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis. 2015;241(1):211-8.
82. Appelros P, Stegmayr B, Terént A. Sex Differences in Stroke Epidemiology. Stroke. 2009;40(4):1082-90.
83. Banerjee A. A review of family history of cardiovascular disease: risk factor and research tool. Int J Clin Pract. 2012;66(6):536-43.
84. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med. 1994;330(15):1041-6.
85. Sun C, Burgner DP, Ponsonby A-L, Saffery R, Huang R-C, Vuillermin PJ, et al. Effects of early-life environment and epigenetics on cardiovascular disease risk in children: highlighting the role of twin studies. Pediatric Research. 2013;73(2):523-30.
86. Forouhi NG, Sattar N. CVD risk factors and ethnicity—A homogeneous relationship? Atherosclerosis Supplements. 2006;7(1):11-9.
87. Gasevic D, Ross ES, Lear SA. Ethnic Differences in Cardiovascular Disease Risk Factors: A Systematic Review of North American Evidence. Canadian Journal of Cardiology. 2015;31(9):1169-79.
88. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med. 1979;90(1):85-91.
89. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626-35.
90. Wiesner P, Watson KE. Triglycerides: A reappraisal. Trends Cardiovasc Med. 2017;27(6):428-32.
91. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829-39.
92. Freedman DS, Otvos JD, Jeyarajah EJ, Shalaurova I, Cupples LA, Parise H, et al. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. Clin Chem. 2004;50(7):1189-200.
93. Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. Atherosclerosis. 2016;248:123-31.
94. Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G. Total and High-Density Lipoprotein Cholesterol and Stroke Risk. Stroke. 2012;43(7):1768-74.
95. Haheim LL, Holme I, Hjermann I, Leren P. Risk factors of stroke incidence and mortality. A 12-year follow-up of the Oslo Study. Stroke. 1993;24(10):1484-9.
96. Oliver MF. Cholesterol and strokes. Cholesterol lowering is indicated for strokes due to carotid atheroma. BMJ. 2000;320(7233):459-60.
97. Hackam DG, Hegele RA. Cholesterol Lowering and Prevention of Stroke. Stroke. 2019;50(2):537-41.
98. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. Jama. 2016;316(12):1289-97.
99. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nature Reviews Cardiology. 2021;18(11):785-802.
100. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet. 2016;388(10060):2665-712.
101. (WHO) WHO. Hypertension 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension.

102. Vishram JK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, et al. Do other cardiovascular risk factors influence the impact of age on the association between blood pressure and mortality? The MORGAM Project. J Hypertens. 2014;32(5):1025-32; discussion 33.
103. Whelton SP, McEvoy JW, Shaw L, Psaty BM, Lima JAC, Budoff M, et al. Association of Normal Systolic Blood Pressure Level With Cardiovascular Disease in the Absence of Risk Factors. JAMA Cardiology. 2020;5(9):1011-8.
104. Reckelhoff JF. Gender differences in the regulation of blood pressure. Hypertension. 2001;37(5):1199-208.
105. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex Differences in Blood Pressure Trajectories Over the Life Course. JAMA Cardiology. 2020;5(3):255-62.
106. Ramirez LA, Sullivan JC. Sex Differences in Hypertension: Where We Have Been and Where We Are Going. Am J Hypertens. 2018;31(12):1247-54.
107. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23.
108. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. JAMA Cardiol. 2017;2(7):775-81.
109. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43(10):1731-7.
110. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018;360:j5855.
111. Banks E, Joshy G, Korda RJ, Stavreski B, Soga K, Egger S, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. BMC Medicine. 2019;17(1):128.
112. European Society of Cardiology (ESC). Smoking leads to five-fold increase in heart disease and stroke un under -50`s 2013 [Available from: https://www.sciencedaily.com/releases/2013/05/130531105328.htm.
113. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. The Lancet. 2011;378(9799):1297-305.
114. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ. 1998;316(7137):1043.
115. Haast RA, Gustafson DR, Kiliaan AJ. Sex differences in stroke. J Cereb Blood Flow Metab. 2012;32(12):2100-7.
116. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. BMJ Global Health. 2017;2(2):e000298.
117. World Health Organization (WHO). Diabetes 2021. https://www.who.int/health-topics/diabetes#tab=tab_1)
118. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. The Lancet. 2005;365(9467):1333-46.
119. Emerging Risk Factors C, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
120. Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014;57(8):1542-51.
121. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. The Lancet. 2014;383(9933):1973-80.
122. World Health Organization (WHO). Obesity and overweight 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
123. World Health Organization (WHO). Waist Circumference and waist-hip ratio 2011.

124. Golay A, Ybarra J. Link between obesity and type 2 diabetes. Best Practice & Research Clinical Endocrinology & Metabolism. 2005;19(4):649-63.
125. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories: A Systematic Review and Meta-analysis. JAMA. 2013;309(1):71-82.
126. Li J, Siegrist J. Physical Activity and Risk of Cardiovascular Disease—A Meta-Analysis of Prospective Cohort Studies. International Journal of Environmental Research and Public Health. 2012;9(2):391-407.
127. Li J, Loerbroks A, Angerer P. Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? Current Opinion in Cardiology. 2013;28(5):575-83.
128. Leon AS, Connett J, Jacobs DR, Jr, Rauramaa R. Leisure-Time Physical Activity Levels and Risk of Coronary Heart Disease and Death: The Multiple Risk Factor Intervention Trial. JAMA. 1987;258(17):2388-95.
129. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010;92(5):1189-96.
130. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 2018;391(10129):1513-23.
131. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. American Journal of Hypertension. 2015;28(11):1295-302.
132. Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. American Journal of Public Health. 1992;82(6):816-20.
133. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. Nature Reviews Cardiology. 2009;6(11):712-22.
134. Ebrahim S, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database Syst Rev. 2006(4):CD001561.
135. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation. 1991;83(1):356-62.
136. Feigin VL, Brainin M, Norrving B, Gorelick PB, Dichgans M, Wang W, et al. What Is the Best Mix of Population‐Wide and High‐Risk Targeted Strategies of Primary Stroke and Cardiovascular Disease Prevention? Journal of the American Heart Association. 2020;9(3):e014494.
137. Brindle P, Jonathan E, Lampe F, Walker M, Whincup P, Fahey T, et al. Predictive accuracy of the Framingham coronary risk score in British men:prospective cohort study. BMJ. 2003;327(7426):1267.
138. Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart. 2006;92(12):1752-9.
139. Collins DR, Tompson AC, Onakpoya IJ, Roberts N, Ward AM, Heneghan CJ. Global cardiovascular risk assessment in the primary prevention of cardiovascular disease in adults: systematic review of systematic reviews. BMJ Open. 2017;7(3):e013650.
140. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2017(3).
141. Studziński K, Tomasik T, Krzysztoń J, Jóźwiak J, Windak A. Effect of using cardiovascular risk scoring in routine risk assessment in primary prevention of cardiovascular disease: an overview of systematic reviews. BMC Cardiovascular Disorders. 2019;19(1):11.
142. Damen JAAG, Hooft L, Schuit E, Debray TPA, Collins GS, Tzoulaki I, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ. 2016;353:i2416.
143. Haq IU, Ramsay LE, Yeo WW, Jackson PR, Wallis EJ. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. Heart. 1999;81(1):40-6.

144. Brindle P, Jonathan E, Lampe F, Walker M, Whincup P, Fahey T, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ. 2003;327(7426):1267.
145. Empana JP, Ducimetière P, Arveiler D, Ferrieres J, Evans A, Ruidavets J, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. European heart journal. 2003;24(21):1903-11.
146. Eichler K, Puhan MA, Steurer J, Bachmann LM. Prediction of first coronary events with the Framingham score: A systematic review. Am Heart J. 2007;153(5):722-31.e8.
147. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.
148. Lindman AS, Selmer R, Tverdal A, Pedersen JI, Eggen AE, Veierød MB. The SCORE risk model applied to recent population surveys in Norway compared to observed mortality in the general population. European journal of cardiovascular prevention and rehabilitation. 2006;13(5):731-7.
149. Lindman AS, Veierød MB, Pedersen JI, Tverdal A, Njølstad I, Selmer R. The ability of the SCORE high-risk model to predict 10-year cardiovascular disease mortality in Norway. Eur J Cardiovasc Prev Rehabil. 2007;14(4):501-7.
150. Hartz I, Njølstad I, Eggen AE. Does implementation of the European guidelines based on the SCORE model double the number of Norwegian adults who need cardiovascular drugs for primary prevention? The Tromsø study 2001. European Heart Journal. 2005;26(24):2673-80.
151. CVDNOR. Cardiovascular Disease in Norway 1994-2014 – The CVDNOR project: Uib.no [Available from: https://cvdnor.w.uib.no/.
152. Næss Ø, Søgaard AJ, Arnesen E, Beckstrøm AC, Bjertness E, Engeland A, et al. Cohort profile: cohort of Norway (CONOR). International journal of epidemiology. 2008;37(3):481-5.
153. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American statistical association. 1999;94(446):496-509.
154. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol. 2015;3(5):339-55.
155. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. Jama. 2007;297(6):611-9.
156. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation. 2008;118(22):2243-51, 4p following 51.
157. http://www.reynoldsriskscore.org/. Reynolds Risk Score calculator [Available from: http://www.reynoldsriskscore.org/.
158. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. Circulation. 2014;129(25_suppl_2):S49-S73.
159. ASCVD risk calculator. CVD risk calculator [Available from: https://www.cvriskcalculator.com/.
160. group Sw, collaboration ECr. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. European Heart Journal. 2021;42(25):2439-54.
161. SCORE2 calculator. SCORE2 risk calculator 2021 [Available from: https://u-prevent.com/calculators/score2.
162. Palmieri L, Rielli R, Demattè L, Donfrancesco C, Ciccarelli P, De Sanctis Caiola P, et al. CUORE project: implementation of the 10-year risk score. European journal of cardiovascular prevention and rehabilitation. 2011;18(4):642-9.
163. de la Iglesia B, Potter JF, Poulter NR, Robins MM, Skinner J. Performance of the ASSIGN cardiovascular disease risk score on a UK cohort of patients from general practice. Heart. 2011;97(6):491-9.
164. ASSIGN risk score calculator. https://www.assign-score.com/estimate-the-risk/ [Available from: https://www.assign-score.com/estimate-the-risk/.

165. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099.
166. QRISK3 calculator. https://qrisk.org/three/ 2017 [Available from: https://qrisk.org/three/.
167. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100(Suppl 2):ii1-ii67.
168. Mirza Y, Prestgaard EE, Selmer R, Liestøl K, Grundvold I, Erikssen JE, et al. Tiårsprediksjon av hjerte-og karsykdom hos friske norske menn basert på NORRISK-2. Tidsskrift for Den norske legeforening. 2020.
169. Rabanal KS, Igland J, Tell GS, Jenum AK, Klemsdal TO, Ariansen I, et al. Validation of the cardiovascular risk model NORRISK 2 in South Asians and people with diabetes. Scand Cardiovasc J. 2021;55(1):56-62.
170. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Annals of internal medicine. 2005;142(4):233-9.
171. Duncan MS, Freiberg MS, Greevy RA, Jr, Kundu S, Vasan RS, Tindle HA. Association of Smoking Cessation With Subsequent Risk of Cardiovascular Disease. JAMA. 2019;322(7):642-50.
172. Rippe JM. Lifestyle Strategies for Risk Factor Reduction, Prevention, and Treatment of Cardiovascular Disease. Am J Lifestyle Med. 2018;13(2):204-12.
173. Pająk A, Wolfshaut-Wolak R, Doryńska A, Jankowski P, Fornal M, Grodzicki T, et al. Longitudinal effects of a nurse-managed comprehensive cardiovascular disease prevention program for hospitalized coronary heart disease patients and primary care high-risk patients. Kardiol Pol. 2020;78(5):429-37.
174. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. JAMA. 2019;321(3):277-87.
175. Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2011(1).
176. Quist-Paulsen P. Statins and inflammation: an update. Current opinion in cardiology. 2010;25(4):399-405.
177. Satny M, Hubacek JA, Vrablik M. Statins and Inflammation. Current Atherosclerosis Reports. 2021;23(12):80.
178. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet (London, England). 2012;380(9841):581-90.
179. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.
180. Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension. European Heart Journal. 2018;39(40):3654-61.
181. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. The American journal of medicine. 2009;122(3):290-300.
182. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs – Overview and meta-analyses. Journal of Hypertension. 2015;33(2).
183. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-67.
184. Barry MJ, Edgman-Levitan S. Shared Decision Making — The Pinnacle of Patient-Centered Care. New England Journal of Medicine. 2012;366(9):780-1.

185. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared Decision Making: A Model for Clinical Practice. Journal of General Internal Medicine. 2012;27(10):1361-7.
186. Naderi SH, Bestwick JP, Wald DS. Adherence to Drugs That Prevent Cardiovascular Disease: Meta-analysis on 376,162 Patients. The American Journal of Medicine. 2012;125(9):882-7.e1.
187. Kim S, Shin DW, Yun JM, Hwang Y, Park SK, Ko Y-J, et al. Medication Adherence and the Risk of Cardiovascular Mortality and Hospitalization Among Patients With Newly Prescribed Antihypertensive Medications. Hypertension. 2016;67(3):506-12.
188. Martin-Ruiz E, Olry-de-Labry-Lima A, Ocaña-Riola R, Epstein D. Systematic Review of the Effect of Adherence to Statin Treatment on Critical Cardiovascular Events and Mortality in Primary Prevention. Journal of Cardiovascular Pharmacology and Therapeutics. 2018;23(3):200-15.
189. Navar AM, Stone NJ, Martin SS. What to say and how to say it: effective communication for cardiovascular disease prevention. Curr Opin Cardiol. 2016;31(5):537-44.
190. UiT The Arctic University of Tromsø About The Tromsø Study [Available from: https://uit.no/research/tromsostudy.
191. Rothman KJ. Epidemiology: An Introduction Oxford University Press 2012 [cited 2022.
192. UiT The Arctic University of Tromsø The Sixth Tromsø Study [Available from: https://uit.no/research/tromsostudy/project?pid=708904.
193. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scand J Public Health. 2013;41(1):65-80.
194. UiT The Arctic University of Tromsø The Seventh Tromsø Study [Available from: https://uit.no/research/tromsostudy/project?pid=708909.
195. Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromsø Study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scandinavian Journal of Public Health.0(0):14034948221092294.
196. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-7.
197. Vo CQ, Samuelsen P-J, Sommerseth HL, Wisløff T, Wilsgaard T, Eggen AE. Validity of self-reported educational level in the Tromsø Study. Scandinavian Journal of Public Health.0(0):14034948221088004.
198. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). Nord J Psychiatry. 2003;57(2):113-8.
199. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
200. Grimby G, Börjesson M, Jonsdottir I, Schnohr P, Thelle D, Saltin B. The "Saltin–Grimby physical activity level scale" and its application to health research. Scandinavian journal of medicine & science in sports. 2015;25:119-25.
201. Kolker A. Game Theory for Cost Allocation in Healthcare. Encyclopedia of Business Analytics and Optimization: IGI Global; 2014. p. 1067-79.
202. Shorrocks AF. Decomposition procedures for distributional analysis: a unified framework based on the Shapley value. Journal of Economic Inequality. 2013;11(1):99-126.
203. Huettner F, Sunder M, editors. REGO: Stata module for decomposing goodness of fit according to Owen and Shapley values. United Kingdom Stata Users' Group Meetings 2012; 2012: Stata Users Group.
204. Shapley L. A value for N-person games In: Kuhn HW TA, editor. The Theory of games 2. Princeton: Princeton University Press 1953. p. 307-17.
205. Porta M. A Dictionary of Epidemiology Oxford, UK: Oxford University Press 2014. 377 p.
206. Gordis L. Epidemiology E-Book: Elsevier Health Sciences; 2013.
207. Bhopal S, Raj. Concepts of Epidemiology: Intergrating the ideas, Theories, Principles and Methods of Epidemiology. . Third ed. Oxford, UK Oxford University Press 2016. 480 p.

208. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Medical Research Methodology. 2012;12(1):143.
209. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol. 2007;17(9):643-53.
210. Arfken CL, Balon R. Declining participation in research studies. Psychother Psychosom. 2011;80(6):325-8.
211. Reinikainen J, Tolonen H, Borodulin K, Harkanen T, Jousilahti P, Karvanen J, et al. Participation rates by educational levels have diverged during 25 years in Finnish health examination surveys. Eur J Public Health. 2018;28(2):237-43.
212. Enzenbach C, Wicklein B, Wirkner K, Loeffler M. Evaluating selection bias in a population-based cohort study with low baseline participation: the LIFE-Adult-Study. BMC Medical Research Methodology. 2019;19(1):135.
213. Catalogue of bias collaboration. Bankhead CR SE, Nunan D , . Information bias. In: Sackett Catalogue Of Biases 2019 2019 [Available from: https://catalogofbias.org/biases/information-bias/.
214. Bound J, Brown C, Mathiowetz N. Chapter 59 - Measurement Error in Survey Data. In: Heckman JJ, Leamer E, editors. Handbook of Econometrics. 5: Elsevier; 2001. p. 3705-843.
215. Bauhoff S. Self-Report Bias in Estimating Cross-Sectional and Treatment Effects. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014. p. 5798-800.
216. Fadnes LT, Taube A, Tylleskär T. How to identify information bias due to self-reporting in epidemiological research. The Internet Journal of Epidemiology. 2009;7(2):28-38.
217. Ephraim RKD, Appiah AA, Sakyi SA, Anto EO. Effect of prolonged venostasis on lipid profile parameters among apparently healthy University students: A case-control study in Ghana. Annals of Medical Laboratory Science. 2021;1(1):1-7.
218. Palatini P, Asmar R. Cuff challenges in blood pressure measurement. The Journal of Clinical Hypertension. 2018;20(7):1100-3.
219. Catalogue of bias collaboration; Brassey J; Mahtani KR; Spencer EA. Apprehension bias. In: Catalogue Of Bias 2019. 2019 [Available from: https://catalogofbias.org/biases/apprehension-bias/.
220. Pioli MR, Ritter AM, de Faria AP, Modolo R. White coat syndrome and its variations: differences and clinical impact. Integr Blood Press Control. 2018;11:73-9.
221. Catalogue of Bias Collaboration SE, Mahtani KR, Brassey J, Heneghan C, . Misclassification bias. In Catalogue Of Bias 2018. 2018 [Available from: https://catalogofbias.org/biases/misclassification-bias/.
222. Kannel WB, McGee DL. Diabetes and Cardiovascular Disease: The Framingham Study. JAMA. 1979;241(19):2035-8.
223. Matheus ASdM, Tannus LRM, Cobas RA, Palma CCS, Negrato CA, Gomes MdB. Impact of Diabetes on Cardiovascular Disease: An Update. International Journal of Hypertension. 2013;2013:653789.
224. Perkins NJ, Cole SR, Harel O, Tchetgen Tchetgen EJ, Sun B, Mitchell EM, et al. Principled Approaches to Missing Data in Epidemiologic Studies. American Journal of Epidemiology. 2017;187(3):568-75.
225. Graham JW, Cumsille PE, Shevock AE. Methods for handling missing data. Handbook of psychology: Research methods in psychology, Vol 2, 2nd ed. Hoboken, NJ, US: John Wiley & Sons, Inc.; 2013. p. 109-41.
226. Molnar C. Shapley Values. 2022. In: Interpretable Machine LearningA Guide for Making Black Box Models Explainable (2nd ed) [Internet]. Available from: https://christophm.github.io/interpretable-ml-book/shapley.html.

227. Sharapov D, Kattuman P, Rodriguez D, Velazquez FJ. Using the SHAPLEY value approach to variance decomposition in strategy research: Diversification, internationalization, and corporate group effects on affiliate profitability. Strategic Management Journal. 2021;42(3):608-23.

228. Statistics Norway (SSB). Table 08921: Persons over 16 years, by region, age and educational level. SSB.no 2022 [cited 2022. Statistics about eduacational level by county.]. Available from:.
229. Statistics Norway (SSB). 06189: Lifestyle habits (per cent), by living habit, region, contents, year and sex 2020 [Available from: https://www.ssb.no/en/statbank/table/06189/tableViewLayout1/.
230. NTNU. HUNT: participation numbers 2020 [Available from: https://www.ntnu.edu/hunt/participation.
231. Ford ES. Trends in predicted 10-year risk of coronary heart disease and cardiovascular disease among U.S. adults from 1999 to 2010. J Am Coll Cardiol. 2013;61(22):2249-52.
232. Diederichs C, Neuhauser H, Rücker V, Busch MA, Keil U, Fitzgerald AP, et al. Predicted 10-year risk of cardiovascular mortality in the 40 to 69 year old general population without cardiovascular diseases in Germany. PloS one. 2018;13(1):e0190441.
233. Ferrario M, Chiodini P, Chambless LE, Cesana G, Vanuzzo D, Panico S, et al. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. International journal of epidemiology. 2005;34(2):413-21.
234. Karam C, Beauchet A, Czernichow S, de Roquefeuil F, Bourez A, Mansencal N, et al. Trends in Cardiovascular Disease Risk Factor Prevalence and Estimated 10-Year Cardiovascular Risk Scores in a Large Untreated French Urban Population: The CARVAR 92 Study. PLoS One. 2015;10(4):e0124817.
235. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3· 0 million participants. The Lancet. 2011;377(9765):578-86.
236. Taddei C, Zhou B, Bixby H, Carrillo-Larco RM, Danaei G, Jackson RT, et al. Repositioning of the global epicentre of non-optimal cholesterol. Nature. 2020;582(7810):73-7.
237. Blais JE, Wei Y, Yap KKW, Alwafi H, Ma T-T, Brauer R, et al. Trends in lipid-modifying agent use in 83 countries. Atherosclerosis. 2021;328:44-51.
238. Patel N, Bhargava A, Kalra R, Parcha V, Arora G, Muntner P, et al. Trends in Lipid, Lipoproteins, and Statin Use Among U.S. Adults: Impact of 2013 Cholesterol Guidelines. J Am Coll Cardiol. 2019;74(20):2525-8.
239. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. Am Heart J. 2011;161(1):145-51.
240. Capewell S, Ford ES. Why have total cholesterol levels declined in most developed countries? BMC Public Health. 2011;11(1):641.
241. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017;389(10064):37-55.
242. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. The Lancet. 2021;398(10304):957-80.
243. Reitsma MB, Fullman N, Ng M, Salama JS, Abajobir A, Abate KH, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. The Lancet. 2017;389(10082):1885-906.
244. Reitsma MB, Kendrick PJ, Ababneh E, Abbafati C, Abbasi-Kangevari M, Abdoli A, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. The Lancet. 2021;397(10292):2337-60.
245. Halkjelsvik T, Lund KE, Kraft P, Rise J. Fear appeals in advanced tobacco control environments: the impact of a national mass media campaign in Norway. Health education research. 2013;28(5):888-97.

246. Løvsletten O, Njølstad I, Wilsgaard T, Hopstock LA, Jacobsen BK, Bønaa KH, et al. Is the ongoing obesity epidemic partly explained by concurrent decline in cigarette smoking? Insights from a longitudinal population study. The Tromsø Study 1994–2016. Preventive Medicine. 2021;147:106533.
247. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Løchen ML, Njølstad I, Mathiesen EB. Declining Incidence of Ischemic Stroke: What Is the Impact of Changing Risk Factors? The Tromsø Study 1995 to 2012. Stroke. 2017;48(3):544-50.
248. Lindbohm JV, Sipilä PN, Mars N, Knüppel A, Pentti J, Nyberg ST, et al. Association between change in cardiovascular risk scores and future cardiovascular disease: analyses of data from the Whitehall II longitudinal, prospective cohort study. The Lancet Digital Health. 2021;3(7):e434-e44.
249. Hjorleifsson Stefan ME, Mildestvedt Thomas Nye retningslinjer skaper titusenvis av pasienter dagensmedisin.no 2017 [updated 26.10.2017. Available from: https://www.dagensmedisin.no/artikler/2017/10/26/nye-retningslinjer-skaper-titusenvis-av-pasienter/.
250. Pate A, van Staa T, Emsley R. An assessment of the potential miscalibration of cardiovascular disease risk predictions caused by a secular trend in cardiovascular disease in England. BMC Medical Research Methodology. 2020;20(1):289.
251. Kirkegaard P, Edwards A, Risør MB, Thomsen JL. Risk of cardiovascular disease? A qualitative study of risk interpretation among patients with high cholesterol. BMC Fam Pract. 2013;14(1):137.
252. Farrimond H, Saukko PM, Qureshi N, Evans PH. Making sense of being at 'high risk' of coronary heart disease within primary prevention. Psychol Health. 2010;25(3):289-304.
253. Honey S, Hill K, Murray J, Craigs C, House A. Patients' responses to the communication of vascular risk in primary care: a qualitative study. Primary Health Care Research & Development. 2015;16(1):61-70.
254. Lönnberg L, Damberg M, Revenäs Å. "It's up to me": the experience of patients at high risk of cardiovascular disease of lifestyle change. Scandinavian Journal of Primary Health Care. 2020;38(3):340-51.
255. Jarbøl DE, Larsen PV, Gyrd-Hansen D, Søndergaard J, Brandt C, Leppin A, et al. Determinants of preferences for lifestyle changes versus medication and beliefs in ability to maintain lifestyle changes. A population-based survey. Prev Med Rep. 2017;6:66-73.
256. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. BMJ. 2014;349:g3743.
257. Newman CB, Tobert JA. Statin intolerance: reconciling clinical trials and clinical experience. Jama. 2015;313(10):1011-2.
258. Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. Intentional and Unintentional Nonadherence to Antihypertensive Medication. Annals of Pharmacotherapy. 2005;39(7-8):1198-203.
259. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens. 2016;34(10):1921-32.
260. (SSB) SN. 07459: Population, by sex and one-year age groups (M) 1986 - 2022 ssb.no Statistcs Norway 2021 [Available from: https://www.ssb.no/en/statbank/table/07459.
261. Eliassen H. Fastlegekrisen er fullstendig ute av kontroll. In: TV2.no, editor. 2022.
262. Pedersen K GG, Rognlien HD, Tyrihjell JB,, Værnø SG IT, Holte J, Abelsen B, Pahle A, Augestad L, Sæther EM. Evaluering av handlingsplan for allmennlegetjenesten 2020–2024: Evalueringsrapport I. . osloeconomics.no 2022.
263. Dayan M, Arora S, Rosen R, Curry N. Is general practice in crisis. London: Nuffield Trust. 2014.
264. Starfield B. Is primary care essential? The lancet. 1994;344(8930):1129-33.
265. Svedahl ER, Pape K, Toch-Marquardt M, Skarshaug LJ, Kaspersen S-L, Bjørngaard JH, et al. Increasing workload in Norwegian general practice – a qualitative study. BMC Fam Pract. 2019;20(1):68.
266. Sandvik H, Hetlevik Ø, Blinkenberg J, Hunskaar S. Continuity in general practice as predictor of mortality, acute hospitalisation, and use of out-of-hours care: a registry-based observational study in Norway. British Journal of General Practice. 2022;72(715):e84-e90.
267. Minicucci MF, Azevedo PS, Polegato BF, Paiva SAR, Zornoff LAM. Heart Failure After Myocardial Infarction: Clinical Implications and Treatment. Clinical Cardiology. 2011;34(7):410-4.

268. Alasady M, Abhayaratna WP, Leong DP, Lim HS, Abed HS, Brooks AG, et al. Coronary artery disease affecting the atrial branches is an independent determinant of atrial fibrillation after myocardial infarction. Heart Rhythm. 2011;8(7):955-60.
269. Dallongeville J, Banegas JR, Tubach F, Guallar E, Borghi C, Backer GD, et al. Survey of physicians' practices in the control of cardiovascular risk factors: the EURIKA study. European Journal of Preventive Cardiology. 2012;19(3):541-50.
270. Gale NK, Greenfield S, Gill P, Gutridge K, Marshall T. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. BMC Fam Pract. 2011;12(1):59.
271. Barfoed BL, Jarbøl DE, Paulsen MS, Christensen PM, Halvorsen PA, Nielsen JB, et al. GPs' Perceptions of Cardiovascular Risk and Views on Patient Compliance: A Qualitative Interview Study. International Journal of Family Medicine. 2015;2015:214146.
272. Presta V, Figliuzzi I, Miceli F, Coluccia R, Fogacci F, Cicero AFG, et al. Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: Analysis of a large real practice database in Italy. Atherosclerosis. 2019;285:40-8.
273. Figliuzzi I, Presta V, Citoni B, Miceli F, Simonelli F, Battistoni A, et al. Achievement of multiple therapeutic targets for cardiovascular disease prevention: Retrospective analysis of real practice in Italy. Clinical Cardiology. 2018;41(6):788-96.
274. Naci H, Brugts JJ, Fleurence R, Ades AE. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. Eur J Prev Cardiol. 2013;20(4):658-70.
275. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ : British Medical Journal. 2015;350:h1551.
276. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. Ann Intern Med. 2001;135(9):825-34.
277. Ju I, Banks E, Calabria B, Ju A, Agostino J, Korda RJ, et al. General practitioners' perspectives on the prevention of cardiovascular disease: systematic review and thematic synthesis of qualitative studies. BMJ Open. 2018;8(11):e021137.
278. Emberson J, Whincup P, Morris R, Walker M, Ebrahim S. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. Eur Heart J. 2004;25(6):484-91.
279. Mollon L, Bhattacharjee S. Health related quality of life among myocardial infarction survivors in the United States: a propensity score matched analysis. Health and Quality of Life Outcomes. 2017;15(1):235.
280. Tsalta-Mladenov M, Andonova S. Health-related quality of life after ischemic stroke: impact of sociodemographic and clinical factors. Neurological Research. 2021;43(7):553-61.
281. Cooney M-T, Dudina A, Whincup P, Capewell S, Menotti A, Jousilahti P, et al. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. European journal of cardiovascular prevention and rehabilitation. 2009;16(5):541-9.
282. Álvarez-Bueno C, Cavero-Redondo I, Martínez-Andrés M, Arias-Palencia N, Ramos-Blanes R, Salcedo-Aguilar F. Effectiveness of multifactorial interventions in primary health care settings for primary prevention of cardiovascular disease: A systematic review of systematic reviews. Preventive Medicine. 2015;76:S68-S75.
283. Lönnberg L, Ekblom-Bak E, Damberg M. Reduced 10-year risk of developing cardiovascular disease after participating in a lifestyle programme in primary care. Upsala Journal of Medical Sciences. 2020;125(3):250-6.

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Secular and longitudinal trends in cardiovascular risk in a general population using a national risk model: The Tromsø Study

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Abstract

Background: Primary prevention guidelines promote the use of risk assessment tools to estimate total cardiovascular risk. We aimed to study trends in cardiovascular risk and contribution of single risk factors, using the newly developed NORRISK 2 risk score, which estimates 10-year risk of fatal and non-fatal cardiovascular events.

Design: Prospective population-based study.

Methods: We included women and men aged 45–74 years attending the sixth and seventh survey of the Tromsø Study (Tromsø 6, 2007–2008, $n = 7284$ and Tromsø 7, 2015–2016, $n = 14{,}858$) to study secular trends in NORRISK 2 score. To study longitudinal trends, we followed participants born 1941–1962 attending both surveys ($n = 4534$). We calculated NORRISK 2 score and used linear regression models to study the relative contribution (%R^2) of each single risk factor to the total score.

Results: Mean NORRISK 2 score decreased and distribution in risk categories moved from higher to lower risk in both sexes and all age-groups between the first and second surveys ($p < 0.001$). In birth cohorts, when age was set to baseline in NORRISK 2 calculations, risk score decreased during follow-up. Main contributors to NORRISK 2 were systolic blood pressure, smoking and total cholesterol, with some sex, age and birth cohort differences.

Conclusion: We found significant favourable secular and longitudinal trends in total cardiovascular risk and single risk factors during the last decade. Change in systolic blood pressure, smoking and cholesterol were the main contributors to risk score change; however, the impact of single risk factors on the total score differed by sex, age and birth cohort.

Keywords

Cardiovascular disease, cohort studies, prevention, risk assessment tools

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Introduction

Cardiovascular disease (CVD) remains a leading cause of death, disability and economic burden for society worldwide.[1] The target of primary CVD prevention is to identify and reduce risk factors to prevent the burden of CVD. Modifiable risk factors are hypercholesterolaemia, hypertension, smoking, diabetes, obesity, psychosocial stress and physical inactivity.[2]

Multivariable CVD risk assessment tools are used to estimate an individual's risk of CVD and are promoted in primary CVD prevention guidelines.[3,4] The Framingham Risk Score was the first, and still

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broadly used, risk score.[5] Several CVD risk prediction models have been developed since, such as the German Prospective Cardiovascular Munster model,[6] the European Systematic Coronary Risk evaluation (SCORE) algorithm,[7] the World Health Organization (WHO) risk chart[8] and the UK QRISK equations.[9]

The NORRISK 2 score model is developed from NORRISK,[10] a Norwegian adaptation of the SCORE model,[7] validated using Norwegian population samples. The NORRISK 2 score estimates the 10-year risk (%) of incident myocardial infarction (MI) and stroke combined, including non-fatal events and death from coronary heart disease (CHD) and stroke, for use in primary CVD prevention.[10] The risk estimation is based on age, sex, systolic blood pressure, serum total cholesterol, daily smoking, family history of premature CHD, low high-density lipoprotein (HDL)-cholesterol and use of antihypertensives,[10] with age-specific thresholds to determine whether an individual is at low, medium or high risk.[10] We aimed to assess secular and longitudinal change in NORRISK 2, and the relative contribution of each single risk factor to the total score, in a general population.

Methods

Study population

The Tromsø Study is an ongoing population-based cohort study in the municipality of Tromsø, North Norway. Seven surveys have been conducted between 1974 and 2016, to which total birth cohorts and representative population samples have been invited (response rates 65–79%).[11] A total of 45,473 women and men participated in at least one survey. The present analysis includes secular and longitudinal follow-up of participants from Tromsø 6 (2007–2008) and Tromsø 7 (2015–2016). After exclusion (Figure 1), we were left with 7284 Tromsø 6 and 14,858 Tromsø 7 participants (45–74 years) for secular trend analysis and followed 4534 participants (born 1941–1962) attending both surveys for longitudinal trend analysis. The Tromsø Study has been approved by the Regional Committee of Medical and Health Research Ethics and the Norwegian Data Protection Authority. The participants provided written consent.

Measurements

Self-reported data on smoking, family history of CHD and antihypertensive medication use were collected by questionnaires. For medication use, a combination of a question ('Do you use antihypertensive medication?') and information from a written list of brand names of regularly used medication (blood pressure lowering drugs ATC C02, C03, C07, C08 and C09) was used. Blood pressure was measured on the right arm of all participants (unless in circumstances where this was not possible), three times at 1-min intervals after 2 min seated rest by a Dinamap ProCare 300 monitor (GE Healthcare, Norway), and the mean of the two final readings was used in the analysis. Non-fasting venous blood samples were collected with standard methods, and the samples were analysed for total and HDL cholesterol within 48 h (with Roche diagnostics, Mannheim, Germany) at the Department of Laboratory Medicine, University Hospital of North Norway. Trained personnel performed all measurements. CVD cases were recorded from study entry until 31 December 2013 by the Tromsø Study CVD registry. Adjudication of hospitalized and out-of-hospital incident MI and stroke was based on information from medical records from hospitals, ambulance services, general practitioners, nursing homes, autopsy reports and death certificates. Validation of each event was based on modified WHO MONICA (Multinational MONItoring of trends and determinants in cardiovascular disease)/MORGAM (Monica Risk, Genetics, Archiving and Monograph) criteria,[12] previously described elsewhere.[13] Due to lack of validated endpoints after 2013, we used questionnaire data ('Have you had a heart attack?', 'Have you had a stroke?') for events between 2014 and 2016.

We used age-specific thresholds defined by Selmer et al.[10] with the following risk categories; age 45–54 years: low risk < 4.0 %, medium risk 4.0–4.9%, high risk ≥ 5.0%; age 55–64 years: low risk < 8.0%, medium risk 8.0–9.9%, high risk ≥ 10.0%; age 65–74 years: low risk < 12.0%, medium risk 12.0–14.9%, high risk ≥ 15.0%.

Statistics

Tables 1 and 2 show the analyses stratified by sex, NORRISK 2 age-groups, and survey for secular trends, and Table 3 shows analyses of birth cohorts for longitudinal trends (follow-up of repeated individual measurements). Means and standard deviations (SDs) are presented for continuous variables, and numbers and percentages for categorical variables. We used *t*-tests and chi square tests to assess time-, sex- and age-group differences in secular trends in mean NORRISK 2 and distributions in the categories low, medium and high risk (Table 1). To assess how each single risk factor included in NORRISK 2 score contributed to the total score and the overall explained variation of the model, we used the Shapley value technique, which assesses the contribution of the coefficient of determination (R^2) in a regression model, a measure of the overall goodness of

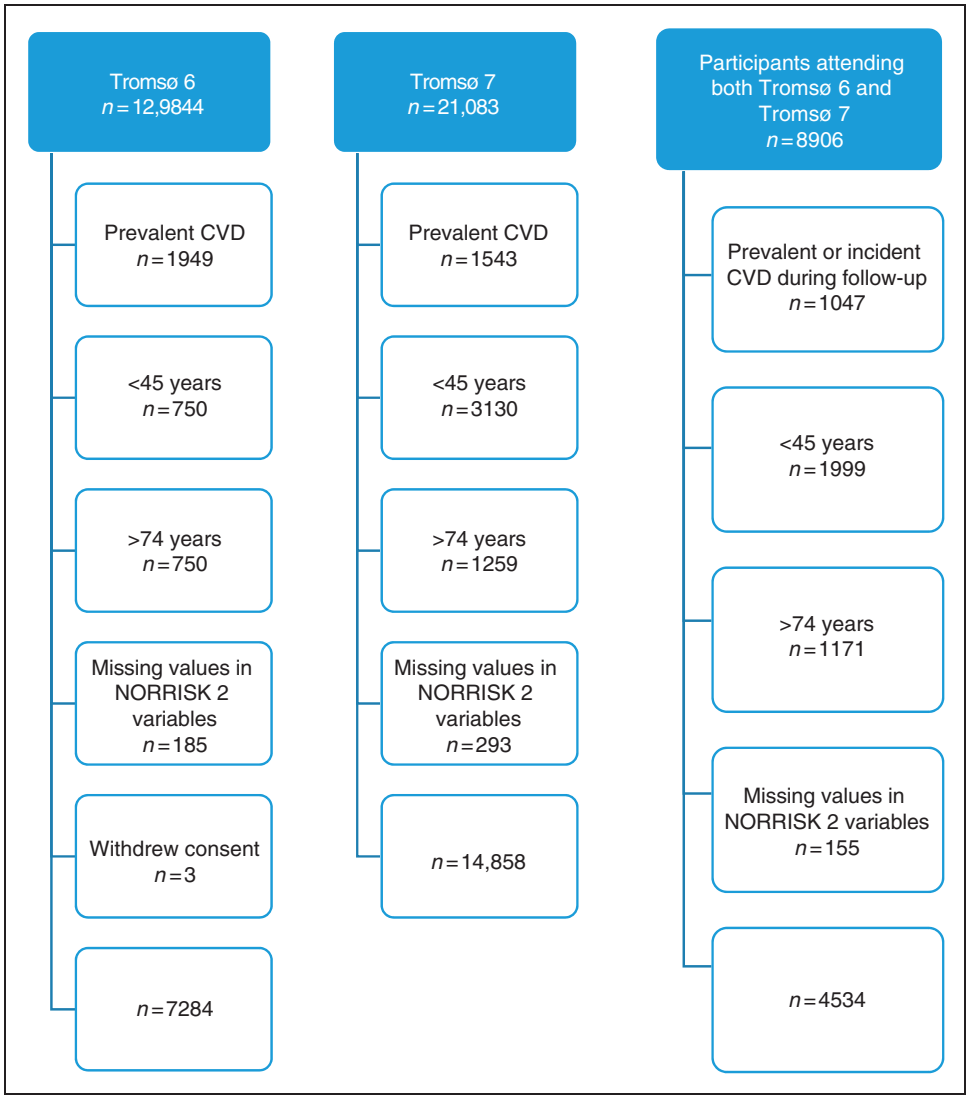

Figure 1. Flowchart of the study sample. The Tromsø Study.

fit[14] (Table 2). The Shapley value regression is a reliable and stable method for estimating predictor importance, even in the presence of high multicollinearity, and guarantees that the marginal contribution of each predictor sums to R^2.[14] Change in NORRISK 2 score was defined as the difference in mean risk score between Tromsø 6 and Tromsø 7 (Table 3). Further, we used the Shapley value to assess the relative importance of change in each risk factor to change in total risk between baseline and the second screening, by birth cohorts (Table 3). The single risk factor age was omitted from the linear regression model, due to almost identical increase in age among all participants between baseline and second screening. Statistical analyses were performed using STATA version 15 (StataCorp. 14, College Station, TX, USA, StataCorp LP).

Results

Secular trends by sex- and age-groups

Table 1 shows NORRISK 2 score and prevalence of NORRISK 2 score categories by time-, sex- and age-groups. Mean NORRISK 2 score was higher in the first compared with the second survey, in both sexes and all age-groups ($p < 0.001$). The distribution in risk categories moved from higher to lower risk categories between the first and second survey. In both surveys, mean NORRISK 2 score was consistently higher in men than in women, and higher in the older than in the younger age-groups ($p < 0.001$ for sex and age difference). Table 1 also shows the contribution of each single risk factor included in the NORRISK 2 score. There is a decrease in systolic blood pressure, total

Table 1. NORRISK 2 score, risk categories and single risk factors by sex, age-group and survey. The Tromsø Study 2007–2008 and 2015–2016.

	Tromsø 6 $n = 1218$	Tromsø 7 $n = 3312$	Tromsø 6 $n = 1715$	Tromsø 7 $n = 2807$	Tromsø 6 $n = 1077$	Tromsø 7 $n = 1888$
Women	Age-group 45–54		Age-group 55–64		Age-group 65–74	
Age, years	49.6 (2.9)	49.5 (2.9)	60.2 (2.7)	59.3 (2.8)	68.7 (2.8)	68.8 (2.8)
NORRISK-2 score	1.7 (1.4)	1.4 (1.2)	5.1 (3.1)	4.1 (2.7)	10.2 (4.5)	9.2 (4.0)
Prevalence by risk categories						
Low risk	93.1 (1134)	96.0 (3180)	85.3 (1463)	91.8 (2576)	71.5 (770)	81.4 (1536)
Medium risk	3.3 (40)	1.9 (63)	6.7 (114)	4.7 (132)	15.0 (162)	10.0 (189)
High risk	3.6 (44)	2.1 (69)	8.1 (138)	3.5 (99)	13.5 (145)	8.6 (163)
NORRISK 2 risk factors						
Total cholesterol, mmol/L	5.6 (1.0)	5.4 (1.0)	6.0 (1.0)	5.9 (1.0)	6.1 (1.1)	5.9 (1.1)
Low HDL cholesterol[a]	17.7 (216)	17.6 (583)	14.7 (252)	14.6 (409)	13.0 (140)	12.5 (236)
Systolic blood pressure, mmHg	123.1 (18.3)	119.3 (16.1)	136.2 (21.2)	127.9 (19.2)	147.8 (23.6)	137.4 (20.8)
Antihypertensives	10.3 (126)	10.2 (338)	23.9 (410)	21.8 (613)	37.9 (408)	38.6 (729)
One relative with CHD	19.7 (240)	18.8 (624)	18.2 (312)	21.2 (594)	18.8 (202)	23.3 (439)
Two or more relatives with CHD	1.7 (21)	3.4 (112)	2.6 (45)	3.7 (104)	1.9 (20)	4.0 (76)
Daily smoking	28.5 (347)	16.1 (533)	20.9 (358)	17.3 (485)	15.0 (161)	13.1 (248)
	Tromsø 6 $n = 1022$	Tromsø 7 $n = 2870$	Tromsø 6 $n = 1395$	Tromsø 7 $n = 2371$	Tromsø 6 $n = 857$	Tromsø 7 $n = 1610$
Men	Age-group 45–54		Age-group 55–64		Age-group 65–74	
Age, years	49.4 (2.8)	49.4 (2.9)	60.0 (2.7)	59.4 (2.9)	68.5 (2.8)	68.8 (2.8)
NORRISK-2 score	4.3 (2.9)	3.7 (2.7)	9.1 (4.3)	7.9 (3.8)	14.6 (5.0)	13.6 (4.8)
Prevalence by risk categories						
Low risk	56.6 (578)	67.8 (1945)	48.2 (673)	60.1 (1425)	32.7 (280)	42.2 (679)
Medium risk	14.3 (146)	11.5 (329)	19.4 (271)	16.8 (399)	28.7 (246)	25.2 (406)
High Risk	29.2 (298)	20.8 (596)	32.3 (451)	23.1 (547)	38.6 (331)	32.6 (525)
NORRISK 2 risk factors						
Total cholesterol, mmol/L	5.8 (1.0)	5.6 (1.0)	5.7 (1.0)	5.6 (1.0)	5.5 (1.0)	5.4 (1.0)
Low HDL cholesterol[b]	12.8 (131)	12.7 (363)	7.9 (110)	9.4 (223)	7.1 (61)	7.8 (126)
Systolic blood pressure, mmHg	131.9 (16.7)	128.2 (15.8)	139.5 (19.7)	133.9 (17.6)	145.7 (21.1)	139.0 (18.8)
Antihypertensives	11.6 (115)	10.7 (307)	22.6 (315)	24.6 (583)	31.7 (272)	42.8 (689)
One relative with CHD	17.1 (175)	18.2 (523)	16.1 (225)	18.6 (440)	13.0 (111)	18.6 (299)
Two or more relatives with CHD	1.5 (15)	2.3 (65)	1.2 (16)	3.4 (80)	0.6 (5)	2.4 (39)
Daily smoking	21.4 (216)	14.5 (417)	19.1 (267)	15.7 (372)	14.9 (128)	10.9 (176)

Values are mean (SD), or per cent (number).
[a]Cut-off value for low HDL cholesterol for women: < 1.3 mmol/L.
[b]Cut-off value for low HDL cholesterol for men: < 1.0 mmol/L.
CHD: coronary heart disease; HDL: high-density lipoprotein

cholesterol and smoking. Use of antihypertensives increased between surveys among the oldest age-groups. Men had a greater decline in NORRISK 2 score between surveys, where the risk score was 0.3–1% lower in the second survey compared with the first for women, while as for men the risk score was 0.6–1.2% lower, respectively. In systolic blood pressure, women had a decline of 4–10 mmHg from the youngest to the oldest age-group, whereas the decline among men was 3.7–6.7 mmHg. The reduced

Table 2. The relative contribution of each risk factor included in NORRISK 2 to the overall variation in the score by sex, age-group and survey. The Tromsø Study 2007–2008 and 2015–2016.

	Age-group 45–54		Age-group 55–64		Age-group 65–74	
	Tromsø 6 $n = 1218$	Tromsø 7 $n = 3312$	Tromsø 6 $n = 1715$	Tromsø 7 $n = 2807$	Tromsø 6 $n = 1077$	Tromsø 7 $n = 1888$
Women	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)
Age, years	20.6 (18.7, 22.8)	26.5 (25.2, 27.8)	21.4 (19.4, 23.5)	25.0 (23.4, 26.5)	26.2 (23.9, 28.9)	27.2 (25.2, 38.1)
Total cholesterol, mmol/L	4.9 (3.6, 6.3)	5.3 (4.5, 6.2)	3.1 (2.3, 4.0)	2.3 (1.8, 3.0)	3.6 (2.6, 4.8)	3.4 (2.7, 4.3)
Low HDL cholesterol[a]	4.7 (3.5, 6.1)	4.7 (4.1, 5.4)	4.8(3.9, 5.9)	5.1 (4.2, 6.0)	5.3 (4.0, 6.7)	6.8 (5.5, 8.0)
Systolic blood pressure, mmHg	26.1 (23.5, 28.4)	24.7 (23.3, 26.2)	33.9 (31.8, 36.1)	30.5 (28.8, 32.4)	34.2 (31.7, 37.2)	30.2 (28.0, 3.3)
Antihypertensives	0.3 (0.3, 0.6)	0.5 (0.4, 0.7)	0.9 (0.8, 1.1)	0.8 (0.7, 0.9)	3.4 (2.6, 4.3)	2.1 (1.8, 2.6)
One relative with CHD	2.3 (1.6, 3.2)	3.1 (2.5, 3.7)	3.1 (2.3, 4.0)	3.5 (2.9, 4.2)	4.5 (3.4, 5.9)	5.5 (4.5, 6.8)
Two or more relatives with CHD	1.4 (0.7, 2.3)	2.7 (2.0, 3.4)	2.9 (1.9, 4.1)	3.7 (2.8, 4.7)	2.8 (1.6, 4.5)	5.5 (4.1, 7.1)
Daily smoking	39.5 (37.2, 41.7)	32.6 (30.8, 34.2)	29.9 (27.6, 32.1)	29.1 (27.3, 30.8)	19.7 (17.0, 22.2)	19.3 (17.4, 21.3)
	Age group 45–54		Age group 55–64		Age group 65–74	
	Tromsø 6 $n = 1022$	Tromsø 7 $n = 2870$	Tromsø 6 $n = 1395$	Tromsø 7 $n = 2371$	Tromsø 6 $n = 857$	Tromsø 7 $n = 1610$
Men	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)	$\%R^2$ (95% CI)
Age, years	15.1 (13.2, 17.2)	19.3 (17.9, 20.7)	16.2 (14.3, 18.5)	19.8 (18.2, 21.3)	23.9 (20.8, 27.0)	24.4 (22.3, 26.8)
Total cholesterol, mmol/L	23.5 (21.0, 25.9)	24.7 (23.3, 26.2)	16.5 (14.7, 18.5)	16.5 (14.9, 18.2)	9.8 (7.9, 11.8)	8.4 (7.0, 10.0)
Low HDL cholesterol[b]	3.7 (2.6, 5.2)	3.0 (2.4, 3.8)	3.1 (2.2, 4.1)	3.7 (2.9, 4.6)	3.6 (2.5, 5.3)	4.6 (3.5, 5.9)
Systolic blood pressure, mmHg	26.8 (24.2, 29.6)	25.4 (23.8, 26.9)	34.5 (31.9, 37.4)	29.5 (27.5, 31.3)	33.0 (29.5, 36.7)	26.8 (24.3, 29.2)
Antihypertensives	1.2 (0.8, 1.7)	1.2 (0.9, 1.5)	5.0 (4.0, 6.2)	4.4 (3.7, 5.2)	11.4 (9.6, 13.5)	11.8 (10.3, 13.3)
One relative with CHD	4.1 (2.8, 5.3)	4.2 (3.5, 5.0)	5.3 (4.2, 6.6)	5.6 (4.7, 6.5)	7.0 (5.3, 9.0)	8.4 (7.1, 9.9)
Two or more relatives with CHD	2.2 (1.0, 3.6)	2.7 (2.0, 3.5)	1.6 (0.8, 2.7)	4.4 (3.3, 5.7)	0.8 (0.2, 1.5)	6.1 (4.1, 8.1)
Daily smoking	23.3 (21.0, 25.8)	19.4 (17.8, 21.1)	17.6 (15.4, 19.4)	16.1 (14.6, 17.8)	10.4 (8.5, 12.7)	9.4 (7.7, 11.0)

Values are Percentage R^2 (95% CI).
CHD: coronary heart disease; CI: confidence interval; HDL: high-density lipoprotein
[a]Cut-off value for low HDL cholesterol for women: < 1.3 mmol/L.
[b]Cut-off value for low HDL cholesterol for men: < 1.0 mmol/L.

Table 3. NORRISK 2 score, single risk factors and the relative contribution of each risk factor to the overall variation in the score by sex, birth cohorts and follow-up. The Tromsø Study 2007–2008 and 2015–2016.

Women	Birth cohort 1953–1962, $n = 987$			Birth cohort 1943–1952, $n = 1303$			Birth cohort 1941–1942, $n = 221$		
	Baseline[a]	Second screening[a]	%R^2 (CI) change[b]	Baseline[a]	Second screening[a]	%R^2 (CI) change[b]	Baseline[a]	Second screening[a]	%R^2 (CI) change[b]
Age, years	49.5 (2.9)	57.7 (2.9)	–	60.1 (2.7)	68.1 (2.7)	–	65.5 (0.5)	73.5 (0.5)	–
NORRISK 2	1.6 (1.3)	3.3 (2.1)	–	4.9 (3.0)	8.6 (3.7)	–	7.4 (3.0)	12.6 (4.0)	–
NORRISK 2 with baseline age[c]	1.6 (1.3)	1.6 (1.2)	–	4.9 (3.0)	4.6 (2.6)	–	7.4 (3.0)	7.2 (3.0)	–
Total cholesterol, mmol/L	5.6 (1.0)	5.8 (1.0)	5.9 (4.3,7.7)	6.0 (1.0)	5.9 (1.1)	6.3 (4.8, 8.1)	6.0 (1.0)	5.7 (1.0)	7.4 (3.4, 12.3)
Low HDL cholesterol[d]	16.9 (167)	14.3 (141)	5.1 (3.5,6.8)	13.5 (176)	11.5 (150)	7.2 (5.5, 8.9)	12.2 (27)	14.9 (33)	8.2 (4.2, 14.3)
Systolic blood pressure, mmHg	122.8 (18.2)	125.0 (18.1)	32.6 (28.8,36.3)	135.4 (20.7)	136.9 (20.3)	37.5 (34.5, 40.8)	143.3 (23.5)	143.0 (20.0)	48.6 (40.1, 56.9)
Antihypertensives	9.8 (97)	19.8 (195)	8.2 (6.0,10.6)	22.4 (292)	36.8 (479)	12.0 (10.1, 13.9)	41.2 (91)	54.3 (120)	13.7 (8.1, 19.9)
One relative with CHD	19.2 (189)	20.7 (204)	1.7 (1.0,2.7)	17.7 (230)	23.2 (302)	4.0 (2.8, 5.3)	18.6 (41)	24.9 (55)	8.1 (4.7, 12.6)
Two or more relatives with CHD	1.7 (17)	4.4 (43)	2.4 (1.4,3.6)	2.5 (32)	4.2 (55)	3.9 (2.8, 5.3)	1.4 (3)	4.5 (10)	–[e]
Daily smoking	25.2 (249)	17.7 (175)	43.9 (39.2,49.0)	18.0 (235)	11.4 (148)	30.0 (25.3, 32.3)	13.6 (30)	10.0 (22)	13.2 (5.6,22.0)
Men	Birth cohort 1953–1962, $n = 776$			Birth cohort 1943–1952, $n = 1048$			Birth cohort 1941–1942, $n = 199$		
	Baseline[a]	Second screening[a]	%R^2 (CI) change[b]	Baseline[a]	Second screening[a]	%R^2 (CI) change[b]	Baseline[a]	Second screening[a]	%R^2 (CI) change[b]
Age, years	49.3 (2.8)	57.3 (2.8)	–	60.0 (2.7)	68.0 (2.7)	–	65.5 (0.5)	73.5 (0.5)	–
NORRISK 2	4.1 (2.7)	6.8 (3.4)	–	8.9 (4.1)	12.9 (4.4)	–	12.1 (4.6)	17.3 (5.2)	–
NORRISK 2 with baseline age[c]	4.1 (2.7)	3.8 (2.5)	–	8.9 (4.1)	7.8 (3.6)	–	12.1 (4.6)	10.8 (4.6)	–
Total cholesterol, mmol/L	5.8 (1.0)	5.6 (0.9)	25.3 (21.6, 29.1)	5.7 (1.0)	5.4 (1.0)	14.5 (12.3, 17.1)	5.5 (1.0)	5.2 (1.0)	8.7 (5.0, 14.1)
Low HDL cholesterol[f]	12.5 (97)	9.9 (77)	3.7 (2.5, 5.3)	7.4 (78)	7.3 (76)	5.1 (3.6, 6.9)	7.0 (14)	8.0 (16)	4.1 (1.6, 9.3)
Systolic blood pressure, mmHg	131.2 (16.1)	132.0 (16,7)	34.7 (30.7, 38.6)	139.9 (19.4)	138.8 (18.9)	35.6 (32.6, 38.9)	144.0 (20.6)	140.9 (19.3)	38.5 (29.9, 46.3)
Antihypertensives	9.9 (77)	21.4 (166)	11.9 (9.3, 15.0)	23.6 (247)	42.3 (443)	21.5 (19.3, 24.0)	30.7 (61)	54.3 (108)	29.5 (24.1, 34.4)
One relative with CHD	17.5 (136)	19.6 (152)	3.3 (2.1, 5.0)	15.3 (160)	18.6 (195)	6.0 (4.4, 7.9)	15.1 (30)	19.6 (39)	8.9 (4.5, 15.3)
Two or more relatives with CHD	1.3 (10)	3.6 (28)	2.8 (1.4, 4.6)	1.1 (11)	2.3 (24)	4.3 (2.6, 6.2)	0.5 (1)	2.0 (4)	–[e]
Daily smoking	18.3 (142)	13.4 (104)	18.1 (14.3, 22.0)	16.0 (168)	9.5 (99)	12.7 (10.1, 15.3)	15.1 (30)	9.6 (19)	9.5 (5.0, 15.5)

[a]Values are mean (SD) or per cent (number).
[b]Percentage R^2 (95% CI), relative contribution for change in NORRISK 2 score between baseline and second screening using Shapley value.
[c]NORRISK 2 calculations performed with baseline age at second screening.
[d]Cut-off value for low HDL cholesterol for women: < 1.3 mmol/L.
[e]Not in the model due to multicollinearity.
[f]Cut-off value for low cholesterol for men: < 1.0 mmol/L.
CHD: coronary heart disease; CI: confidence interval; HDL: high-density lipoprotein

prevalence of daily smoking was greater among men than women. Overall, there was no sex difference in change in total cholesterol.

Table 2 shows the relative contribution of each risk factor to the total NORRISK 2 score (as $\%R^2$). In both surveys age, systolic blood pressure, smoking and total cholesterol were the main contributors to the score in both surveys; however, age contributed more in the first survey compared with the second survey. We found some age and sex differences in the contribution of risk factors, where in both surveys total cholesterol explained more of the variation among the youngest age-groups and more for men than women, where in the youngest age-group total cholesterol explained about 5% for women and 25% for men. Daily smoking explained more of the variation in the youngest age-groups, but more for women than men, where daily smoking explained about 35% of the score for women and 20% for men. Overall, we found that systolic blood pressure explained more in the oldest age-groups compared with the youngest, with only minor sex differences. Use of antihypertensives, low HDL cholesterol and family history of CHD explained more of the variation in the score in the oldest age-group, with only minor sex differences.

Longitudinal trends by sex and birth cohorts

Table 3 shows mean NORRISK 2 score and single risk factors included in the score between baseline and second screening, together with the relative importance of change in each risk factor (as $\%R^2$) to the variation of change in NORRISK 2 score, by sex and birth cohorts. For all birth cohorts, the mean NORRISK 2 score increased between baseline and second screening, and the increase was larger in men. When age at baseline was used in NORRISK 2 calculations at second screening, we found a decrease in NORRISK 2 score in both sexes and all birth cohorts. Overall, use of antihypertensive and family history of CHD increased and daily smoking decreased during follow-up in all subgroups, both sexes and all birth cohorts. Total cholesterol decreased during follow-up for all, except for the youngest women. The change in proportion of low HDL cholesterol and mean systolic blood pressure varied between the sexes and birth cohorts.

Overall, change in daily smoking, systolic blood pressure, total cholesterol and use of antihypertensives were the main contributors to explain the total variation in change in NORRISK 2 score during follow-up. We found that daily smoking explained more of the total variation for the youngest birth cohort and for women, where daily smoking contributed 44% for change in NORRISK 2 score for women, and 18% for men. Change in systolic blood pressure contributed more to the change in score in the oldest birth cohorts, and explained 10% more among women in the oldest birth cohort compared with men. Change in total cholesterol contributed more to the change in risk score for the oldest birth cohorts among women, while this was the opposite in men. In the youngest birth cohort change in total cholesterol explained 6% for women, and 25% for men. Use of antihypertensives contributed more to change in NORRISK 2 score during follow-up for the oldest than for the youngest birth cohorts, and more for men than women.

Discussion

In this study of secular and longitudinal trends in total CVD risk as well as single CVD risk factors, we found a significant decrease in risk over time in both sexes, all age-groups and birth cohorts. The impact of single risk factor to the total score differed by sex, age and birth cohorts.

Change in cardiovascular risk – secular trends

The proportion of participants at high risk at the latest survey was lower than reported in other recent European studies.[15,16] A study using SCORE to predict 10-year risk of CVD in a general population in Germany aged 40–69 years, 22% of the women and 67% of the men in age-group 65–69 years were at high risk of CVD,[15] as compared with 9% of the women and 33% of the men in our analyses. However, in the German study,[15] participants with additional comorbidities were defined as high risk subjects regardless of the SCORE value, which makes comparison with NORRISK 2 challenging. In an Italian study using the CUORE equation (an Italian multivariate risk assessment tool), 10-year risk showed an overall prevalence of high risk of 16%, where 32% of men and 2% of women were at high risk,[16] a gender difference similar to our findings.

The observed decline in mean NORRISK 2 scores between 2007–2008 and 2015–2016, and a change from high to lower risk, is in line with findings from the USA and Europe using various risk assessment tools.[17,18] A US study using the Framingham Risk Score found a reduction in mean 10-year risk of CVD from 9.2% to 8.7% between 1999 and 2010, among those of 30–74 years,[17] with a larger decline in risk score and proportion of change from high to low risk in men than women. Similarly, a study from England reported a decrease in high risk (QRISK2 > 20%) of 2.4% and 6.8%, and medium risk (QRISK2 ≥ 10%) of 3.2% and 5.3%, in 10-year risk of CVD per decade during 1994–2013, for women and men, respectively.[18] We found increasing age and male sex to be persistently

associated with higher risk. A previous analysis from the Tromsø Study showed that men had twice the risk of MI compared with women after adjustment for traditional risk factors, a gender gap that persisted throughout life, although women's risk also increased steadily with age.[19]

The reduction in total cholesterol, blood pressure and smoking are consistent with findings from international studies.[20,21] There has been a substantial decline in systolic blood pressure[22] and total cholesterol[23] in both sexes, all age-groups and birth cohorts in the Tromsø Study during the last 40 years, partially explained by an increased use of antihypertensive medication[22] and lipid-lowering drugs,[23] or the latter particularly important for the decrease in the older birth cohorts.[23] Further, there has been a substantial reduction in smoking,[13] driven by the Norwegian national strategy for tobacco control.[24] The decline in these major risk factors is the major contributor to the observed decline in CHD in this population.[13]

Overall, systolic blood pressure, total cholesterol and smoking status were the most important contributors to the NORRISK 2 score. The observed sex differences of total cholesterol contributing more to the score for men, and smoking more to the score for women, can be explained by the difference in how each risk factor is weighted in the algorithm, which is based on an analysis of a large population-based study (Cohort of Norway; CONOR) linked to 'Cardiovascular disease in Norway' (CVDNOR).[10] Further, more women than men were smokers, which also contributes to explaining the observed sex differences in contribution to change in NORRISK 2 score.

Change in cardiovascular risk – longitudinal trends

In the longitudinal analysis, we found that mean NORRISK 2 increased between the screenings for both sexes and all birth cohorts, as older compared with younger and men compared with women had higher baseline risk and larger increase in risk score over time. A follow-up of EPIC Norfolk Study participants using the Framingham Risk Score reported a 2% increase in 10-year risk of CVD in a median of four years.[25] A Dutch cohort study with baseline measurements in 1987–1991 and follow-up in 1998–2002 found that 42% stayed at high risk or worsened their risk during follow-up.[26] An increase in risk can be explained by increasing age during follow-up. In our study when age was set to baseline, we found a decrease in risk of CVD in both sexes and all birth cohorts, demonstrating the effect of reduction in modifiable risk factors.

Similar to the analysis of secular trends, we found total cholesterol, systolic blood pressure, use of antihypertensives and smoking to be the major contributors to the change in risk score. Total cholesterol decreased during follow-up in birth cohorts except among the youngest women, which could be explained by use of lipid lowering drugs among men and older age-groups. We found variation in change in systolic blood pressure between the sexes, where men had a more favourable overall change during follow-up. In an English cohort study with a 10-year follow-up from 1989 to 1999, similar to our findings, total cholesterol decreased among men in both low and high risk groups, while in women total cholesterol decreased only in the high risk group and increased for women at low risk.[27] Similar to our findings, where we found that more women than men stopped smoking during follow-up, the prevalence of being a daily smoker was, however, higher among women than men.

Cardiovascular risk scoring

A Cochrane review found that using CVD risk scoring in primary prevention care increased the use of antihypertensives and lipid-lowering drugs, and contributed to favourable changes in modifiable risk factors, but also highlighted the need for high-quality evidence to determine whether this improves CVD outcomes.[28] The use of risk assessment tools in primary prevention is, however, not without limitations. Using scores without age-differentiation can be misleading, as a limitation of risk assessment tools are that they assume the effect of risk factors to be constant, despite increase in age.[29] European guidelines for CVD prevention are based on the 10-year risk of death of CVD with the same threshold for high risk in all age-groups.[4] Age is an independent risk factor for CVD; however, it has been argued that the contribution of age reflects the effect of duration of other major CVD risk factors,[30] emphasizing the importance of starting interventions and treatment earlier for younger individuals at high risk. This issue has been addressed in the development of the NORRISK 2 score by using age-specific thresholds for high, medium and low CVD risk.[10]

Strengths and limitations

A major strength of this study is the possibility to investigate both secular and longitudinal trends in the same individuals in a population-based sample. Data sources include validated endpoints, all measurements were performed by trained personnel using standardized protocols and instruments, and brand names of medication used reported by participants were validated against the Norwegian prescription database. Further, the NORRISK 2 scoring tool has been validated by using a Norwegian population sample and can accurately be used in estimating risk in this population.

A strength of the NORRISK 2 score is the age-specific thresholds to determine whether participants are at low, medium or high CVD risk. A limitation is that several well-known CVD risk factors, such as lipid-lowering drugs and diabetes diagnosis, are not included in the score. A limitation of the present study is the challenge to compare the results with previous studies, as various scoring tools use different cut-off values, thus, comparison of results should be done with caution. A general limitation is that individuals who participate in cohort studies are generally healthier than non-participants, thus there is a potential selection bias.

Conclusion

Risk assessment tools are meant to be used to identify high risk individuals in primary care. We used a newly developed risk score to study secular and longitudinal trends in CVD risk in a Norwegian general population. We found a decline in overall risk score and a reduced proportion of individuals being in high risk during the last decade, explained by favourable changes in modifiable risk factors. Total cholesterol had a larger impact on the total score in men than in women, whereas smoking was the major single risk factor in women.

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Author contribution

LAH and AN contributed to the conception and design of the work. AEE, MLL, IN and TW contributed to the data acquisition, AN and TW contributed to the data analysis, and all authors contributed to the interpretation of the work. AN drafted the manuscript. TAH, KTL, AEE, MLL, IN, TW and LAH critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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References

1. Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation* 2015; 132: 1667–1678.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* 2004; 364: 937–952.
3. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2935–2959.
4. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016; 23: NP1–NP96.
5. Kannel WB, McGee D and Gordon T. A general cardiovascular risk profile: The Framingham Study. *Am J Cardiol* 1976; 38: 46–51.
6. Assmann G, Cullen P and Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation* 2002; 105: 310–315.
7. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J* 2003; 24: 987–1003.
8. World Health Organization. Prevention of cardiovascular disease: Guidelines for assessment and management of total cardiovascular risk, http://apps.who.int/iris/bitstream/handle/10665/43685/9789241547178_eng.pdf (2007, accessed 6 February 2019).
9. Hippisley-Cox J, Coupland C and Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: Prospective cohort study. *BMJ* 2017; 357: j2099.
10. Selmer R, Igland J, Ariansen I, et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. *Eur J Prev Cardiol* 2017; 24: 773–782.
11. The Tromsø study. The Tromsø study, www.tromsoundersokelsen.no (2019, accessed 6 February 2019).
12. Niemela MKS, Joseph B, Saarela O, et.al. Ascertainment of first-ever fatal or nonfatal MI followed a detailed protocol according to a slightly modified version of the WHO MONICA/MORGAM protocol 2009, https://thl.fi/publications/morgam/qa/followup/followup.htm#CE_diagnosis (2007, accessed 6 February 2019).
13. Mannsverk J, Wilsgaard T, Mathiesen EB, et al. Trends in modifiable risk factors are associated with declining incidence of hospitalized and nonhospitalized acute coronary heart disease in a population. *Circulation* 2016; 133: 74–81.
14. Shapley LS. A value for N-person games. In: Kuhn HW and Tucker AW (eds) *The theory of games (Vol. 2) Annals of mathematical studies*. Princeton: Princeton University Press, 1953, pp.307–317.

15. Diederichs C, Neuhauser H, Rucker V, et al. Predicted 10-year risk of cardiovascular mortality in the 40 to 69 year old general population without cardiovascular diseases in Germany. *PLoS One* 2018; 13: e0190441.
16. Di Castelnuovo A, Costanzo S, Persichillo M, et al. Distribution of short and lifetime risks for cardiovascular disease in Italians. *Eur J Prev Cardiol* 2012; 19: 723–730.
17. Ford ES. Trends in predicted 10-year risk of coronary heart disease and cardiovascular disease among U.S. adults from 1999 to 2010. *J Am Coll Cardiol* 2013; 61: 2249–2252.
18. Alageel S, Wright AJ and Gulliford MC. Changes in cardiovascular disease risk and behavioural risk factors before the introduction of a health check programme in England. *Prev Med* 2016; 91: 158–163.
19. Albrektsen G, Heuch I, Lochen ML, et al. Lifelong gender gap in risk of incident myocardial infarction: The Tromso Study. *JAMA Intern Med* 2016; 176: 1673–1679.
20. Farzadfar F, Finucane MM, Danaei G, et al. National, regional, and global trends in serum total cholesterol since 1980: Systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet* 2011; 377: 578–586.
21. NCDRF Collaboration. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389: 37–55.
22. Hopstock LA, Bonaa KH, Eggen AE, et al. Longitudinal and secular trends in blood pressure among women and men in birth cohorts born between 1905 and 1977: The Tromso Study 1979 to 2008. *Hypertension* 2015; 66: 496–501.
23. Hopstock LA, Bonaa KH, Eggen AE, et al. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905–1977 in the population-based Tromso Study 1979–2016. *BMJ Open* 2017; 7: e015001.
24. Halkjelsvik T, Lund KE, Kraft P, et al. Fear appeals in advanced tobacco control environments: The impact of a national mass media campaign in Norway. *Health Educ Res* 2013; 28: 888–897.
25. Chamnan P, Simmons RK, Sharp SJ, et al. Repeat cardiovascular risk assessment after four years: Is there improvement in risk prediction? *PLoS One* 2016; 11: e0147417.
26. Hulsegge G, Smit HA, van der Schouw YT, et al. Quantifying the benefits of achieving or maintaining long-term low risk profile for cardiovascular disease: The Doetinchem Cohort Study. *Eur J Prev Cardiol* 2015; 22: 1307–1316.
27. McCluskey S, Baker D, Percy D, et al. Reductions in cardiovascular risk in association with population screening: A 10-year longitudinal study. *J Public Health* 2007; 29: 379–387.
28. Karmali KN, Persell SD, Perel P, et al. Risk scoring for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017; 3: CD006887.
29. Cooney MT, Dudina AL and Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: A review for clinicians. *J Am Coll Cardiol* 2009; 54: 1209–1227.
30. Sniderman AD and Furberg CD. Age as a modifiable risk factor for cardiovascular disease. *Lancet* 2008; 371: 1547–1549.

Paper II

openheart

Change in cardiovascular risk assessment tool and updated Norwegian guidelines for cardiovascular disease in primary prevention increase the population proportion at risk: the Tromsø Study 2015–2016

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ABSTRACT

Aims To compare the population proportion at high risk of cardiovascular disease (CVD) using the Norwegian NORRISK 1 that predicts 10-year risk of CVD mortality and the Norwegian national guidelines from 2009, with the updated NORRISK 2 that predicts 10-year risk of both fatal and non-fatal risk of CVD and the Norwegian national guidelines from 2017.

Methods We included participants from the Norwegian population-based Tromsø Study (2015–2016) aged 40–69 years without a history of CVD (n=16 566). The total proportion eligible for intervention was identified by NORRISK 1 and the 2009 guidelines (serum total cholesterol ≥8 mmol/L, systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) and NORRISK 2 and the 2017 guidelines (serum total cholesterol ≥7 mmol/L, low density lipoprotein (LDL) cholesterol ≥5 mmol/L, systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg).

Results The total proportion at high risk as defined by a risk score was 12.0% using NORRISK 1 and 9.8% using NORRISK 2. When including single risk factors specified by the guidelines, the total proportion eligible for intervention was 15.5% using NORRISK 1 and the 2009 guidelines and 18.9% using NORRISK 2 and the 2017 guidelines. The lowered threshold for total cholesterol and specified cut-off for LDL cholesterol stand for a large proportion of the increase in population at risk.

Conclusion The population proportion eligible for intervention increased by 3.4 percentage points from 2009 to 2017 using the revised NORRISK 2 score and guidelines.

Key questions

What is already known about this subject?

- Risk assessment tools and primary prevention guidelines for cardiovascular disease are used to identify individuals eligible for preventive interventions.
- There is a need to balance risk of overtreatment, healthcare cost and potential side effects versus undertreatment.

What does this study add?

- We demonstrate how change of cardiovascular risk assessment tool and updated guidelines increase the population proportion eligible for preventive interventions.

How might this impact on clinical practice?

- New insights into the impact of risk assessment scoring to identify individuals at risk and accurate estimates of the proportion of the total population at risk are essential for health authorities to target interventions.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death and disability worldwide and an economic burden for the society, thereby calling for an active preventive approach.[1] Cardiovascular risk prediction tools have been developed to objectively estimate risk and to guide clinical decision-making on initiating, intensifying or discontinuing medical treatment for CVD primary prevention.[2] The Framingham Risk Score, developed from the Framingham Heart Study in the USA, was the first and most broadly used risk score, and several other risk scores have been developed later.[3] The European guidelines for CVD primary prevention included the Framingham Risk Score in 1994 and 1998,[4 5] but studies found the risk score to overestimate risk in European populations.[6 7] The Systematic Coronary Risk Evaluation (SCORE) risk chart was developed from European cohort studies, and separate

risk charts have been developed for low-risk and high-risk regions in Europe.[8] CVD primary prevention guidelines highlight the use of cardiovascular risk assessment tools to identify high-risk individuals and to indicate when to start treatment, through risk assessment scoring and treatment guidelines for single risk factors.[9 10] In Norway, the 2009 guidelines for CVD primary prevention[11] recommended the use of a risk assessment tool to identify high-risk individuals and proposed NORRISK 1, a national calibrated variant of the SCORE prediction model to predict 10-year risk of fatal CVD.[12] The guideline revision in 2017[13] recommended the updated risk assessment tool NORRISK 2 to predict 10-year risk of both fatal and non-fatal CVD.[14]

Guideline updates will change the definition of the population at risk. Lowering the threshold for defining individuals at high risk and eligible for primary prevention of CVD causes a larger proportion of individuals in need of lifestyle changes and potentially drug treatment with antihypertensives and/or lipid-lowering drugs. However, a change in threshold can also result in the potential of preventing more fatal and non-fatal events of CVD. There is a need for balancing between the risk of undertreatment with risk of disease or death and overtreatment, medication-related side effects, financial cost and healthcare priorities.[15–17] The aim of this study was to compare the population proportion at risk and eligibility for intervention as defined by NORRISK 1 and the Norwegian national guidelines from 2009 with NORRISK 2 and the national guidelines from 2017 using a Norwegian population-based sample.

METHODS

Study population

The Tromsø Study is an ongoing population-based cohort study in the municipality of Tromsø, Northern Norway. The study includes seven surveys conducted between 1974 and 2016 (Tromsø 1–7). Both total birth cohorts and representative samples of the population have been invited, and a total of 45 473 women and men have participated in one or more surveys (attendance 65%–79%).[18] Data collection includes questionnaires, interviews, biological sampling and clinical examinations. In this study, we included participants from Tromsø 7 (2015–2016), to which all inhabitants aged 40 years or older (n=32 591) were invited, and 21 083 women and men participated (65%). We excluded participants 70 years and older (n=3437), those with previous myocardial infarction (MI) or stroke (n=704) and those without valid data for NORRISK 1 and NORRISK 2 risk calculation (n=376), leaving 16 566 participants for the current analysis. All participants gave written informed consent. The study was approved by the Regional Committee for Medical and Health Research Ethics North (reference 1778/2015).

Case validation

Cases of MI and stroke were recorded and validated from study entry until 31 December 2014 by the Tromsø Study CVD registry and were available for all participants attending Tromsø 7 and one or more of the previous six surveys. Adjudication of hospitalised and out-of-hospital events was performed by an independent end-point committee reviewing medical records and medical notes, autopsy records and death certificates. The national unique 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of MI and stroke were identified by linkage to the discharge diagnosis registry at the University Hospital of North Norway, the only hospital in the area, with search for International Classification of Diseases described in detail elsewhere.[19] Due to the lack of validated endpoints after 2014 and among participants attending Tromsø 7 only, we also used self-reported MI or stroke ('Have you had a heart attack?' and 'Have you had a stroke?') to exclude individuals with previous MI or stroke.

Measurements

Self-reported data on smoking, diabetes, family history of coronary heart disease (CHD) and use of lipid-lowering and antihypertensive medication were collected via questionnaires. For medication use, a combination of a question ('Do you use blood pressure lowering drugs?' and 'Do you use lipid-lowering drugs?') and information from a self-reported written list of brand names of regularly used medication (antihypertensives (ATC codes C02, C03, C07, C08 and C09) and lipid-lowering drugs (ATC code C10) was used. Blood pressure was measured on the right arm of all participants (unless in circumstances where this was not possible) three times at 1 min intervals after 2 min seated rest by a Dinamap ProCare 300 monitor (GE Healthcare, Norway), and the mean of the two final readings was used in the analysis. Non-fasting venous blood samples were collected with standard methods, and the samples were analysed within 48 hours for total, LDL and high density lipoprotein (HDL) cholesterol by enzymatic colorimetric methods (with Roche Diagnostics, Mannheim, Germany) and glycated haemoglobin (HbA1c) by high-performance liquid chromatography (with Tosoh G8, Tosoh Bioscience, San Francisco, USA) at the department of laboratory medicine, University Hospital of North Norway. Trained personnel performed all measurements.

NORRISK 1 and the 2009 guidelines

The multivariable CVD risk assessment tool NORRISK 1 is a Norwegian adaption of the European SCORE model and predicts 10-year risk (%) of death due to atherosclerotic CVD in individuals aged 40–69 years.[12] Together with the Norwegian guidelines from 2009, NORRISK intended to identify high-risk individuals and guide decision-making in CVD primary prevention. The 10-year risk estimation is based on age, sex, systolic blood pressure, serum total cholesterol and daily smoking habits. Additional risk factors HbA1c levels and first-degree family member with a history of premature CHD were used to recalculate risk with specific cut-offs.[11 12] Age-specific thresholds are set to determine need of lifestyle advice and/or therapy with

antihypertensives and/or lipid-lowering drugs, where indication to initiate treatment is set to NORRISK 1 score: 40–49 years score ≥1%, 50–59 years score ≥5% and 60–69 years score ≥10%. The 2009 guideline defined individuals with elevated values of total cholesterol ≥8 mmol/L, systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg to be eligible for intervention regardless of their NORRISK 1 score. In this study, we also calculated the proportion eligible for intervention based on the international definition of hypertension: blood pressure ≥140/90 mm Hg.

NORRISK 2 and the 2017 guidelines

In 2017, the revised national guidelines for CVD prevention were introduced, and an updated and revised risk assessment tool, NORRISK 2, was presented to identify high-risk individuals eligible for intervention.[13] NORRISK 2 predicts the 10-year risk (%) of incident MI and stroke combined, including both non-fatal and fatal events of CHD and stroke. The 10-year risk estimation is based on age, sex, systolic blood pressure, serum total cholesterol, daily smoking habits, first-degree family member with a history of premature MI (before the age of 60 years), low serum HDL cholesterol based on sex specific cut-off values (1.0 mmol/L in men and 1.3 mmol/L in women) and use of antihypertensives (where current use increases the score). Selmer *et al*[14] suggest age-specific thresholds in age groups 45–54, 55–64 and 65–74 years to determine whether an individual is at low, medium or high risk of CVD. Elevated values on single risk factors, that is, serum total cholesterol ≥7 mmol/L, LDL cholesterol ≥5 mmol/L (does not apply for women over 50 years), systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg, identify individuals eligible for intervention regardless of the NORRISK 2 score. In addition, in individuals with diabetes, LDL cholesterol ≥2.5 mmol/L and blood pressure ≥140/90 mm Hg indicate eligibility for intervention.[16] In this study, we also calculated the proportion eligible for intervention by the international definition of hypertension: blood pressure ≥140/90 mm Hg. Additional risk factors (South Asian ethnicity and diagnosis of rheumatoid arthritis) can be used to recalculate the risk score, with specific cut-offs. Abdominal obesity, mental strain and stress are additional risk factors without a specific cut-off value.[13] In this study, we did not use the proposed additional risk factors to recalculate the NORRISK 2 score.

Statistics

We calculated means and proportions of cardiovascular risk factors and sociodemographic factors including self-reported education and cardiovascular risk including measured body mass index (BMI) (normal, overweight and obesity defined as <25, 25–29.9 and 30 kg/m^2, respectively) and waist circumference (obesity defined as ≥88 and≥102 cm in women and men, respectively) and self-reported current diabetes and physical activity level to present study population characteristics (table 1). We calculated the proportion of participants eligible for intervention according to NORRISK 1 and the 2009 guidelines and NORRISK 2 and the 2017 guidelines (table 2), overall and stratified by sex and age groups. In addition, we calculated the proportion eligible for intervention using NORRISK 1 without the additional risk factors HbA1c level and family history of premature CHD (online supplemental table 1). We also recalculated the proportion in need of intervention with systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg as cut-off (online supplemental table 2). To compare sex differences, we used t-tests for continuous variables and χ^2 tests for categorical variables and McNemar test for pairwise data comparing differences in risk score. Results were considered statistically significant when a p value less than 5% was attained. To visualise the overlap of high-risk participants defined by NORRISK 1 and NORRISK 2 scores, as well as risk score with additional risk factors from the concurrent guidelines, we present area-proportional Venn diagrams (figure 1), overall and by sex. All analyses were performed using Stata V.16 (StataCorp, 2019; Stata Statistical Software).

RESULTS

Study population and CVD risk factors

Study population characteristics are presented in table 1. Mean age was 53 years for both sexes. Compared with women, men had higher LDL cholesterol, blood pressure, prevalence of obesity (BMI >30 kg/m^2), diabetes, sedentary lifestyle and use of lipid-lowering drugs and antihypertensives but lower HDL cholesterol, prevalence of smoking, abdominal obesity and a lower proportion with higher education.

NORRISK 1 versus NORRISK 2

The total proportion at high risk (ie, eligible for intervention) defined by risk score only was 12.0% for NORRISK 1 and 9.8% for NORRISK 2 (table 2). The proportion of high-risk individuals using NORRISK 1 was 8.6% calculated without the additional risk factors HbA1c and family history (online supplemental table 1). In all age groups, a higher proportion of men than women was defined as high-risk individuals (p<0.001) (table 2). Among men aged 40–49 years, a larger proportion was identified as high risk using NORRISK 1 compared with NORRISK 2 (p<0.001), whereas in men aged 50–59 years, more men were identified as high risk using NORRISK 2 (p<0.001).

Total proportion eligible for intervention

The total proportion eligible for intervention identified by risk score or elevated values for single CVD risk factors was 3.4 percentage points higher using NORRISK 2 and the 2017 guidelines compared with NORRISK 1 and the 2009 guidelines (18.9% vs 15.5%). The total proportion eligible for intervention was higher using NORRISK 2 and the 2017 guidelines in both sexes and all age groups, except among men aged 40–49 years (table 2). In women, the proportion eligible for intervention increased by 3.0 percentage

Table 1 Characteristics of study participants by sex and age groups. The Tromsø Study 2015–2016

		Women				Men			
	Overall n=16 566	Overall n=8896	40–49 years n=3286	50–59 years n=3115	60–69 years n=2495	Overall n=7670	40–49 years n=2943	50–59 years n=2579	60–69 years n=2148
Age, years	53.4 (8.4)	53.5 (8.4)	44.5 (2.8)	54.3 (2.9)	64.2 (2.9)	53.4 (8.4)	44.6 (2.8)	54.4 (2.9)	64.3 (2.8)
Total cholesterol, mmol/L	5.5 (1.0)	5.5 (1.0)	5.1 (0.9)	5.7 (1.0)	5.9 (1.0)	5.5 (1.0)	5.5 (1.0)	5.6 (1.0)	5.5 (1.0)
LDL cholesterol, mmol/L	3.6 (1.0)	3.6 (1.0)	3.2 (0.9)	3.7 (0.9)	3.8 (1.0)	3.7 (0.9	3.7 (0.9)	3.9 (0.9)	3.7 (0.9)
HDL cholesterol, mmol/L	1.6 (0.5)	1.7 (0.5)	1.6 (0.4)	1.7 (0.5)	1.8 (0.5)	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)	1.5 (0.4)
Use of lipid-lowering drugs, % (n)	8.5 (1409)	7.9 (706)	1.5 (49)	6.9 (214)	17.8 (443)	9.2 (703)	3.6 (106)	8.5 (219)	17.6 (378)
Systolic blood pressure, mm Hg	126.8 (18.3)	123.3 (18.6)	116.5 (14.6)	123.0 (17.6)	132.6 (20.5)	130.9 (17.1)	126.8 (14.8)	131.0 (17.1)	136.5 (18.3)
Diastolic blood pressure, mm Hg	75.5 (10.1)	72.6 (9.6)	71.2 (9.3)	73.3 (9.7)	73.7 (9.7)	78.9 (9.6)	77.5 (9.4)	79.9 (9.8)	79.7 (9.5)
Use of antihypertensives, % (n)	16.7 (2761)	15.6 (1384)	6.8 (223)	14.5 (451)	28.5 (710)	18.0 (1377)	7.3 (216)	16.0 (412)	34.9 (749)
Current smoking, % (n)	14.7 (2435)	15.3 (1364)	12.7 (417)	18.0 (560)	15.5 (387)	14.0 (1071)	12.7 (373)	15.8 (408)	13.5 (290)
HbA1c, %	5.6 (0.6)	5.6 (0.5)	5.4 (0.5)	5.6 (0.6)	5.7 (0.5)	5.7 (0.6)	5.5 (0.6)	5.7 (0.6)	5.8 (0.7)
Diabetes, % (n)	3.6 (598)	3.1 (279)	2.0 (67)	2.9 (90)	4.9 (122)	4.2 (319)	2.4 (70)	4.2 (108)	6.6 (141)
Body mass index, % (n)									
Normal (<25 kg/m^2)	33.6 (5548)	42.0 (3729)	44.4 (1457)	42.1 (1310)	38.7 (962)	23.8 (1819)	22.7 (668)	23.5 (606)	25.4 (545)
Overweight (25–29.9 kg/m^2)	43.1 (7117)	36.2 (3204)	32.6 (1070)	36.7 (1141)	39.9 (993)	51.1 (3913)	50.4 (1479)	51.9 (1337)	51.2 (1097)
Obese (>30 kg/m^2)	23.4 (3868)	21.9 (1943)	23.0 (753)	21.2 (659)	21.4 (531)	25.1 (1925)	26.9 (790)	24.6 (635)	23.3 (500)
Abdominal obesity*, % (n)	47.6 (7888)	54.0 (4804)	49.0 (1611)	54.6 (1700)	59.8 (1493)	40.2 (3084)	38.3 (1127)	40.4 (1043)	42.6 (914)
Sedentary leisure time physical activity level, %, (n)	13.7 (2232)	12.6 (1097)	13.8 (448)	11.8 (362)	11.9 (287)	15.0 (1135)	16.2 (471)	13.8 (352)	14.8 (312)
Education, % (n)									
Primary	18.3 (3004)	17.7 (1567)	7.3 (240)	17.0 (526)	32.5 (801)	18.9 (1437)	11.8 (347)	19.6 (501)	27.7 (589)
High school	28.1 (4628)	25.9 (2285)	23.4 (766)	27.9 (864)	26.6 (655)	30.8 (2343)	31.6 (926)	32.6 (833)	27.5 (584)
College/university <4 years	20.4 (3360)	19.2 (1691)	21.8 (711)	19.8 (614)	14.8 (366)	21.9 (1669)	22.0 (645)	22.6 (577)	21.0 (447)
College/university ≥4 years	33.2 (5455)	37.2 (3288)	47.5 (1552)	35.3 (1091)	26.2 (645)	28.5 (2167)	34.7 (1017)	25.2 (644)	23.8 (506)

Values are means (SD) and percent (numbers).
*Men ≥102 cm women ≥88 cm.
HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2 Proportion (%) of participants eligible for intervention defined by NORRISK 1 and the 2009 guidelines and NORRISK 2 and the 2017 guidelines, separate and in combination as total proportion eligible for intervention, by sex and age group. The Tromsø Study 2015–2016

		Women				Men			
Eligible for intervention	**Total n=16 566**	**Overall n=8896**	**Age group 40–49 n=3286**	**Age group 50–59 n=3115**	**Age group 60–69 n=2495**	**Overall n=7670**	**Age group 40–49 n=2943**	**Age group 50–59 n=2579**	**Age group 60–69 n=2148**
NORRISK 1 high risk, % (n)	12.0 (1987)	2.2 (199)	0.8 (25)	0.4 (12)	6.5 (162)	23.3 (1788)	26.9 (791)	12.4 (320)	31.5 (677)
NORRISK 1 low and elevated single risk factors (2009 guidelines)									
Total cholesterol ≥8 mmol/L, % (n)	1.0 (147)	1.4 (120)	0.4 (13)	1.8 (57)	2.1 (50)	0.5 (27)	0.4 (8)	0.7 (16)	0.2 (3)
Systolic blood pressure ≥160 mm Hg, % (n)	2.7 (397)	3.3 (283)	0.9 (29)	3.2 (98)	6.7 (156)	1.9 (114)	0.5 (10)	3.0 (67)	2.5 (37)
Diastolic blood pressure ≥100 mm Hg, % (n)	0.7 (98)	0.4 (37)	0.3 (11)	0.5 (16)	0.4 (10)	1.0 (61)	0.3 (6)	1.9 (42)	0.9 (13)
Total proportion eligible for intervention (NORRISK 1 and/or single risk factors), % (n)	15.5 (2570)	6.8 (607)	2.1 (70)	5.5 (170)	14.7 (367)	25.6 (1963)	27.6 (813)	16.6 (427)	33.7 (723)
NORRISK 2 high risk, % (n)	9.8 (1621)	2.4 (217)	0.2 (5)	2.5 (77)	5.4 (135)	18.3 (1404)	7.5 (221)	23.5 (605)	26.9 (578)
NORRISK 2 low and elevated single risk factors (2017 guidelines)									
Total cholesterol ≥7 mmol/L*, % (n)	2.8 (414)	1.2 (100)	3.1 (100)	*	*	5.0 (314)	5.8 (159)	5.0 (99)	3.6 (56)
LDL cholesterol ≥5 mmol/L*, % (n)	3.6 (535)	1.3 (112)	3.4 (112)	*	*	6.8 (423)	7.3 (198)	7.2 (143)	5.2 (82)
Systolic blood pressure ≥160 mm Hg, % (n)	3.1 (470)	3.5 (302)	1.0 (33)	2.8 (85)	7.8 (184)	2.7 (168)	1.8 (48)	2.3 (46)	4.7 (74)
Diastolic blood pressure ≥100 mm Hg, % (n)	0.6 (95)	0.4 (34)	0.4 (14)	0.4 (11)	0.4 (9)	1.0 (61)	0.9 (24)	0.9 (18)	1.2 (19)
Diabetes and LDL cholesterol >2.5 mmol/L, % (n)	2.7 (399)	2.5 (213)	1.7 (54)	2.3 (70)	3.8 (89)	3.0 (186)	1.8 (50)	3.2 (63)	4.7 (73)
Diabetes and blood pressure ≥140/90 mm Hg, % (n)	0.9 (140)	0.9 (76)	0.3 (10)	0.8 (24)	1.8 (42)	1.0 (64)	0.4 (10)	0.8 (15)	2.5 (39)
Total proportion eligible for intervention (NORRISK 2 and/or single risk factors), % (n)	18.9 (3122)	9.8 (871)	6.9 (227)	7.5 (233)	16.5 (411)	29.4 (2251)	18.6 (548)	34.2 (881)	38.3 (822)

Values are percentages (numbers).
*Indication to start intervention at total cholesterol concentration ≥7 mmol/L and LDL cholesterol ≥5 mmol/L does not apply for women >50 years.
LDL, low density lipoprotein.

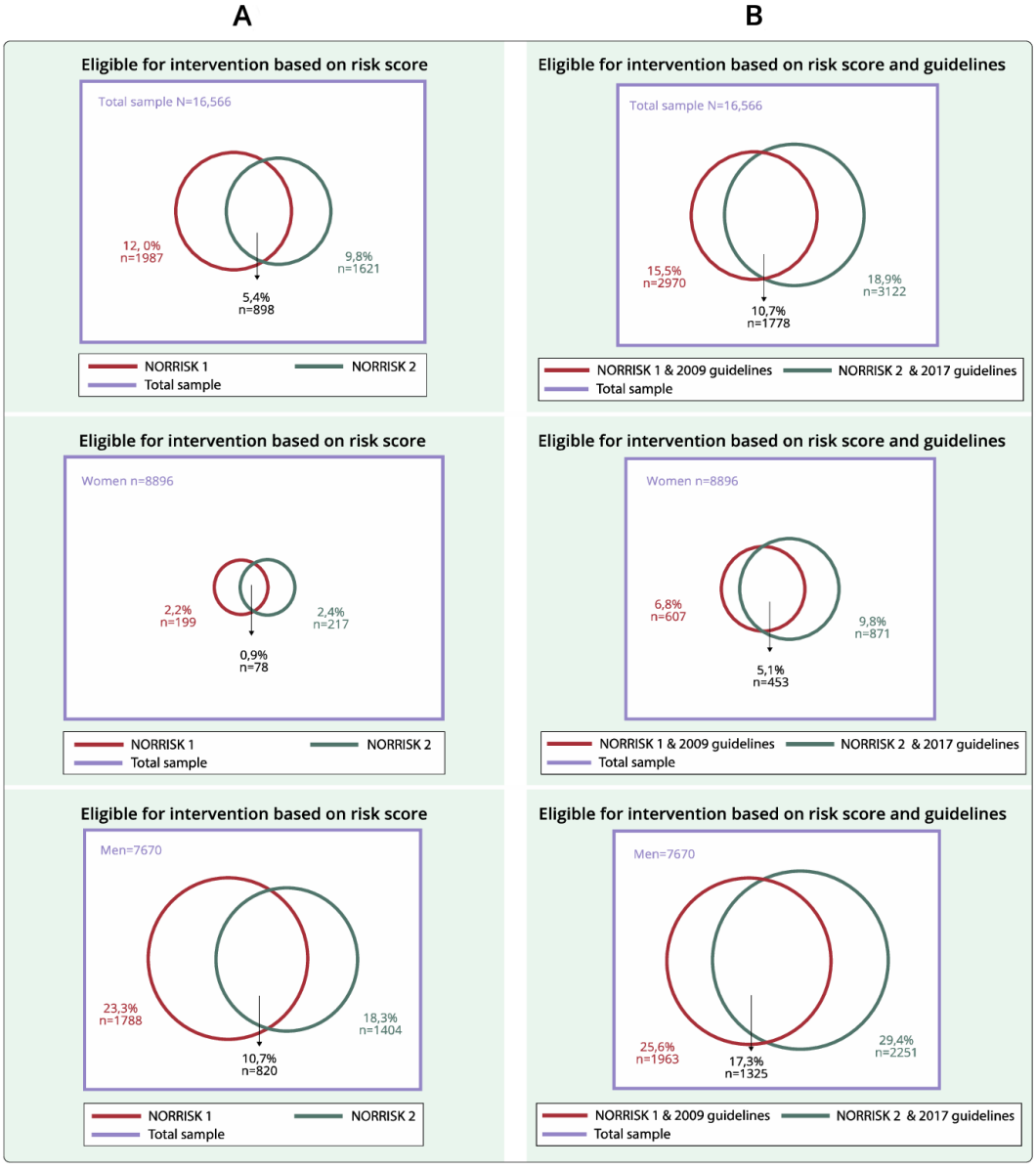

Figure 1 Venn diagram presenting the overlap of identification of high-risk participants defined by NORRISK 1 (red circle) and NORRISK 2 (green circle) in the total sample (purple square) (panel A) and NORRISK 1 and NORRISK 2 combined with single risk factors in 2009 (red circle) and 2017 (green circle) guidelines in the sample (purple square) (panel B) by sex. The Tromsø Study 2015–2016.

points from 6.8% to 9.8%, and the increase among men was 3.8 percentage points from 25.6% to 29.4% by NORRISK 1 and the 2009 guidelines, compared with NORRISK 2 and the 2017 guidelines, respectively. Overall, participants defined as being at low risk by risk score were to a greater extent identified as eligible for intervention by single risk factors when using the 2017 guidelines compared with the 2009 guidelines. This was due to change in the cut-off value for serum total cholesterol and the introduction of a specified value for LDL cholesterol. One percent of the participants with low risk by NORRISK 1 had total cholesterol above the threshold of ≥8 mmol/L, whereas the lowering of the threshold in the 2017 guideline to ≥7 mmol/L increased the proportion to 2.8% in individuals with low risk by NORRISK 2. Specifying a threshold for LDL cholesterol to ≥5 mmol/L in the 2017 guideline identified 3.6% individuals above threshold among individuals identified as low risk by NORRISK 2. Among participants defined as being at low risk by NORRISK 1, systolic blood pressure identified an additional 2.7% of the study population as high risk with the 2009 guideline, and 3.1% of participants defined as low risk by NORRISK 2 were identified as being at high risk by the 2017 guidelines. When including the diabetes-specific threshold in the 2017 guidelines for those with self-reported diabetes, 2.7% had LDL cholesterol ≥2.5 mmol/L, and 0.9% had blood pressure ≥140/90 mm Hg but were defined as low risk by NORRISK 2. A larger proportion of women compared with men was identified as eligible for intervention by single risk factors only using the 2009 guidelines, while applying single risk factors only to the 2017 guidelines identified a

higher proportion of men than women eligible for intervention. When we recalculated the total proportion eligible for intervention based on systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg, we found 29.3% based on NORRISK 1 and the 2009 guidelines and 32.4% using NORRISK 2 and the 2017 guidelines (online supplemental table 2).

Overlap between risk scores only and risk scores and the guidelines combined

Among individuals identified as high risk by risk score only, NORRISK 1 identified in total 12.0% (2.2% of women and 23.3% of men) as high risk, while NORRISK 2 identified in total 9.8% (2.4% of women and 18.3% of men) as high risk. The overlapping proportion identified as high risk in both risk scores was in total 5.4% (0.9% of women and 10.7% of men). Combining NORRISK 1 and the 2009 guidelines, 15.5% in total (6.8% women and 25.6% men) was identified as eligible for intervention, while when using NORRISK 2 and the 2017 guidelines, the proportion was 18.9% in total (9.8% women and 29.4% men). Overall, the overlapping proportion of 10.7% (5.1% women and 17.3% men) was identified as eligible for intervention in both risk scores with their respective guidelines (figure 1).

DISCUSSION

In this study, we compared the proportion at high CVD risk and eligible for intervention using two consecutive versions of guidelines and risk assessment tools in a Norwegian general population of women and men aged 40–69 years. The main finding is that the proportion eligible for intervention increased from 15.5% using the risk assessment tool NORRISK 1 and the 2009 guidelines to 18.9% using the revised NORRISK 2 and the 2017 guidelines.

Change in cardiovascular risk assessment tool

The proportion of high-risk individuals defined by risk score only was lower using the updated NORRISK 2 compared with the previous NORRISK 1. This can be explained by the fundamental differences in the risk scores, as they measure different endpoints and thus are not directly comparable. NORRISK 1 predicts 10-year risk of fatal CVD, whereas NORRISK 2 predicts the 10-year risk of MI, stroke and fatal CVD.[12 14] The European guidelines for CVD primary prevention encourage the calibration of risk assessment tools to the target population by adjusting for secular changes in risk factor levels and CVD mortality.[20] A reduction over time in the major CVD risk factors serum total cholesterol, blood pressure and smoking in the general population has been shown both in large international studies[21 22] and in the Tromsø Study population,[19 23 24] and we have previously demonstrated a decline in total CVD risk in the Tromsø Study[25] similar to findings from the UK[26] and the USA.[27] Further, there has been a major decline in mortality and morbidity of CVD in Norway.[28] The reduction in risk factors, morbidity and mortality over time can explain the lower proportion eligible for intervention by the updated risk assessment tool NORRISK 2. NORRISK 1 is a national calibrated version of the European SCORE algorithm, based on national mortality rates from 1993 to 2003, and mean level risk factors from Norwegian Health Surveys from 2000 to 2003,[12] while NORRISK 2 is based on the 10-year follow-up of a large population-based cohort (Cohort of Norway (CONOR)) through linkage to the Cardiovascular Disease in Norway (CVDNOR) project, a database of CVD hospital discharge diagnoses and mortality in Norway in 1994–2009.[14] Another explanation of this finding can be the use of additional risk factors in our analysis, where we included additional risk factors in the calculation of NORRISK 1 (HbA1c levels and family history of CHD) and did not include the additional risk factors (rheumatoid arthritis, South Asian ethnicity, abdominal obesity and/or mental stress) in the calculation of NORRISK 2. A recent study found NORRISK 2 to underestimate CVD risk in South Asians and proposed an update (NORRISK 2-SADia) improving the predictions of 10-year risk in this population.[29] In our study, valid data regarding the proposed additional risk factors with specified cut-offs (ethnicity and diagnosis of rheumatoid arteritis) were not available.[30] Almost half of the study population had abdominal obesity, and in real patient consultations, this could lead to a higher proportion at high risk using NORRISK 2. However, this risk factor is without a multiplication factor and hence not used to calculate the proportion eligible for intervention in this study.

Single risk factors defined in treatment guidelines

In this study, we found that the updated risk score with additional guidelines increased the proportion of participants eligible for intervention, where the decrease in threshold for total cholesterol levels and a defined value of LDL cholesterol stand for a large proportion of this increase. The impact on the risk of CVD by lowering cholesterol levels is well known. A lowering of LDL cholesterol levels by 1 mmol/L corresponds to a 20%–25% reduction in non-fatal MI and death due to CVD.[10] Our findings are in line with a study from Denmark where the authors found that the updated 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines doubled the proportion of individuals eligible for statin therapy compared with the previous guidelines,[31] findings that are similar to other studies.[32 33]

For blood pressure, there was no difference in threshold between the 2009 and 2017 guidelines where systolic blood pressure ≥160 mm Hg and diastolic blood pressure ≥100 mm Hg urge immediate start of pharmacological treatment (regardless of NORRISK score), in line with the European ESC/EAS guidelines.[34] In the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the recommendation is that blood pressure ≥140/90 mm Hg should lead to direct initiation of antihypertensive drugs.[35] Hypertension is defined as blood pressure ≥140/90 mm Hg; however, in Norway, lifestyle modification is encouraged before starting medical treatment. By replacement of blood pressure cut-off from ≥160/100 mm Hg to ≥140/90 mm Hg, we found that the proportion eligible for intervention by NORRISK 1 and the 2009 guidelines increased by

13.8 percentage points, and when using NORRISK 2 and the 2017 guidelines, the proportion eligible for intervention increased by 13.4 percentage points. However, in the important debate regarding treatment target in blood pressure levels in primary prevention, it has been suggested that lifestyle modification should be emphasised to a larger degree before initiating pharmacological treatment.[36]

Combining risk score and additional risk factors

To the best of our knowledge, there have been few previous studies combining both risk score assessment tools and additional guidelines to compare the proportion at risk of CVD and eligibility of intervention in a general population. A study from Germany used the risk assessment tool SCORE Deutschland with additional risk factors (diabetes, total cholesterol ≥8 mmol/L, renal insufficiency and stage 3 hypertension (blood pressure ≥180/110 mm Hg)) and found 13.4% of the study population to be at high risk of 10-year CVD mortality.[37] Interestingly, the authors found that among men, the majority of high-risk individuals were eligible for intervention because of SCORE ≥5%, contrary to women where the majority of women were classified as high risk based on additional risk factors,[37] which is in line with our findings. Other studies have also found that adding comorbidities and single risk factors increases the proportion of individuals at high risk, demonstrating the challenge of comparing our findings with other studies.[38 39]

In conclusion, we found that updated CVD primary prevention guidelines increased the proportion at risk and eligible for intervention by 3.4 percentage points in individuals aged 40–69 years, where the increase was 3.0 percentage points in women and 3.8 percentage points in men. In Norway, there are about 2.1 million inhabitants aged 40–69 years.[40] Therefore, this increase causes almost 70 000 more individuals eligible for intervention using NORRISK 2 and the 2017 guidelines in this age group. Individuals identified to be at high risk and eligible for intervention may be given the opportunity from their primary physician to make necessary lifestyle changes. The guideline[13] suggests that individuals at high risk are given 3–12 months to make changes such as smoking cessation, increased physical activity and dietary changes to lower blood pressure and cholesterol levels before considering initiating drug treatment with antihypertensives and/or lipid-lowering drugs. However, among individuals with very high blood pressure, cholesterol levels or high total risk, drug treatment may be initiated directly. An increase of 3.4 percentage points means a higher number of individuals in need of time from their primary physician to give lifestyle advice, follow up the effect of this advice and assess whether to start drug treatment. Among individuals that start drug treatment, there is a need for follow-up to evaluate drug efficacy and whether treatment targets are achieved, as well as side effects. Change in the guidelines of CVD prevention may lead to a higher burden of the healthcare system, but this also translates into a higher number of individuals who can avoid a fatal or non-fatal event of CVD. The main goal in the use of risk assessment tools is to identify the right individuals to keep the balance between avoiding the potential negative effects such as side effects, overtreatment, undertreatment and a higher cost for the healthcare system on one side and preventing high-risk individuals from developing CVD on the other.[2]

CONCLUSION

The population proportion eligible for intervention increased by 3.4 percentage points from 2009 to 2017 using the revised NORRISK 2 score and guidelines, where the lowering of threshold in total cholesterol and specified cut-off for LDL cholesterol stand for a large proportion of the increase in population at risk.

Strengths and limitations

A strength of this study is the use of a sample from a large population-based study, with validated endpoints for exclusion of prevalent cases and risk factor measurements performed by trained personnel using standardised protocols and instruments. A limitation is that participants in population-based studies in general tend to be healthier than non-attenders. This potential selection bias might cause underestimation of the true population proportion in need of intervention.

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REFERENCES

1 Roth GA, Johnson C, Abajobir A, *et al*. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017;70:1–25.
2 Rossello X, Dorresteijn JA, Janssen A, *et al*. Risk prediction tools in cardiovascular disease prevention: a report from the ESC prevention of CVD programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Prev Cardiol* 2019;26:1534–44.
3 Anderson KM, Odell PM, Wilson PW, *et al*. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–8.
4 Pyörälä K, De Backer G, Graham I, *et al*. Prevention of coronary heart disease in clinical practice. recommendations of the task force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Eur Heart J* 1994;15:121–61.
5 Wood D, De Backer G, Faergeman O, *et al*. Prevention of coronary heart disease in clinical practice: recommendations of the second joint task force of European and other societies on coronary prevention. *Atherosclerosis* 1998;140:199–270.
6 Bastuji-Garin S, Deverly A, Moyse D, *et al*. The Framingham prediction rule is not valid in a European population of treated hypertensive patients. *J Hypertens* 2002;20:1973–80.
7 Emberson J, Whincup P, Morris R, *et al*. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. *Eur Heart J* 2004;25:484–91.
8 Conroy RM, Pyörälä K, Fitzgerald AP, *et al*. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987–1003.
9 Goff DC, Lloyd-Jones DM, Bennett G, *et al*. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American heart association Task force on practice guidelines. *Circulation* 2014;129:S49–73.
10 Piepoli MF, Hoes AW, Agewall S. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016;37:2315–81.
11 Norheim OF GB, Kjeldsen SE. Retningslinjer for individuell primærforebygging AV hjerte- OG karsykdommer. Oslo Helsedirektoratet, 2009. Available: https://docplayer.me/7978075-Is-1550-nasjonale-retningslinjer-for-individuell-primaerforebygging-av-hjerte-og-karsykdommer.html
12 Selmer R, Lindman AS, Tverdal A, *et al*. [Model for estimation of cardiovascular risk in Norway]. *Tidsskr Nor Laegeforen* 2008;128:286–90.
13 The health directory of Norway. Forebygging AV hjerte- OG karsykdommer, 2017. Available: https://www.helsedirektoratet.no/retningslinjer/forebygging-av-hjerte-og-karsykdom
14 Selmer R, Igland J, Ariansen I, *et al*. NORRISK 2: a Norwegian risk model for acute cerebral stroke and myocardial infarction. *Eur J Prev Cardiol* 2017;24:773–82.
15 Stewart J, Addy K, Campbell S, *et al*. Primary prevention of cardiovascular disease: updated review of contemporary guidance and literature. *JRSM Cardiovasc Dis* 2020;9:204800402094932.
16 Klemsdal TO, Gjelsvik B, Elling I. New guidelines for the prevention of cardiovascular disease. *Tidsskr Nor Laegeforen*2017;137.
17 Cooney MT, Dudina A, D'Agostino R, *et al*. Cardiovascular risk-estimation systems in primary prevention: do they differ? do they make a difference? can we see the future? *Circulation* 2010;122:300–10.
18 Jacobsen BK, Eggen AE, Mathiesen EB, *et al*. Cohort profile: the Tromso study. *Int J Epidemiol* 2012;41:961–7.
19 Mannsverk J, Wilsgaard T, Mathiesen EB, *et al*. Trends in modifiable risk factors are associated with declining incidence of hospitalized and nonhospitalized acute coronary heart disease in a population. *Circulation* 2016;133:74–81.
20 Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis* 2019;290:140–205.
21 Farzadfar F, Finucane MM, Danaei G, *et al*. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. *Lancet* 2011;377:578–86.
22 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017;389:37–55.
23 Hopstock LA, Bønaa KH, Eggen AE, *et al*. Longitudinal and secular trends in blood pressure among women and men in birth cohorts born between 1905 and 1977: the Tromsø study 1979 to 2008. *Hypertension* 2015;66:496–501.
24 Hopstock LA, Bønaa KH, Eggen AE, *et al*. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromsø study 1979-2016. *BMJ Open* 2017;7:e015001.
25 Nilsen A, Hanssen TA, Lappegård KT, *et al*. Secular and longitudinal trends in cardiovascular risk in a general population using a national risk model: the Tromsø study. *Eur J Prev Cardiol* 2019;26:1852–61.
26 Alageel S, Wright AJ, Gulliford MC. Changes in cardiovascular disease risk and behavioural risk factors before the introduction of a health check programme in England. *Prev Med* 2016;91:158–63.
27 Ford ES. Trends in predicted 10-year risk of coronary heart disease and cardiovascular disease among U.S. adults from 1999 to 2010. *J Am Coll Cardiol* 2013;61:2249–52.
28 Norwegian Institute of Public Health. Cardiovascular disease in Norway, 2020. Available: https://www.fhi.no/en/op/hin/health-disease/cardiovascular-disease-in-norway-/
29 Rabanal KS, Igland J, Tell GS, *et al*. Validation of the cardiovascular risk model NORRISK 2 in South Asians and people with diabetes. *Scand Cardiovasc J* 2021;55:56–62.
30 Kvien TK, Glennås A, Knudsrød OG, *et al*. The validity of self-reported diagnosis of rheumatoid arthritis: results from a population survey followed by clinical examinations. *J Rheumatol* 1996;23:1866–71.
31 Mortensen MB, Nordestgaard BG. 2019 vs. 2016 ESC/EAS statin guidelines for primary prevention of atherosclerotic cardiovascular disease. *Eur Heart J* 2020;41:3005–15.
32 Pagidipati NJ, Navar AM, Mulder H, *et al*. Comparison of recommended eligibility for primary prevention statin therapy based on the US preventive services Task force recommendations vs the ACC/AHA guidelines. *JAMA* 2017;317:1563–7.
33 Pencina MJ, Navar-Boggan AM, D'Agostino RB, *et al*. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014;370:1422-31.
34 Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–104.
35 Whelton PK, Carey RM, Aronow WS, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American college of cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2018;71:2199–269.
36 Hong KN, Fuster V, Rosenson RS, *et al*. How Low to Go With Glucose, Cholesterol, and Blood Pressure in Primary Prevention of CVD. *J Am Coll Cardiol* 2017;70:2171–85.
37 Diederichs C, Neuhauser H, Rücker V, *et al*. Predicted 10-year risk of cardiovascular mortality in the 40 to 69 year old general population without cardiovascular diseases in Germany. *PLoS One* 2018;13:e0190441.
38 Karjalainen T, Adiels M, Björck L, *et al*. An evaluation of the performance of SCORE Sweden 2015 in estimating cardiovascular risk: the Northern Sweden MONICA study 1999-2014. *Eur J Prev Cardiol* 2017;24:103–10.
39 Holm A-SS, Olsen GS, Borglykke A, *et al*. Estimating the proportion of Danes at high risk of fatal cardiovascular disease. *Scand J Public Health* 2011;39:571–6.
40 Norway S. Population by age. statistical variable and year, 2021. Available: http://www.ssb.no/en/statbank/table/07459

Supplementary table 1: Proportion of participants in eligible for intervention defined by NORRISK 1 without additional risk factors HbA1c and first-degree family member with premature CHD and 2009 guidelines, NORRISK 2, 2017 guidelines, separate and in combination as total proportion eligible for intervention, by sex and age group. The Tromsø Study 2015-2016

Eligible for intervention		**Women**				**Men**			
	Total	**Overall**	**Age group 40-49**	**Age group 50-59**	**Age group 60-69**	**Overall**	**Age group 40-49**	**Age group 50-59**	**Age group 60-69**
	N=16566	**n=8896**	**n=3286**	**n=3115**	**n=2495**	**n=7670**	**n=2943**	**n=2579**	**n=2148**
NORRISK 1 high risk, % (n)	8.6 (1421)	1.2 (104)	0.2 (6)	0.1 (3)	3.8 (95)	17.2 (1317)	20.7 (608)	7.4 (191)	24.1 (518)
NORRISK 1 low & elevated single risk factors (2009 guidelines)									
Total cholesterol ≥8 mmol/L, % (n)	1.1 (166)	1.5 (129)	0.4 (13)	1.9 (59)	2.4 (57)	0.6 (37)	0.4 (9)	1.0 (23)	0.3 (5)
Systolic blood pressure ≥160 mm Hg, % (n)	3.1 (464)	3.5 (309)	1.0 (32)	3.6 (101)	7.3 (176)	2.4 (155)	0.6 (15)	3.7 (89)	3.1 (51)
Diastolic blood pressure ≥100 mm Hg, % (n)	0.8 (115)	0.5 (42)	0.4 (13)	0.6 (18)	0.5 (11)	1.2 (73)	0.3 (7)	2.1 (50)	1.0 (16)
Total proportion eligible for intervention (NORRISK 1 and/or single risk factors), % (n)	12.6 (2091)	6.1 (545)	1.6 (54)	5.3 (166)	13.0 (325)	20.2 (1546)	21.6 (636)	12.8 (330)	27.0 (580)
NORRISK 2 high risk, & (n)	9.8 (1621)	2.4 (217)	0.2 (5)	2.5 (77)	5.4 (135)	18.3 (1404)	7.5 (221)	23.5 (605)	26.9 (578)
NORRISK 2 low & elevated single risk factors (2017 guidelines)									
Total cholesterol ≥7 mmol/l *, % (n)	2.8 (414)	1.2 (100)	3.1 (100)	*	*	5.0 (314)	5.8 (159)	5.0 (99)	3.6 (56)
LDL cholesterol ≥5 mmol/L *, % (n)	3.6 (535)	1.3 (112)	3.4 (112)	*	*	6.8 (423)	7.3 (198)	7.2 (143)	5.2 (82)
Systolic blood pressure ≥160 mm Hg, % (n)	3.1 (470)	3.5 (302)	1.0 (33)	2.8 (85)	7.8 (184)	2.7 (168)	1.8 (48)	2.3 (46)	4.7 (74)
Diastolic blood pressure ≥100 mm Hg, % (n)	0.6 (95)	0.4 (34)	0.4 (14)	0.4 (11)	0.4 (9)	1.0 (61)	0.9 (24)	0.9 (18)	1.2 (19)
Diabetes & LDL cholesterol >2.5 mmol/L, % (n)	2.7 (399)	2.5 (213)	1.7 (54)	2.3 (70)	3.8 (89)	3.0 (186)	1.8 (50)	3.2 (63)	4.7 (73)
Diabetes & blood pressure ≥140/90 mm Hg, % (n)	0.9 (140)	0.9 (76)	0.3 (10)	0.8 (24)	1.8 (42)	1.0 (64)	0.4 (10)	0.8 (15)	2.5 (39)
Total proportion eligible for intervention (NORRISK 2 and/or single risk factors), % (n)	18.9 (3122)	9.8 (871)	6.9 (227)	7.5 (233)	16.5 (411)	29.4 (2251)	18.6 (548)	34.2 (881)	38.3 (822)

Values are percentages (numbers).
*Indication to start intervention at total cholesterol concentration ≥7 mmol/L and LDL-cholesterol ≥ 5 mmol/L does not apply for women >50 years.

Supplementary table 2: Proportion of individuals eligible for intervention defined by NORRISK 1, 2009 guidelines, NORRISK 2, 2017 guidelines with blood pressure cut off 140/90 mmHg, separate and in combination as total proportion eligible for intervention, by sex and age group. The Tromsø Study 2015-2016.

Eligible for intervention		**Women**				**Men**			
	Total	**Overall**	**Age group 40-49**	**Age group 50-59**	**Age group 60-69**	**Overall**	**Age group 40-49**	**Age group 50-59**	**Age group 60-69**
	N=16566	**n=8896**	**n=3286**	**n=3115**	**n=2495**	**n=7670**	**n=2943**	**n=2579**	**n=2148**
NORRISK 1 high risk, % (n)	12.0 (1987)	2.2 (199)	0.8 (25)	0.4 (12)	6.5 (162)	23.3 (1788)	26.9 (791)	12.4 (320)	31.5 (677)
NORRISK 1 low & elevated single risk factors (2009 guidelines)									
Total cholesterol ≥8 mmol/L, % (n)	1.0 (147)	1.4 (120)	0.4 (13)	1.8 (57)	2.1 (50)	0.5 (27)	0.4 (8)	0.7 (16)	0.2 (3)
Systolic blood pressure ≥140 mm Hg, % (n)	17.4 (2534)	16.7 (1455)	6.9 (225)	16.7 (517)	30.6 (713)	18.3 (1079)	9.4 (202)	22.4 (506)	25.2 (371)
Diastolic blood pressure ≥90 mm Hg, % (n)	6.0 (870)	4.2 (366)	3.3 (107)	5.2 (161)	4.2 (98)	8.6 (504)	5.2 (111)	12.3 (278)	7.8 (115)
Total proportion eligible for intervention (NORRISK 1 and/or single risk factors)	29.3 (4845)	20.5 (1822)	9.1 (298)	19.6 (609)	36.7 (915)	39.4 (3023)	35.4 (1043)	35.1 (904)	50.1 (1076)
NORRISK 2 high risk, % (n)	9.8 (1621)	2.4 (217)	0.2 (5)	2.5 (77)	5.4 (135)	18.3 (1404	7.5 (221)	23.5 (605)	26.9 (578)
NORRISK 2 low & elevated single risk factors (2017 guidelines)									
Total cholesterol ≥7 mmol/l *, % (n)	2.8 (414)	1.2 (100)	3.1 (100)	*	*	5.0 (314)	5.8 (159)	5.0 (99)	3.6 (56)
LDL cholesterol ≥5 mmol/L *, % (n)	3.6 (535)	1.3 (112)	3.4 (112)	*	*	6.8 (423)	7.3 (198)	7.2 (143)	5.2 (82)
Systolic blood pressure ≥140 mm Hg, % (n)	18.4 (2752)	16.9 (1468)	7.2(235)	15.8 (481)	31.9 (752)	20.5 (1284)	15.4 (420)	19.6 (386)	30.5 (478)
Diastolic blood pressure ≥90 mm Hg, % (n)	6.1 (914)	4.3 (371)	3.5 (116)	4.8 (146)	4.6 (109)	8.7 (543)	8.1 (219)	10.0(197)	8.1 (127)
Diabetes & LDL cholesterol >2.5 mmol/L, % (n)	2.7 (399)	2.5 (213)	1.7 (54)	2.3 (70)	3.8 (89)	3.0 (186)	1.8 (50)	3.2 (63)	4.7 (73)
Diabetes & blood pressure ≥140/90 mm Hg, % (n)	0.9 (140)	0.9 (76)	0.3 (10)	0.8 (24)	1.8 (42)	1.0 (64)	0.4 (10)	0.8 (15)	2.5 (39)
Total proportion eligible for intervention (NORRISK 2 and/or single risk factors)	32.4 (5360)	22.8 (2029)	13.4 (439)	20.6 (641)	38.0(949)	43.3 (3331)	31.6 (930)	47.1 (1214)	55.3(1187)

Values are percentages (numbers).

* Indication to start intervention at total cholesterol concentration ≥7 mmol/L and LDL-cholesterol ≥ 5 mmol/L does not apply for women >50 years.

Paper III

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ORIGINAL ARTICLE
Epidemiology & prevention

Achievements of primary prevention targets in individuals with high risk of cardiovascular disease: an 8-year follow-up of the Tromsø study

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Aims To study change over 8 years in cardiovascular risk, achievement of national guideline-based treatment targets of lipids, blood pressure (BP) and smoking in primary prevention of cardiovascular disease (CVD), medication use, and characteristics associated with target achievement among individuals with high CVD risk in a general population.

Methods and results We followed 2524 women and men aged 40–79 years with high risk of CVD attending the population-based Tromsø study in 2007–08 (Tromsø6) to their participation in the next survey in 2015–16 (Tromsø7). We used descriptive statistics and regression models to study change in CVD risk and medication use, and characteristics associated with treatment target achievement. In total, 71.4% reported use of BP- and/or lipid-lowering medication at second screening. Overall, CVD risk decreased during follow-up, with a larger decrease among medication users compared with non-users. Treatment target achievement was 31.0% for total cholesterol <5 mmol/L, 27.3% for LDL cholesterol <3 mmol/L, 43.4% for BP <140/90 (<135/85 if diabetes) mmHg, and 85.4% for non-smoking. A total of 9.8% reached all treatment targets combined. Baseline risk factor levels and current medication use had the strongest associations with treatment target achievement.

Conclusion We found an overall improvement in CVD risk factors among high-risk individuals over 8 years. However, guideline-based treatment target achievement was relatively low for all risk factors except smoking. Medication use was the strongest characteristic associated with achieving treatment targets. This study has demonstrated that primary prevention of CVD continues to remain a major challenge.

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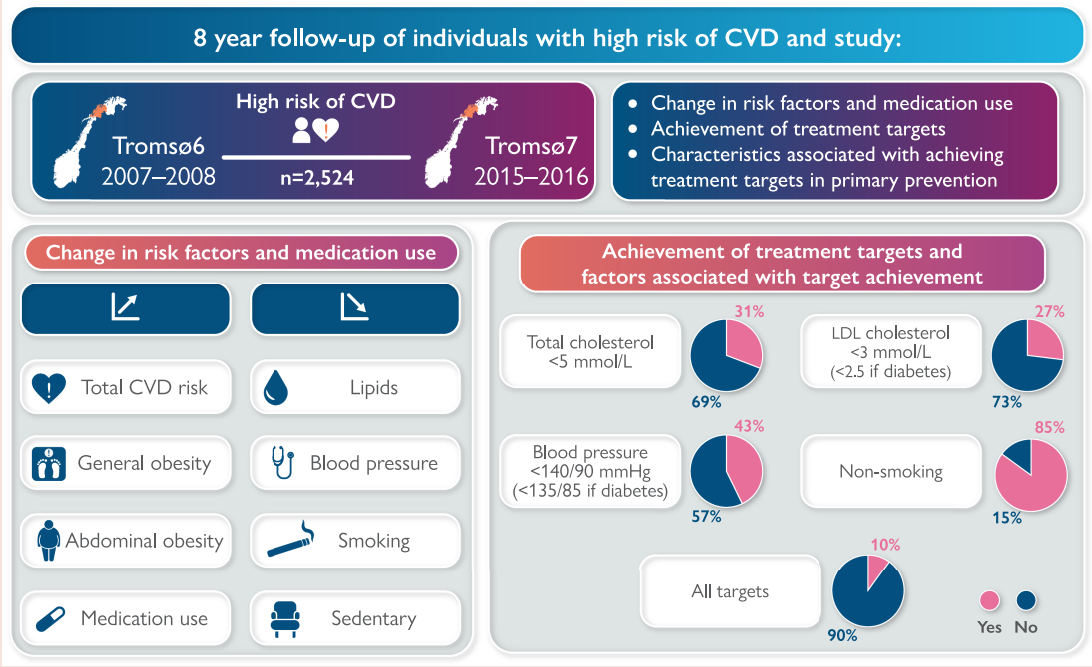
Graphical Abstract



Keywords Cardiovascular disease • Antihypertensives • Lipid-lowering drugs • Primary prevention • Cohort studies

Introduction

Cardiovascular disease (CVD) incidence and mortality rates are declining in many European countries.[1] However, CVD is still a major cause of death and disability and an economic burden for the society, calling for an active preventive approach.[1,2] The main goals of CVD prevention are to delay or prevent the onset of CVD and reduce morbidity and premature mortality.[3] Cardiovascular disease primary prevention guidelines are designed to identify high-risk individuals and highlight the use of cardiovascular risk assessment tools to estimate risk and to guide clinical decision-making on lifestyle interventions and initiating or adjusting medical treatment.[3,4] In Europe, a large proportion of individuals with high CVD risk has an unhealthy lifestyle and there is a discrepancy between evidence-based guidelines and clinical practice.[5,6] We aimed to follow individuals with high risk of CVD from a general population over 8 years to investigate: (i) primary prevention treatment target achievement in lipids, blood pressure (BP), and smoking; (ii) change in cardiovascular risk factors and medication use; and (iii) characteristics associated with achieving primary prevention treatment targets.

Methods

Study design and oversight

The present study followed participants with high risk of CVD attending Tromsø6[7] 2007–08 (attendance 66%) and Tromsø7[8] 2015–16 (attendance 65%). The Tromsø study is a population-based study in the municipality of Tromsø, Norway, and comprising seven surveys conducted between 1974 and 2016 (Tromsø1–Tromsø7). Total birth cohorts and representative population samples have been invited; a total of 45 473 women and men participated in one or more surveys (attendance 65–79%). This study includes data from questionnaires, biological samples, and clinical examinations. We followed high-risk individuals and studied change in CVD risk factors, medication use, treatment targets of lipids, BP, and smoking. Further, we assessed patient characteristics associated with achieving treatment targets in the primary prevention of CVD. The study was approved by the Regional Committee for Medical and Health Research Ethics North (reference 1778/2015).

Methods of data collection

We used questionnaire data to assess diabetes (*Do you have, or have you had diabetes?* yes/no), educational level (*What is the highest level of education you have completed*? primary/secondary school, modern secondary school, technical school, vocational school, senior high school or high school diploma dichotomized to 'lower education' and college/university as 'higher education'), marital status (single, widow/widower, divorced/separated dichotomized to 'single' and married/registered partner as 'married/partner'), smoking status (*Do you/did you smoke daily?* yes now dichotomized to 'smoking', yes previously or never as 'non-smoking'), physical activity level (*Exercise and physical exertion in leisure time the last 12 months?* reading, watching TV or other sedentary activity dichotomized to 'sedentary' and walking, cycling, or other forms of exercise at least 4 h a week, participation in recreational sports, heavy gardening at least 4 h a week, hard training or sports competitions regularly several times a week as 'not sedentary'), psychological distress (Hopkins's symptom checklist-10 summarized with a mean score of ≥1.85 previously validated as the cut-off value for psychological distress[9]), self-perceived health (*How do you in general consider your own health to be?* bad, or neither good nor bad dichotomized to 'poor', and good or excellent as 'good'), and family history of coronary heart disease (CHD) (*Have any family members had a heart attack before the age of 60 years?* with alternatives parents, siblings, and/or children). Non-fasting venous blood samples were analysed for total, LDL- and HDL cholesterol within 48 h by enzymatic colorimetric methods (Roche Diagnostics, Mannheim, Germany) at the Department of Laboratory Medicine,

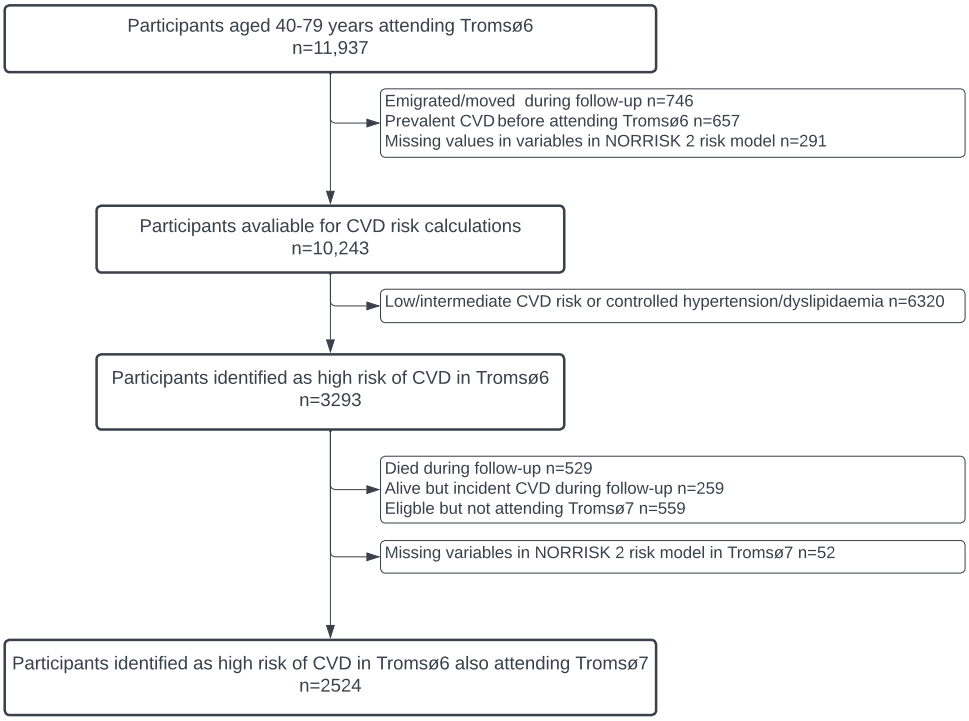


Figure 1 Flowchart of the study. Created in Lucidchart (www.lucidchart.com).

Table 1 Baseline characteristics of the study participants, overall and stratified by sex, the Tromsø Study 2007–08

	Overall ($n = 2524$)	Women ($n = 1094$)	Men ($n = 1430$)
Age, years, mean, SD	60.6 (9.1)	62.1 (8.9)	59.4 (9.1)
Age ≥60 years, % (*n*)	63.7 (1608)	70.3 (769)	58.7 (839)
Diabetes, % (*n*)	8.9 (227)	9.8 (107)	8.4 (120)
Higher education[a], % (*n*)	31.4 (783)	24.8 (268)	36.5 (515)
Married/partner, % (*n*)	66.0 (1666)	60.5 (662)	70.2 (1004)
Psychological distress, % (*n*)	9.9 (251)	15.2 (166)	5.9 (85)
Self-reported health good/very good, % (*n*)	65.1 (1627)	60.2 (652)	68.9 (975)

SD, standard deviation.
[a]Higher education; college/university < and ≥4 years.

University Hospital of North Norway. Blood pressure was measured on the right arm of all participants three times at 1 min intervals after 2 min' seated rest by a Dinamap ProCare 300 monitor (GE Healthcare, Norway), and the mean of the two final readings was used in the analysis. General obesity was defined as body mass index (BMI) ≥30 kg/m^2, calculated as bodyweight in kilograms divided by body height in metres squared. Abdominal obesity was defined as waist circumference ≥88 and ≥102 cm in women and men, respectively, measured to the nearest 0.1 cm with a Seca measurement tape at the level of the umbilicus. Trained personnel performed all measurements. Medication use was defined by a combination of a questionnaire questions (*Do you use blood pressure lowering drugs, Do you use lipid-lowering drugs?* yes now, yes previously, no), and a self-reported written list of brand names of regularly used medication; BP-lowering drugs: ATC-codes C02, C03, C07, C08, C09 and lipid-lowering drugs: ATC-code C10. Current medication use was defined by 'yes now' and/or the ATC-codes.

Study population

We included participants aged 40–79 years identified with high risk of CVD by the risk assessment tool NORRISK 2, elevated single risk factors from the 2017 Norwegian CVD prevention guidelines,[10] or treated but uncontrolled hypertension and/or dyslipidaemia.

We excluded participants with prevalent and incident CVD during follow-up. Cases of first ever myocardial infarction (MI) and cerebral stroke were recorded from the first study entry until 31 December 2014 by the Tromsø Study CVD registry. The national unique 11-digit identification number allowed register-linkage. Cases of MI and ischaemic stroke were identified by linkage to the University Hospital of North Norway's discharge diagnosis registry, the only hospital in the area, with search for International Classification of Diseases, 10th Revision codes. Adjudication of hospitalized and out-of-hospital events was performed by an independent endpoint committee examining medical records, described in detail elsewhere.[11] Due to lack of validated endpoints after 2014, we also used self-reported MI or stroke (yes/no) to exclude participants with CVD after 2014 and before participation in Tromsø7. Emigration from the municipality and/or Norway was identified by linkage to the National Population Register. Death before Tromsø7 was identified by linkage to the Norwegian Cause of Death Registry.

After exclusions (*Figure 1*), the present study included 2524 participants attending both surveys. All participants gave written informed consent.

Risk calculations and identification of high-risk individuals

In 2017, the current Norwegian national guidelines for CVD prevention and the NORRISK 2 score were introduced to identify individuals with high total CVD risk eligible for intervention.[10,12] NORRISK 2 predicts the 10-year risk (%) of incident non-fatal/fatal MI and stroke combined. The risk estimation is

Table 2 Changes in cardiovascular disease risk factors and medication use among individuals with high risk of cardiovascular disease, overall and stratified by sex, the Tromsø Study 2007–16

	Overall ($n = 2524$)		Women ($n = 1094$)		Men ($n = 1430$)	
	Baseline	Second screening	Baseline	Second screening	Baseline	Second screening
Age, years	60.6 (9.2)	68.6 (9.2)	62.1 (8.9)	70.1 (8.9)	59.4 (9.1)	67.4 (9.1)
Cardiovascular risk factors						
Total CVD risk[a], mean	9.9 (6.1)	13.2 (7.5)	8.3 (5.6)	11.6 (7.1)	11.0 (6.1)	14.2 (7.6)
Total cholesterol, mmol/L	6.0 (1.1)	5.6 (1.2)	6.1 (1.0)	5.7 (1.2)	6.0 (1.1)	5.5 (1.2)
LDL cholesterol, mmol/L	3.9 (0.9)	3.7 (1.1)	3.9 (0.9)	3.7 (1.1)	4.0 (1.0)	3.7 (1.1)
Low HDL cholesterol[b], %	15.5 (390)	13.6 (343)	20.4 (234)	17.6 (192)	11.7 (167)	10.6 (151)
Systolic blood pressure, mmHg	150.3 (21.3)	143.7 (21.2)	153.5 (23.3)	145.6 (23.0)	147.9 (19.4)	142.3 (19.6)
Diastolic blood pressure, mmHg	83.4 (11.0)	77.6 (10.5)	80.4 (10.8)	75.3 (10.3)	85.8 (10.7)	79.3 (10.3)
Smoking, %	21.4 (539)	14.6 (368)	20.8 (227)	14.2 (155)	21.8 (312)	14.9 (213)
General obesity[c], %	27.0 (682)	29.8 (749)	28.3 (309)	31.0 (338)	26.1 (373)	28.8 (411)
Abdominal obesity[d], %	58.8 (1484)	59.6 (1505)	70.6 (772)	71.0 (777)	49.8 (712)	50.9 (728)
Sedentary physical activity level, %	20.6 (481)	18.1 (432)	20.4 (199)	19.6 (196)	20.7 (282)	17.0 (236)
Primary prevention medication use						
Antihypertensives and/or lipid-lowering drugs, %	48.1 (1214)	71.4 (1803)	62.0 (678)	80.1 (876)	37.5 (503)	64.8 (927)
Antihypertensives only, %	26.2 (660)	35.5 (895)	32.9 (360)	38.3 (419)	21.0 (300)	33.3 (476)
Lipid-lowering drugs only, %	8.2 (207)	10.2 (258)	11.7 (128)	11.0 (120)	5.5 (79)	9.7 (138)
Antihypertensives and lipid-lowering drugs, %	13.8 (347)	25.8 (650)	17.4 (190)	30.8 (337)	11.0 (157)	21.9 (313)

Numbers are means (SDs) or proportions (numbers).
[a]Total cardiovascular risk: NORRISK 2 score; 10-year risk of fatal and non-fatal MI or stroke.
[b]Low HDL cholesterol, <1.3 mmol/L women, <1.0 mmol/L men.
[c]Body mass index ≥30 kg/m^2.
[d]Waist circumference men ≥102 cm, women ≥88 cm.

based on age, sex, systolic BP (SBP), total cholesterol, smoking, first-degree family member with premature MI (aged <60 years), low HDL cholesterol (men <1.0 mmol/L, women <1.3 mmol/L), and use of antihypertensive medication (current use increases the score). Selmer *et al.*[12] suggested age-specific thresholds in age groups 45–54, 55–64, and 65–74 years to determine low, medium, or high risk of CVD. Elevated values of single risk factors, i.e. total cholesterol ≥7 mmol/L, LDL cholesterol ≥5 mmol/L (does not apply for women >50 years and men >74 years), SBP ≥160 mmHg or diastolic BP (DBP) ≥100 mmHg identifies individuals eligible for intervention regardless of their NORRISK 2 score.[10] In individuals with diabetes, LDL cholesterol ≥2.5 mmol/L and BP ≥140/90 mmHg indicate intervention.[10] We also identified and included participants with treated but uncontrolled hypertension (BP ≥140/90 mmHg) and/or dyslipidaemia (total cholesterol ≥5 mmol/L and/or LDL cholesterol ≥3 mmol/L).

Outcomes

The outcomes of this study were change in CVD risk factors and primary prevention medication use (antihypertensives and lipid-lowering drugs). Furthermore, the proportion achieving treatment targets for primary prevention defined by the national guidelines: BP <140/90 (<135/85 if diabetes) mmHg, total cholesterol <5 mmol/L, LDL cholesterol <3 (<2.5 if diabetes) mmol/L, and non-smoking. In addition, baseline characteristics, risk factors, and current medication use associated with achieving treatment targets.

Statistics

Means and standard deviations (SDs) were presented for continuous variables, and categorical variables were described as percentages (%). Characteristics at baseline and second screening were presented as appropriate (*Tables 1* and *2*). In separate analyses, we used regression models to compare the study sample with participants lost to follow-up in Tromsø7 due to non-attendance, incident CVD, or death before Tromsø7 (see Supplementary material online, *Table S1*). Regression models were used to present age-adjusted characteristics among non-users and users of medication at second screening, overall and stratified by sex (*Table 3*). We calculated the proportion that achieved the treatment targets at second screening (*Figure 2*), and used multivariable logistic regression with odds ratios (ORs) and 95% confidence intervals (CIs) to identify characteristics associated with treatment target achievement adjusted for age and sex (*Table 4*), adjusted for age, sex, education, and medication use (see Supplementary material online, *Table S2*). *P*-values of <5% were considered statistically significant. Analyses were performed using Stata version 16 (StataCorp. 2019, Stata Statistical Software: StataCorp LLC, College Station, TX, USA).

Results

Study sample

At baseline, the mean age was 60.5 years, 63.7% was older than 60 years, 31.4% had higher education, and 8.9% had diabetes (*Table 1*). High-risk individuals not re-attending in Tromsø7 (regardless of cause) were older, had higher mean total CVD risk, a larger proportion had diabetes, low HDL cholesterol, were daily smokers, were sedentary, and had lower educational (see Supplementary material online, *Table S1*).

Change in cardiovascular risk factors and medication use

All CVD risk factors except total CVD risk and obesity improved during follow-up. Change in CVD risk factors was similar among the sexes,

Table 3 Characteristics of non-users and users of antihypertensives and/or lipid-lowering drugs at second screening among individuals with high risk of cardiovascular disease, overall and stratified by sex, the Tromsø Study 2007–16

	Overall ($n = 2524$)			Women ($n = 1094$)			Men ($n = 1430$)		
	Non-user ($n = 721$)	User ($n = 1803$)	*P*-value	Non-user ($n = 218$)	User ($n = 876$)	*P*-value	Non-user ($n = 503$)	User ($n = 927$)	*P*-value
Demographics									
Age, mean	57.4 (56.7, 58.0)	61.9 (61.3, 62.3)	<0.001	58.1 (56.9, 59.2)	63.1 (62.5, 63.7)	<0.001	57.1 (56.2, 57.9)	60.6 (59.9, 61.3)	<0.001
Higher education[a], %	34.8 (31.3, 38.3)	30.0 (27.8, 32.2)	0.021	30.3 (24.3, 36.2)	23.3 (20.8, 26.1)	0.032	37.2 (32.9, 41.5)	36.0 (32.9, 39.2)	0.669
Married/partner, %	65.8 (62.4, 69.3)	66.1 (63.8, 68.2)	0.908	56.4 (49.7, 63.1)	61.5 (58.2, 64.8)	0.177	69.9 (66.1, 73.9)	70.3 (67.4, 73.3)	0.874
Self-reported good/very good health, %	72.9 (69.6, 76.1)	62.0 (59.7, 64.3)	<0.001	68.5 (62.0, 74.2)	58.1 (54.8, 64.2)	0.008	75.0 (71.1, 78.7)	65.4 (62.4, 69.3)	0.001
Psychological distress, %	7.2 (5.3, 9.1)	11.0 (9.6, 12.5)	0.005	10.8 (6.5, 15.0)	16.3 (13.9, 18.9)	0.052	5.4 (3.4.7.4)	6.3 (4.4, 7.9)	0.513
Baseline risk factors									
Total CVD risk[b], mean	11.0 (10.6, 11.3)	9.4 (9.1, 9.6)	<0.001	9.1 (8.6, 9.6)	8.1 (7.8, 8.3)	<0.001	11.7 (11.3, 11.9)	10.6 (10.3, 10.9)	<0.001
Diabetes, %	6.7 (4.8, 8.5)	9.9 (8.4, 11.1)	0.012	12.5 (8.0, 16.9)	9.0 (7.1, 10.9)	0.137	4.2 (2.5, 6.0)	10.8 (8.8, 12.8)	<0.001
Total cholesterol, mmol/L	6.3 (6.2, 6.4)	5.9 (5.8, 5.9)	<0.001	6.4 (6.2, 6.6)	6.0 (5.9, 6.1)	<0.001	6.3 (6.2, 6.4)	5.8 (5.7, 5.9)	<0.001
LDL cholesterol, mmol/L	4.2 (4.1, 4.3)	3.9 (3.7, 3.9)	<0.001	4.1 (4.0, 4.3)	3.8 (3.7, 3.9)	<0.001	4.2 (4.3, 4.3)	3.8 (3.8, 3.9)	<0.001
Low HDL cholesterol[c], %	12.8 (10.5, 15.2)	16.6 (14.6, 18.3)	0.018	18.4 (13.0, 23.3)	20.9 (17.9, 23.7)	0.397	10.3 (7.7, 12.8)	12.3 (10.0, 14.5)	0.205
Systolic blood pressure, mmHg	143.5 (142.0, 144.9)	153.1 (152.2, 154.1)	<0.001	147.0 (144.1, 149.8)	155.1 (153.8, 156.5)	<0.001	141.5 (139.9, 143.1)	151.1 (150.3, 152.6)	<0.001
Diastolic blood pressure, mmHg	80.2 (79.4, 81.0)	84.8 (84.3, 85.3)	<0.001	76.4 (75.0, 77.9)	81.3 (80.7, 82.0)	<0.001	82.1 (81.2, 83.0)	87.8 (87.1, 88.4)	<0.001
Smoking, %	29.5 (26.1, 32.8)	17.8 (15.9, 19.6)	<0.001	25.9 (20.3, 31.7)	19.3 (16.6, 21.9)	0.028	31.2 (27.2, 35.3)	16.5 (13.8, 18.9)	<0.001
General obesity[d], %	16.3 (13.6, 19.0)	31.5 (29.3, 33.7)	<0.001	19.6 (14.3, 24.9)	30.5 (27.6, 33.5)	0.002	15.0 (12.1, 18.3)	32.3 (29.3, 35.4)	0.001
Abdominal obesity[e], %	45.9 (42.2, 49.6)	64.0 (61.7, 66.2)	<0.001	59.0 (52.0, 65.4)	73.4 (70.5, 76.5)	<0.001	39.7 (35.3, 44.0)	55.3 (5.9, 58.5)	<0.001
Sedentary activity level, %	20.5 (17.5, 23.6)	20.6 (18.3, 22.4)	0.955	21.7 (15.8, 27.6)	20.0 (17.1, 22.9)	0.616	20.2 (16.7, 23.7)	21.0 (18.2, 23.7)	0.729
Mean change in risk factors during follow-up									
Total CVD risk[b], mean	+5.7 (5.4, 6.0)	+2.3 (2.1, 2.5)	<0.001	+5.3 (4.7, 5.9)	+2.9 (2.5, 3.1)	<0.001	+5.6 (5.3, 6.2)	+1.9 (1.5, 2.2)	<0.001
Total cholesterol, mmol/L	−0.2 (−0.1,−0.2)	−0.6 (−0.5,−0.7)	<0.001	0.0 (0.0, −0.1)	−0.5 (−0.3, −0.6)	<0.001	−0.2 (−0.1, −0.3)	−0.7 (−0.6, −0.7)	<0.001
LDL cholesterol, mmol/L	+0.1 (0.0, 0.2)	−0.4 (−0.3, −0.4)	<0.001	+0.2 (0.0, 0.3)	−0.3 (−0.2, −0.4)	<0.001	0.0 (−0.1, 0.1)	−0.5 (−0.4, 0.5)	<0.001
Systolic blood pressure, mmHg	+2.4 (0.8, 4.0)	−10.3 (−9.3, −11.4)	<0.001	+1.6 (−1.6, 4.8)	−10.2 (−9.0, 11.8)	<0.001	+2.8 (1.0, 4.5)	−10.3 (−8.9, −11.5)	<0.001
Diastolic blood pressure, mmHg	−1.5 (−0.7, −2.3)	−7.6 (−7.1, −8.2)	<0.001	−0.4 (−1.7, 1.1)	−6.3 (−5.7, −7.1)	<0.001	−2.1 (−1.2, −3.0)	−8.8 (−8.1, −9.5)	<0.001
Daily smoking, %	−6.8 (−4.5, −9.1)	−6.7 (−0.5, −8.1)	0.973	−6.2 (−2.2, −10.2)	−6.7 (−4.5, −8.4)	0.816	−7.2 (−4.3, −10.0)	−6.8 (−4.5, 8.9)	0.843

Values are means (95% CI) or percentages (95% CI). All values are age-adjusted using linear and logistic regression models.
P = difference between non-users and users of primary prevention medication.
[a]Higher education; college/university < and ≥4 years.
[b]Total cardiovascular risk: NORRISK 2 score; 10-year risk of fatal and non-fatal MI or stroke.
[c]Low HDL cholesterol, <1.3 mmol/L women, <1.0 mmol/L men.
[d]Body mass index ≥30 kg/m^2.
[e]Waist circumference men ≥102 cm women ≥88 cm.

except for a greater decrease in SBP among women compared with men (*Table 2*). The proportion of participants on medication increased from 48.1 to 71.4%. At both time points, a larger proportion of the study participants used antihypertensives only, followed by antihypertensives and lipid-lowering drugs combined, while the lowest proportion used lipid-lowering drugs only. At both time points, more women than men used medication while men had a higher increase in medication use than women (*Table 2*).

Second screening medication users vs. non-users: characteristics at baseline and follow-up

Users and non-users of medication at second screening differed in characteristics at both time points (*Table 3*). Users were older, had higher educational level, reported poorer self-reported health and more psychological distress, and had less favourable levels at baseline of some of the risk factors, except for total CVD risk and lipid levels, a larger proportion were women, and a lower proportion were daily smokers compared with non-users. Among medication users at second screening, total CVD risk increased less from baseline compared with non-users (*Table 3*). Total cholesterol and DBP decreased in both groups, but users had a larger decrease. Systolic BP and LDL cholesterol decreased in users and increased in non-users.

Treatment target achievement and characteristics associated with reaching targets

At second screening, 31.0% achieved the treatment target for total cholesterol and 27.3% for LDL cholesterol (*Figure 2*). Medication use was the strongest characteristic associated with achieving targets (*Table 4*). Higher values of total CVD risk at baseline were associated with lower odds of reaching the lipid targets, 7 and 6% lower odds per 1% increase in CVD risk, respectively. Higher baseline values of total cholesterol were associated with lower odds of reaching the lipid targets, 54 and 46% reduced odds per 1 mmol/L increase, respectively. Higher baseline values of LDL cholesterol were associated with lower odds of reaching the lipid targets, 52 and 55% reduced odds per 1 mmol/L increase, respectively. Other characteristics associated with reaching lipid targets were male sex (total cholesterol only), age ≥60 years, having diabetes, and poor self-perceived health (*Table 4*). General and abdominal obesity were associated with reaching target for total cholesterol (*Table 4*), but adjusted for education and medication use, the association was no longer statistically significant (see Supplementary material online, *Table S2*).

Overall, 43.4% achieved treatment target for BP (*Figure 2*). Higher baseline total CVD risk were associated with 6% lower odds for reaching target. Higher baseline SBP and DBP were associated with lower odds for reaching the BP target, 32 and 30% reduced odds per 10 mmHg increase, respectively. Further, age <60 years and baseline daily smoking was also associated with reaching BP target. Antihypertensive medication alone was associated with reduced odds of reaching the BP target (*Table 4*), and this was persistent when adjusting for education (see Supplementary material online, *Table S2*). Concomitant use of antihypertensives and lipid-lowering drugs was associated with increased odds of reaching the BP target.

Non-smoking was achieved by 85.4% of the study population (*Figure 2*), and age ≥60 years, having higher education, being married/partner, having obesity, and using medication were all individually associated with reaching the non-smoking target (*Table 4*).

A total of 9.8% reached all treatment targets, where medication use was the strongest characteristic associated with achieving all targets combined. Other significant characteristics were male sex, lower baseline total CVD risk, lipid, and BP levels, having diabetes, and poor self-perceived health. General and abdominal obesity were associated with increased odds of reaching all target (*Table 4*), but when adjusted for education and medication use, this association was no longer significant (see Supplementary material online, *Table S2*).

Discussion

We followed 2524 individuals with high risk of CVD. Despite improvements in risk factor levels, <10% achieved all CVD primary prevention treatment targets combined (i.e. lipids, BP, and smoking status).

Change in cardiovascular risk factors

The observed decrease in single risk factors but increase in total CVD risk could be explained by the impact of age in the NORRISK 2 score, as previously demonstrated.[13] During follow-up, favourable changes were found in lipid and BP levels and smoking status, which are modifiable risk factors with major impact on reducing CVD risk. Previous studies have shown that a reduction of 1 mmol/L in LDL cholesterol is associated with a 22% reduction in CVD events,[14] a 10 mmHg decrease in SBP can reduce risk by 20%,[15] and smoking cessation is associated with 50% risk reduction within 1 year, making smoking cessation the most effective intervention to reduce CVD risk.[16,17] We observed a reduction in the proportion of participants reporting a sedentary physical activity level, but at the same time we observed an increase in both general and abdominal obesity, in line with findings from the general population in Norway[18] as well as worldwide.[19] This is of worry as obesity is associated with development of Type 2 diabetes and CVD.[20]

Medication use in primary prevention

At the second screening, the proportion using primary prevention medication increased from baseline by 23.3% age points to 71.4%. This is lower compared with other studies.[2,5,6] Although medication use increased more in men over time, we found that more women were medication users at baseline as well as at follow-up. A systematic review[21] and meta-analysis of sex differences in medication prescription found statin use was slightly higher among women than men, while the opposite was found for the use of antihypertensives among individuals with a high risk of CVD.

In the present study, users and non-users of medication at second screening differed in several characteristics that may have impacted decision-making in initiation of medical treatment. Compared with medication users at second screening, non-users had lower baseline BP levels, and a significantly larger proportion were daily smokers. In the clinical setting, smoking cessation could be prioritized since it is considered the most cost-effective and important intervention to reduce CVD risk.[22] The decrease in CVD risk factors over time was larger in medication users at second screening compared with non-users. Still, among non-users, the observed decline in total cholesterol, slight increase in LDL cholesterol and SBP, and decrease in DBP may have several explanations. Lifestyle change is key in primary prevention[3] and the relatively stable levels in risk factors could be due to positive lifestyle changes. A substantial decline in lipid and BP levels over time in the general population has been found both in Norway[23,24] and worldwide.[25,26] This has also been shown in the Tromsø study population[27,28] among both medication users and non-users, although more pronounced among users. However, the larger decline in lipid and BP levels among medication users vs. non-users demonstrates the impact of medication treatment.

Treatment target achievement

In our study, 31% achieved the target of total cholesterol <5 mmol/L and 27% for LDL cholesterol <3 mmol/L, while 24% achieved both

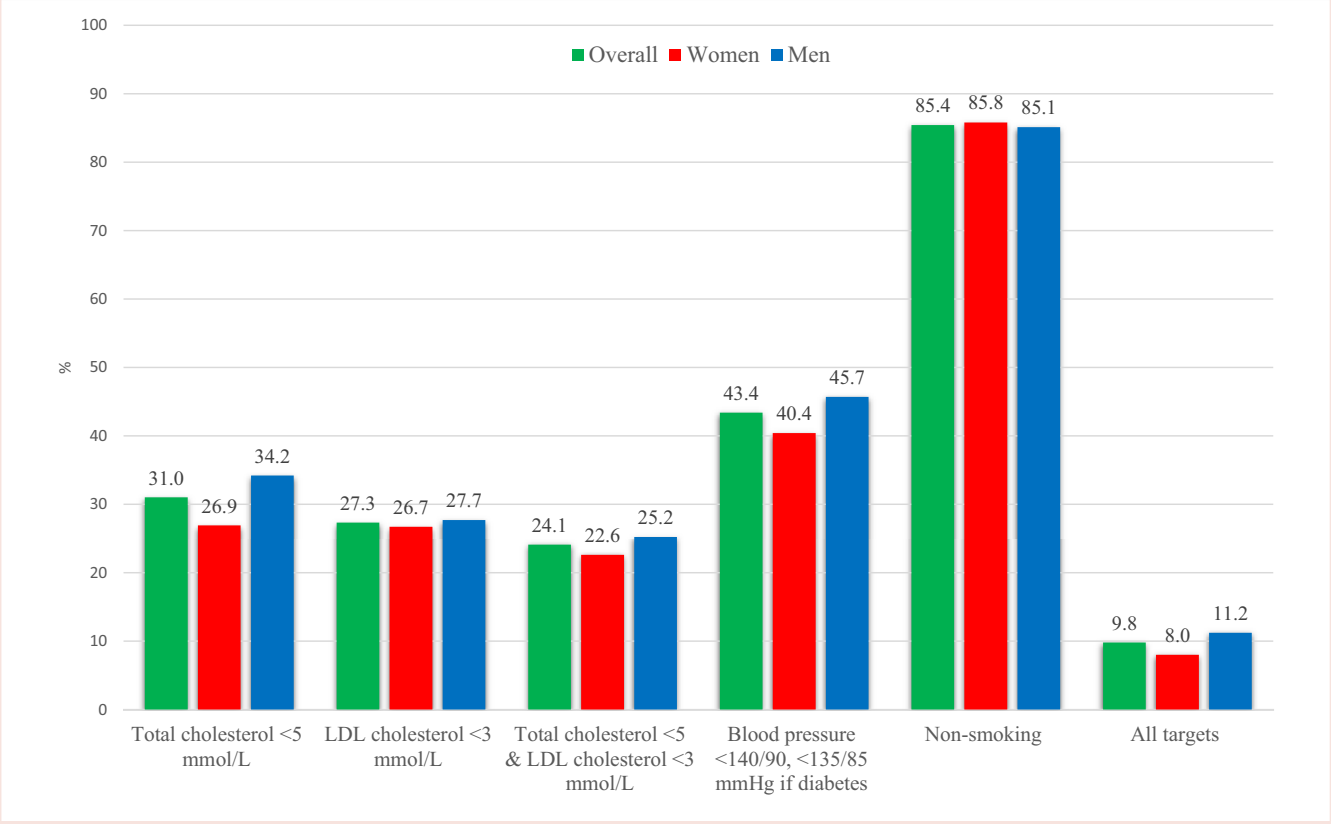


Figure 2 Attained cardiovascular disease primary prevention treatment targets in high-risk individuals, overall and stratified by sex. The Tromsø study 2007–16.

targets. The proportion in our study reaching the lipid targets is lower than in the EURIKA 2009 study, where 43% treated for dyslipidaemia achieved the total cholesterol target, and 41% achieved targets for both total- and LDL cholesterol.[5] In the primary care arm of the EUROASPIRE IV 2014–15 study, 33% of the users of lipid-lowering drugs and 11% of the non-users achieved the LDL target of <2.5 mmol//L.[6] In the more recent EUROASPIRE V 2017–18, 47% of users of lipid-lowering drugs and only 19% of the non-users achieved the LDL target of <2.6 mmol/L.[2]

For BP, we found ~40% achieved the BP target of <140/90 (<135/85 if diabetes) mmHg, comparable to the findings from the EURIKA study, where 39% achieved the BP target,[5] but lower than EUROASPIRE IV where 43% achieved the target,[6] and lower than EUROASPIRE V[2] where 47% achieved the BP target.

Our finding of a smoking prevalence of 15% at second screening in 2015–16 is similar to or slightly lower than findings from EURIKA and the EUROASPIRE studies, ranging from 17 to 22%.[2,5,6] Differences could be explained by the variation in smoking prevalence over time in European countries included in these studies, as reduction in smoking has occurred at different rates in European populations.[29]

Direct comparisons of target achievement in various studies should be interpreted cautiously due to variation in study populations and time points as well as different thresholds in treatment target. Our result of only 1 in 10 high-risk individuals achieving all targets is worrisome. Achieving treatment targets of lipids and BP is associated with reduced risk of CVD,[30,31] and modifying lipids, BP, and smoking reduces the risk of future CVD events substantially,[14–17] highlighting the importance of efforts in primary prevention of CVD.

Characteristics associated with achieving target

We identified several baseline characteristics associated with achieving primary CVD prevention treatment targets. First, higher levels of total CVD risk were associated with lower odds of reaching targets for lipids, BP, smoking, and all targets combined. Further, we found that higher baseline lipid levels were associated with lower odds of achieving lipid targets and all targets combined, and higher baseline BP was associated with lower odds of achieving treatment goals for BP and all targets combined. This is in line with findings from a study finding total CVD risk as an independent predictor of poor target achievement.[32] Thus, individuals with highest risk of CVD, who will benefit significantly from risk reduction, have the lowest probability of achieving treatment goals.

We found that medication use was the characteristic with the strongest association of achieving lipid targets, smoking cessation, and all targets combined. Previous studies have found that greater proportion of medication users achieve targets compared with non-users.[2,5,6] In our study, antihypertensive medication alone was associated with lower odds of reaching the BP target, while concomitant use of antihypertensives and lipid-lowering drugs was associated with increased odds of reaching the BP target. Although not controlled for in this study, other studies have highlighted the importance of medication non-adherence as a key contributor to uncontrolled hypertension.[33] Further, hypertension control may require use of two or more BP-lowering agents to reach targets, as emphasized in the current European guidelines for primary prevention,[3] making this a complex matter in clinical practice.

Table 4 Odds ratios of cardiovascular disease primary prevention target achievement, adjusted for age and sex, the Tromsø Study 2007–16

	Control of TC		Control of LDL		Control of hypertension		Control of smoking		Control of all targets	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Demographics										
Men vs. women[a]	1.51 (1.3, 1.8)	<0.001	1.14 (0.9, 1.4)	0.146	1.08 (0.9, 1.3)	0.354	1.06 (0.8, 1.3)	0.643	1.46 (1.0, 1.9)	0.007
Age ≥60 vs. <60[b]	1.59 (1.3, 1.9)	<0.001	1.77 (1.5, 2.2)	<0.001	0.43 (0.3, 0.5)	<0.001	1.98 (1.6, 2.5)	<0.001	1.10 (0.8, 1.4)	0.462
Higher vs. lower education[c]	0.83 (0.7, 1.0)	0.054	0.88 (0.7, 1.1)	0.221	1.08 (0.8, 1.3)	0.430	1.75 (1.3, 2.3)	<0.001	0.98 (0.7, 1.3)	0.881
Single/separated vs. married/partner[d]	0.97 (0.8, 1.2)	0.705	0.93 (0.7, 1.1)	0.442	0.92 (0.8, 1.1)	0.370	0.74 (0.6, 0.9)	0.009	1.11 (0.8, 1.4)	0.444
Risk factors at baseline										
Total CVD risk, mean[d,e], %	0.93 (0.9–0.9)	<0.001	0.94 (0.9–0.9)	<0.001	0.94 (0.9–0.9)	<0.001	0.83 (0.9–0.9)	<0.001	0.86 (0.8–0.9)	<0.001
Total cholesterol, mmol/L[d,f]	0.46 (0.4, 0.5)	<0.001	0.54 (0.4, 0.6)	<0.001	1.09 (1.0, 1.2)	0.030	0.95 (0.8, 1.1)	0.275	0.58 (0.5, 0.7)	<0.001
LDL cholesterol, mmol/L[d,f]	0.48 (0.4, 0.5)	<0.001	0.45 (0.4, 0.5)	<0.001	1.08 (0.9, 1.2)	0.076	0.94 (0.8, 1.0)	0.487	0.55 (0.5, 0.6)	<0.001
Systolic BP, mmHg[d,g]	0.98 (0.9, 1.0)	0.385	0.98 (0.9, 1.1)	0.538	0.68 (0.6, 0.7)	<0.001	1.24 (1.2, 1.3)	<0.001	0.84 (0.8, 0.9)	<0.001
Diastolic BP, mmHg[d,g]	1.03 (0.9, 1.1)	0.461	0.99 (0.9, 1.1)	0.822	0.70 (0–6, 0.8)	<0.001	1.37 (1.2, 1.5)	<0.001	0.92 (0.8, 1.1)	0.185
Diabetes vs. no diabetes[d]	3.48 (2.7, 4.6)	<0.001	3.02 (2.3, 4.0)	<0.001	1.23 (0.9, 1.6)	0.151	1.30 (0.8, 1.9)	0.213	2.79 (1.9, 4.0)	<0.001
Smoking vs. non-smoking[d]	0.76 (0.6, 0.9)	0.015	0.84 (0.7, 1.1)	0.123	1.29 (1.0, 1.6)	0.010	—		0.36 (0.2, 0.6)	<0.001
Baseline health factors										
General obesity vs. overweight/normal weight[d,h]	1.40 (1.2, 1.7)	<0.001	1.13 (0.9, 1.4)	0.238	1.19 (0.9, 1.4)	0.063	1.64 (1.2, 2.1)	0.001	1.50 (1.1, 1.9)	0.006
Abdominal obesity vs. normal WC[d,h]	1.33 (1.1, 1.6)	0.002	1.09 (0.9, 1.3)	0.351	1.17 (0.9, 1.4)	0.070	1.58 (1.3, 2.0)	<0.001	1.42 (1.1, 1.9)	0.012
Sedentary vs. physical active at leisure time[d]	1.10 (0.8, 1.4)	0.366	1.10 (0.8, 1.3)	0.392	0.95 (0.8, 1.2)	0.655	0.62 (0.5, 0.8)	0.001	0.96 (0.7, 1.4)	0.819
Poor health vs. good health[d]	1.49 (1.2, 1.8)	<0.001	1.36 (1.1, 1.6)	0.001	1.12 (0.9, 1.3)	0.186	0.68 (0.5, 0.9)	0.001	1.24 (0.9, 1.6)	0.126
Psychological distress vs. no distress[d]	0.94 (0.6, 1.3)	0.683	0.78 (0.5, 1.1)	0.129	1.09 (0.8, 1.4)	0.533	0.73 (0.5, 1.0)	0.080	0.95 (0.6, 1.5)	0.840
Current medication use										
Antihypertensives and/or lipid-lowering drugs[d]	4.95 (3.9, 6.4)	<0.001	5.68 (3.9, 7.0)	<0.001	1.20 (1.0, 1.5)	0.056	2.42 (1.9, 3.1)	<0.001	8.67 (4.9, 15.1)	<0.001
Antihypertensives only[d]	0.35 (0.3, 0.5)	<0.001	0.23 (0.2, 0.3)	<0.001	0.78 (0.7, 0.9)	0.004	2.12 (1.7, 2.9)	<0.001	0.34 (0.3, 0.5)	<0.001
Lipid-lowering drugs only[d]	2.09 (1.7, 2.7)	<0.001	2.62 (2.0, 3.4)	<0.001	1.78 (1.4, 2.3)	<0.001	0.89 (0.6, 1.2)	0.450	2.54 (1.9, 3.7)	<0.001
Antihypertensives and lipid-lowering drugs[d]	7.94 (6.5, 9.8)	<0.001	8.89 (6.9, 10.5)	<0.001	1.22 (0.9, 1.5)	0.034	1.38 (1.0, 1.8)	0.026	5.27 (3.8, 6.9)	<0.001

Control of target: TC, total cholesterol <5 mmol/L, LDL <3.0 (2.5 if diabetes) mmol/L, hypertension BP <140/90 (<135/85 if diabetes) mmHg.
[a]Adjusted for age.
[b]Adjusted for sex.
[c]Higher education: College/university < and≥4 years.
[d]Adjusted for age and sex.
[e]Total cardiovascular risk: NORRISK 2 score; 10-year risk of fatal and non-fatal MI or stroke.
[f]Odds ratio per one unit increase (1 mmol/L) in TC and LDL cholesterol.
[g]Odds ratio per 10-unit increase (10 mmHg) in systolic and diastolic BP.
[h]General obesity; BMI ≥30 kg/m^2, abdominal obesity; waist circumference men ≥102 cm women ≥88 cm.

Male sex and age >60 years were associated with reaching target of total cholesterol, in line with findings from other studies.[2,5,6] These studies also found women had higher odds of achieving the BP target,[2,5,6] contrary to our findings. Diabetes was positively associated with achieving target for lipids, and all targets combined; in line with findings from another study demonstrating diabetes to be predictor for reaching lipid targets.[34] This could be explained by the slight difference in cut-off values to be identified as high risk, and the lipid target. Further, diabetics should receive regular follow-up including monitoring of lipid and BP levels. This is an opportunity to initiate or adjust medical treatment and to provide lifestyle advice that could lead to increased risk awareness. Age <60 years, lower education, and being single were associated with lower odds of being a non-smoker, in line with findings from other studies.[5,6,35]

Potential explanations for not achieving treatment targets

The low proportion of reaching treatment targets in our study can be explained by several factors such as 'clinical inertia' (i.e. the failure of clinicians to initiate or intensify therapy when therapeutic targets are not reached)[36] dose prescriptions, not up-titrated doses, poor patient adherence, and barriers within the healthcare system to follow up high-risk individuals.[37] Another study found that high-risk individuals without previous CVD had lower adherence to medication and more uncontrolled risk factors than those with established CHD.[35] Therefore, clinically oriented counselling is suggested as a key component. Counselling should not only focus on biomedical risk factors, but also address psychosocial and economic factors as underlying causes of risk.[35]

Strengths and limitations

A strength of this study is the use of data from a population-based longitudinal study allowing follow-up of high-risk individuals from the general population, as previous studies were based on cross-sectional analyses of patients from clinical settings.[2,5,6] Another strength is the use of validated measurements by trained personnel using standardized protocols, and self-reported medication use which has shown high validity compared with dispensing data.[38] A study limitation is survivor bias, a form of selection bias,[39] as we included high-risk participants in Tromsø6 who met for second screening in Tromsø7. This means that those who died, experienced MI/stroke during follow-up or did not re-attend due to other causes were lost to-follow-up. In addition, all participants received standardized letters with information about selected measurements. Additional feedback was given to participants (<80 years) above thresholds with a recommendation to see their general practitioner. The thresholds were SBP $145.8 + 0.68 \times$ age or ≥170 mmHg. DBP $94.2 + 0.32 \times$ age or ≥100 mmHg. Total cholesterol (mmol/L) in women ≥6.78–8, in men ≥6.26–8.00, and all ≥8.00. Thus, attendance in the Tromsø study could influence attitudes and behaviours. Survivor bias and attendance can lead to overly optimistic interpretation and overestimation of change in risk factors and treatment target achievement. Another limitation is the application of NORRISK 2 and 2017 guidelines in a time-period when this tool and guidelines did not exist, which can introduce bias in the study sample.

Conclusions

We found favourable changes in most CVD risk factors. However, the majority of high-risk individuals did not achieve treatment targets for lipids and BP, <10% achieved all primary prevention targets combined. We also showed the impact of medication use, the strongest characteristic associated with achieving targets. In line with previous studies, our study has demonstrated a great potential for improvement in the primary prevention of CVD.

Authors contributions

A.N.H., I.A., and L.A.H. contributed to the conception and design of the work. A.E.E., M.-L.L., I.N., and T.W. contributed to data acquisition. A.N.H. and T.W. contributed to the data analysis, and all authors contributed to the interpretation of the work. A.N.H. drafted the manuscript. All critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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Amalie Nilsen Hagen is an RN, MSc and a PhD student at Nordland Hospital in Bodø Norway and the Arctic University of Tromsø. Her main research focus is preventive cardiology, epidemiology, and public health.

Data availability

All data are incorporated into the article and its Supplementary material online.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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References

1. Roth Gregory A, Mensah George A, Johnson Catherine O, Addolorato Giovanni, Ammirati Enrico, Baddour Larry M, Barengo Noël C, Beaton Andrea Z, Benjamin Emelia J, Benziger Catherine P, Bonny Aimé, Brauer Michael, Brodmann Marianne, Cahill Thomas J, Carapetis Jonathan, Catapano Alberico L, Chugh Sumeet S, Cooper Leslie T, Coresh Josef, Criqui Michael, DeCleene Nicole, Eagle Kim A, Emmons-Bell Sophia, Feigin Valery L, Fernández-Solà Joaquim, Fowkes Gerry, Gakidou Emmanuela, Grundy Scott M, He Feng J, Howard George, Hu Frank, Inker Lesley, Karthikeyan Ganesan, Kassebaum Nicholas, Koroshetz Walter, Lavie Carl, Lloyd-Jones Donald, Lu Hong S, Mirijello Antonio, Temesgen Awoke Misganaw, Mokdad Ali, Moran Andrew E, Muntner Paul, Narula Jagat, Neal Bruce, Ntsekhe Mpiko, de Oliveira Glaucia Moraes, Otto Catherine, Owolabi Mayowa, Pratt Michael, Rajagopalan Sanjay, Reitsma Marissa, Ribeiro Antonio Luiz P, Rigotti Nancy, Rodgers Anthony, Sable Craig, Shakil Saate, Sliwa-Hahnle Karen, Stark Benjamin, Sundström Johan, Timpel Patrick, Tleyjeh Imad M, Valgimigli Marco, Vos Theo, Whelton Paul K, Yacoub Magdi, Zuhlke Liesl, Murray Christopher, Fuster Valentin, GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;**76**:2982–3021.
2. Kotseva Kornelia, De Backer Guy, De Bacquer Dirk, Rydén Lars, Hoes Arno, Grobbee Diederick, Maggioni Aldo, Marques-Vidal Pedro, Jennings Catriona, Abreu Ana, Aguiar Carlos, Badariene Jolita, Bruthans Jan, Cifkova Renata, Davletov Kairat, Dilic Mirza, Dolzhenko Maryna, Gaita Dan, Gotcheva Nina, Hasan-Ali Hosam, Jankowski Piotr, Lionis Christos, Mancas Silvia, Milićić Davor, Mirrakhimov Erkin, Oganov Rafael, Pogosova Nana, Reiner Željko, Vulić Duško, Wood David, EUROASPIRE V Investigators. Primary prevention efforts are poorly developed in people at high

cardiovascular risk: a report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. *Eur J Prev Cardiol* 2021;**28**:370–379.
3. Visseren Frank L J, Mach François, Smulders Yvo M, Carballo David, Koskinas Konstantinos C, Bäck Maria, Benetos Athanase, Biffi Alessandro, Boavida José-Manuel, Capodanno Davide, Cosyns Bernard, Crawford Carolyn, Davos Constantinos H, Desormais Ileana, Di Angelantonio Emanuele, Franco Oscar H, Halvorsen Sigrun, Richard Hobbs F D, Hollander Monika, Jankowska Ewa A, Michal Matthias, Sacco Simona, Sattar Naveed, Tokgozoglu Lale, Tonstad Serena, Tsioufis Konstantinos P, van Dis Ineke, van Gelder Isabelle C, Wanner Christoph, 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2021;**42**:3227–3337.
4. Rossello Xavier, Dorresteijn Jannick An, Janssen Arne, Lambrinou Ekaterini, Scherrenberg Martijn, Bonnefoy-Cudraz Eric, Cobain Mark, Piepoli Massimo F, Visseren Frank Lj, Dendale Paul. Risk prediction tools in cardiovascular disease prevention: a report from the ESC prevention of CVD programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Prev Cardiol* 2019;**26**:1534–1544.
5. Banegas José R., López-García Esther, Dallongeville Jean, Guallar Eliseo, Halcox Julian P., Borghi Claudio, Massó-González Elvira L., Jiménez Francisco J., Perk Joep, Steg Philippe Gabriel, De Backer Guy, Rodríguez-Artalejo Fernando. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. *Eur Heart J* 2011;**32**:2143–2152.
6. Kotseva Kornelia, De Bacquer Dirk, De Backer Guy, Rydén Lars, Jennings Catriona, Gyberg Viveca, Abreu Ana, Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. *Eur J Prev Cardiol* 2020;**23**:2007–2018.
7. Elise Eggen Anne, Mathiesen Ellisiv B, Wilsgaard T, Jacobsen Bjarne K, Njolstad I. The sixth survey of the Tromso study (Tromso 6) in 2007–08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. *Scand J Public Health* 2013;**41**:65–80.
8. Hopstock Laila A, Grimsgaard Sameline, Johansen Heidi, Kanstad Kristin, Wilsgaard Tom, Eggen Anne Elise. The seventh survey of the Tromsø study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. *Scand J Public Health* 2022:14034948221092294.
9. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry* 2003;**57**:113–118.
10. The Health Directory of Norway. Retningslinjer forebygging av hjerte- og karsykdommer. https://www.helsedirektoratet.no/retningslinjer/forebygging-av-hjerte-og-karsykdom (1 August 2022).
11. Mannsverk Jan, Wilsgaard Tom, Mathiesen Ellisiv B, Løchen Maja-Lisa, Rasmussen Knut, Thelle Dag S, Njølstad Inger, Hopstock Laila Arnesdatter, Bønaa Kaare Harald. Trends in modifiable risk factors are associated with declining incidence of hospitalized and non-hospitalized acute coronary heart disease in a population. *Circulation* 2016;**133**:74–81.
12. Selmer Randi, Igland Jannicke, Ariansen Inger, Tverdal Aage, Njølstad Inger, Furu Kari, Tell Grethe S, Klemsdal Tor Ole, Selmer Randi, Igland Jannicke, Ariansen Inger, *et al.* NORRISK 2: a Norwegian risk model for acute cerebral stroke and myocardial infarction. *Eur J Prev Cardiol* 2017;**24**:773–782.
13. Nilsen Amalie, Hanssen Tove A, Lappegård Knut T, Eggen Anne E, Løchen Maja-Lisa, Njølstad Inger, Wilsgaard Tom, Hopstock Laila. Secular and longitudinal trends in cardiovascular risk in a general population using a national risk model: the Tromso study. *Eur J Prev Cardiol* 2019;**26**:1852–1861.
14. Stein EA, Raal FJ. Lipid-lowering drug therapy for CVD prevention: looking into the future. *Curr Cardiol Rep* 2015;**17**:104.
15. Ettehad Dena, Emdin Connor A, Kiran Amit, Anderson Simon G, Callender Thomas, Emberson Jonathan, Chalmers John, Rodgers Anthony, Rahimi Kazem. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–967.
16. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. *Circulation* 1997;**96**:3243–3247.
17. Duncan Meredith S, Freiberg Matthew S, Greevy Jr, Suman Kundu Robert A, Vasan Ramachandran S, Tindle Hilary A. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA* 2019;**322**:642–650.
18. Norwegian Institute of Public Health. Overweight and obesity in adults (indicator 14). https://www.fhi.no/en/op/Indicators-for-NCD/Overweight-and-obesity/overvekt-og-fedme-blant-voksne-indikator-14/ (13 February 2022).
19. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metab Clin Exp* 2019;**92**:6–10.
20. Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism* 2019;**92**:98–107.
21. Zhao Min, Woodward Mark, Vaartjes Ilonca, Millett Elizabeth R C, Klipstein-Grobusch Kerstin, Hyun Karice, Carcel Cheryl, Peters Sanne A E. Sex differences in cardiovascular medication prescription in primary care: a systematic review and meta-analysis. *J Am Heart Assoc* 2020;**9**:e014742.
22. Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L. Primary prevention of cardiovascular disease: cost-effectiveness comparison. *Int J Technol Assess Health Care* 2007;**23**:71–79.
23. Norwegian Institute of Public Health. Total cholesterol level (Indicator 17). https://www.fhi.no/en/op/Indicators-for-NCD/cholesterol/kolesterolniva-indikator-17/ (13 February 2022).
24. Norwegian Institute of Public Health. Blood pressure level (Indicator 11). https://www.fhi.no/en/op/Indicators-for-NCD/blood-pressure/blodtrykksniva-indikator-11/ (13 February 2022).
25. Farzadfar Farshad, Finucane Mariel M, Danaei Goodarz, Pelizzari Pamela M, Cowan Melanie J, Paciorek Christopher J, Singh Gitanjali M, Lin John K, Stevens Gretchen A, Riley Leanne M, Ezzati Majid, National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet* 2011;**377**:578–586.
26. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017;**389**:37–55.
27. Hopstock Laila Arnesdatter, Bønaa Kaare Harald, Eggen Anne Elise, Grimsgaard Sameline, Jacobsen Bjarne K, Løchen Maja-Lisa, Mathiesen Ellisiv B, Njølstad Inger, Wilsgaard Tom. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905–1977 in the population-based Tromsø study 1979–2016. *BMJ Open* 2017;**7**:e015001.
28. Hopstock Laila Arnesdatter, Bønaa Kaare Harald, Eggen Anne Elise, Grimsgaard Sameline, Jacobsen Bjarne K, Løchen Maja-Lisa, Mathiesen Ellisiv B, Njølstad Inger, Wilsgaard Tom. Longitudinal and secular trends in blood pressure among women and men in birth cohorts born between 1905 and 1977: the Tromsø study 1979 to 2008. *Hypertension* 2015;**66**:496–501.
29. Reitsma Marissa B, Fullman Nancy, Ng Marie, Salama Joseph S, Abajobir Amanuel, Abate Kalkidan Hassen, Abbafati Cristiana, Abera Semaw Ferede, Abraham Biju, Abyu Gebre Yitayih, Adebiyi Akindele Olupelumi, Al-Aly Ziyad, Aleman Alicia V, Ali Raghib, Alkerwi Ala'a Al, Allebeck Peter, Al-Raddadi Rajaa Mohammad, Amare Azmeraw T, Amberbir Alemayehu, Ammar Walid, Amrock Stephen Marc, Antonio Carl Abelardo T, Asayesh Hamid, Atnafu Niguse Tadela, Azzopardi Peter, Banerjee Amitava, Barac Aleksandra, Barrientos-Gutierrez Tonatiuh, Basto-Abreu Ana Cristina, Bazargan-Hejazi Shahrzad, Bedi Neeraj, Bell Brent, Bello Aminu K, Bensenor Isabela M, Beyene Addisu Shunu, Bhala Neeraj, Biryukov Stan, Bolt Kaylin, Brenner Hermann, Butt Zahid, Cavalleri Fiorella, Cercy Kelly, Chen Honglei, Christopher Devasahayam Jesudas, Ciobanu Liliana G, Colistro Valentina, Colomar Mercedes, Cornaby Leslie, Dai Xiaochen, Damtew Solomon Abrha, Dandona Lalit, Dandona Rakhi, Dansereau Emily, Davletov Kairat, Dayama Anand, Degfie Tizta Tilahun, Deribew Amare, Dharmaratne Samath D, Dimtsu Balem Demtsu, Doyle Kerrie E, Endries Aman Yesuf, Ermakov Sergey Petrovich, Estep Kara, Aquino Faraon Emerito Jose, Farzadfar Farshad, Feigin Valery L, Feigl Andrea B, Fischer Florian, Friedman Joseph, G/Hiwot Tsegaye Tewelde, Gall Seana L, Gao Wayne, Gillum Richard F, Gold Audra L, Gopalani Sameer Vali, Gotay Carolyn C, Gupta Rahul, Gupta Rajeev, Gupta Vipin, Hamadeh Randah Ribhi, Hankey Graeme, Harb Hilda L, Hay Simon I, Horino Masako, Horita Nobuyuki, Dean Hosgood H, Husseini Abdullatif, Ileanu Bogdan Vasile, Islami Farhad, Jiang Guohong, Jiang Ying, Jonas Jost B, Kabir Zubair, Kamal Ritul, Kasaeian Amir, Kesavachandran Chandrasekharan Nair, Khader Yousef S, Khalil Ibrahim, Khang Young-Ho, Khera Sahil, Khubchandani Jagdish, Kim Daniel, Kim Yun Jin, Kimokoti Ruth W, Kinfu Yohannes, Knibbs Luke D, Kokubo Yoshihiro, Kolte Dhaval, Kopec Jacek, Kosen Soewarta, Kotsakis Georgios A, Koul Parvaiz A, Koyanagi Ai, Krohn Kristopher J, Krueger Hans, Defo Barthelemy Kuate, Bicer Burcu Kucuk, Kulkarni Chanda, Anil Kumar G, Leasher Janet L, Lee Alexander, Leinsalu Mall, Li Tong, Linn Shai, Liu Patrick, Liu Shiwei, Lo Loon-Tzian, Lopez Alan D, Ma Stefan, El Razek Hassan Magdy Abd, Majeed Azeem, Malekzadeh Reza, Malta Deborah Carvalho, Manamo Wondimu Ayele, Martinez-Raga Jose, Mekonnen Alemayehu Berhane, Mendoza Walter, Miller Ted R, Mohammad Karzan Abdulmuhsin, Morawska Lidia, Musa Kamarul Imran, Nagel Gabriele, Neupane Sudan Prasad, Nguyen Quyen, Nguyen Grant, Oh In-Hwan, Oyekale Abayomi Samuel, Pa Mahesh, Pana Adrian, Park Eun-Kee, Patil Snehal T, Patton George C, Pedro Joao, Qorbani Mostafa, Rafay Anwar, Rahman Mahfuzar, Rai Rajesh Kumar, Ram Usha, Ranabhat Chhabi Lal, Refaat Amany H, Reinig Nickolas, Roba Hirbo Shore, Rodriguez Alina, Roman Yesenia, Roth

Gregory, Roy Ambuj, Sagar Rajesh, Salomon Joshua A, Sanabria Juan, de Souza Santos Itamar, Sartorius Benn, Satpathy Maheswar, Sawhney Monika, Sawyer Susan, Saylan Mete, Schaub Michael P, Schluger Neil, Schutte Aletta Elisabeth, Sepanlou Sadaf G, Serdar Berrin, Shaikh Masood Ali, She Jun, Shin Min-Jeong, Shiri Rahman, Shishani Kawkab, Shiue Ivy, Sigfusdottir Inga Dora, Silverberg Jonathan I, Singh Jasvinder, Singh Virendra, Slepak Erica Leigh, Soneji Samir, Soriano Joan B, Soshnikov Sergey, Sreeramareddy Chandrashekhar T, Stein Dan J, Stranges Saverio, Subart Michelle L, Swaminathan Soumya, Szoeke Cassandra E I, Tefera Worku Mekonnen, Topor-Madry Roman, Tran Bach, Tsilimparis Nikolaos, Tymeson Hayley, Ukwaja Kingsley Nnanna, Updike Rachel, Uthman Olalekan A, Violante Francesco Saverio, Vladimirov Sergey K, Vlassov Vasiliy, Vollset Stein Emil, Vos Theo, Weiderpass Elisabete, Wen Chi-Pan, Werdecker Andrea, Wilson Shelley, Wubshet Mamo, Xiao Lin, Yakob Bereket, Yano Yuichiro, Ye Penpeng, Yonemoto Naohiro, Yoon Seok-Jun, Younis Mustafa Z, Yu Chuanhua, Zaidi Zoubida, Zaki Maysaa El Sayed, Zhang Anthony Lin, Zipkin Ben, Murray Christopher J L, Forouzanfar Mohammad H, Gakidou Emmanuela Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* 2017;**389**:1885–1906.

30. Lindgren Peter, Borgström Fredrik, Stålhammar Jan, Alemao Evo, Yin Donald Donping, Jönsson Linus. Association between achieving treatment goals for lipid-lowering and cardiovascular events in real clinical practice. *Eur J Cardiovasc Prev Rehabil* 2005;**12**: 530–534.
31. Ko Min Jung, Jo Ae Jung, Park Chan Mi, Kim Hyo Jeong, Kim Yun Jung, Park Duk-Woo. Level of blood pressure control and cardiovascular events: SPRINT criteria versus the 2014 hypertension recommendations. *J Am Coll Cardiol* 2016;**67**:2821–2831.
32. Figliuzzi Ilaria, Presta Vivianne, Citoni Barbara, Miceli Francesca, Simonelli Francesca, Battistoni Allegra, Coluccia Roberta, Ferrucci Andrea, Volpe Massimo and Tocci Giuliano. Achievement of multiple therapeutic targets for cardiovascular disease prevention: retrospective analysis of real practice in Italy. *Clin Cardiol* 2018;**41**:788–796.
33. Burnier M, Egan BM. Adherence in hypertension. *Circ Res* 2019;**124**:1124–1140.
34. Presta Vivianne, Figliuzzi Ilaria, Miceli Francesca, Coluccia Roberta, Fogacci Federica, Giuseppe Cicero Arrigo Francesco, Ferrucci Andrea, Borghi Claudio, Volpe Massimo, Tocci Giuliano, Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: analysis of a large real practice database in Italy. *Atherosclerosis* 2019;**285**:40–48.
35. Ludt Sabine, Wensing Michel, Campbell Stephen M, Ose Dominik, van Lieshout Jan, Rochon Justine, Uhlmann Lorenz, Szecseny Joachim. The challenge of cardiovascular prevention in primary care: implications of a European observational study in 8928 patients at different risk levels. *Eur J Prev Cardiol* 2020;**21**:203–213.
36. Phillips Lawrence S., Branch Jr, Curtiss B. Cook William T., Doyle Joyce P., El-Kebbi Imad M., Gallina Daniel L., Miller Christopher D., Ziemer David C. and Barnes Catherine S.. Clinical inertia. *Ann Intern Med* 2001;**135**:825–834.
37. Dallongeville Jean, Banegas José R, Tubach Florence, Guallar Eliseo, Borghi Claudio, De Backer Guy, Halcox Julian P J, Massó-González Elvira L, Perk Joep, Sazova Ogün, Steg Philippe Gabriel, Artalejo Fernando Rodriguez, EURIKA Investigators. Survey of physicians' practices in the control of cardiovascular risk factors: the EURIKA study. *Eur J Prev Cardiol* 2012;**19**:541–550.
38. Pedersen Elisabeth, Truong Kieu Nhi Lise, Garcia Beate Hennie, Halvorsen Kjell H, Svendsen Kristian, Eggen Anne Elise, Waaseth Marit. Self-reported medication use among coronary heart disease patients showed high validity compared with dispensing data. *J Clin Epidemiol* 2021;**135**:115–124.
39. Gordis L. *Epidemiology E-Book*. Philadelphia, PA: Elsevier Health Sciences; 2013.

Supplementary table 1: Baseline demographics, cardiovascular risk factors and medication use among high-risk individuals, stratified by participants also attending Tromsø7 and participants lost to follow-up. The Tromsø Study 2007-2016.

	Overall n=3871			Women n=1696			Men n=2175		
	Study population n=2524	Lost to follow-up n=1347	p	Study population n=1094	Lost to follow-up n=602	P	Study population n=1430	Lost to-follow-up n= 745	P
Demographics									
Age, mean	60.6 (60.2,61.0)	65.2 (64.7,65.7)	<0.001	62.1 (61.6,62.6)	67.5 (66.7,68.2)	0.001	59.4 (58.9,60.0)	63.3 (62.6,64.0)	<0.001
Sex; Women, %	43.3 (41.2,45.2)	44.7 (42.1,47.4)	0.092	--	--		--	--	
Higher education[1], %	30.2 (28.5,31.9)	26.2 (23.8,28.7)	0.017	23.0 (20.6,25.4)	18.5 (15.2,21.9)	0.080	35.8 (33.3,38.3)	32.0 (28.5,35.4)	0.082
Married/partner, %	66.5 (64.8,68.3)	57.1 (54.4,59.8)	<0.001	60.0 (57.1,63.0)	51.6 (47.5,55.7)	0.001	71.2 (69.0,73.7)	61.2 (58.1,65.2)	<0.001
Self-reported good/very good health, %	64.5 (62.8,66.7)	52.1 (49.4,54.9)	<0.001	59.5 (56.5,62.4)	49.8 (45.7,53.9)	<0.001	68.9 (66.3,71.2)	53.9 (50.2,57.5)	<0.001
Psychological distress, %	10.0 (8.9,11.2)	14.3 (12.3,16.2)	<0.001	15.5 (13.3,17.7)	18.1 (14.9,21.2)	0.180	5.8 (4.6,7.0)	11.7 (9.2,14.0)	<0.001
Baseline risk factors									
Total CVD risk[2], mean	10.6 (10.4,10.8)	12.0 (11.7,12.2)	<0.001	9.2 (8.9,9.5)	10.6 (10.3,10.9)	<0.001	11.7 (11.5,11.9)	12.9 (12.6,13.2)	<0.001
Diabetes, %	8.9 (7.8,10.0)	12.3 (10.5)	0.001	9.3 (7.6,11.0)	15.1 (12.0,18.2)	0.001	8.4 (6.9,9.8)	10.4 (8.1,12.6)	0.134
Total cholesterol, mmol/L	6.0 (5.9,6.0)	6.0 (5.9,6.1)	0.429	6.1 (6.0,6.1)	6.1 (5.9,6.1)	0.717	6.0 (5.9,6.0)	5.9 (5.8,5.9)	<0.001
LDL-cholesterol, mmol/L	3.9 (3.8,3.9)	3.9 (3.8,3.9)	0.488	3.9 (3.8,3.9)	3.8 (3.8,3.9)	0.677	3.9 (3.8,3.9)	3.9 (3.8,4.0)	0.373
Low HDL cholesterol[3],%	14.9 (13.5,16.3)	18.9 (16.8,21.1)	0.002	19.3 (17.0,21.6)	26.5 (22.8,30.1)	0.001	11.2 (9.6,12.9)	13.6 (11.0,16.1)	0.118
Systolic blood pressure, mmHg	151.6 (150.8,152.4)	152.8 (151.7,153.9)	0.085	155.3 (154.1,156.6)	156.2 (154.5,157.9)	0.433	148.7 (147.7,149.7)	150.1 (148.6,161.5)	0.136
Diastolic blood pressure,mmHg	83.1 (82.7,83.6)	83.6 (82.9,84.2)	0.243	80.2 (79.5,80.8)	80.7 (79.9,81.6)	0.305	85.6 (85.0,86.1)	85.7 (84.8,86.4)	0.890
Daily smoking, %	20.4 (18.9,21.9)	33.1 (30.6,35.7)	<0.001	19.3 (17.0,21.5)	32.8 (28.9,36.7)	<0.001	21.1 (19.1,23.2)	33.7 (30.2,37.2)	<0.001
General obesity[4] %	26.8 (25.1,28.5)	25.2 (22.8,27.5)	0.291	28.0 (25.3,30.7)	27.1 (23.5,30.1)	0.705	25.7 (23.5,28.1)	23.7 (20.6,26.7)	0.288
Abdominal obesity[5], %	59.2 (57.2,61.1)	56.6 (53.9,59.2)	0.132	70.5 (67.8,73.2)	69.6 (65.8,73.3)	0.698	49.9 (47.3,52.5)	47.2 (43.6,50.9)	0.242
Sedentary activity level, %	20.2 (18.6,21.9)	27.0 (24.4,29.6)	<0.001	20.4 (17.8,22.3)	27.8 (23.6,31.8)	0.002	20.2 (18.1,22.3)	26.3 (22.9,29.6)	0.002
Primary prevention medication use									
Antihypertensives and/or lipid-lowering drugs, %	50.3 (48.3,52.2)	50.3 (47.7,52.9)	0.977	64.3 (61.5,67.0)	59.2 (55.1,63.1)	0.039	39.1 (36.5,41.5)	43.9 (40.3,47.4)	0.029
Antihypertensives only, %	27.3 (25.5,29.1)	29.2 (26.9,31.5)	0.219	34.1 (31.2,36.9)	34.5 (30.7,38.3)	0.863	21.8 (19.6,24.0)	25.4 (22.2,28.5)	0.063
Lipid-lowering drugs only, %	8.3 (7.1,9.3)	6.1 (4.8,7.3)	0.017	11.7 (9.7,13.6)	8.3 (6.0,10.6)	0.041	5.6 (4.3,6.7)	4.5 (3.0,6.0)	0.308
Antihypertensives & lipid-lowering drugs, %	14.9 (13.5,16.3)	14.6 (12.8,16.3)	0.780	18.9 (16.5,21.3)	16.1 (13.2,18.9)	0.143	11.7 (10.0,13.5)	13.5 (11.1,15.8)	0.234

Values are means (95% CI) or percentages (95% CI). All values are age-adjusted using linear and logistic regression models.

P= difference between individuals in the study population and participants lost to follow-up

[1] Higher education; college/university < & ≥4 years. [2] Total cardiovascular risk: NORRISK 2 score; 10-year risk of fatal and non-fatal myocardial infarction or stroke. [3] Low HDL cholesterol, <1.3 mmol/L women, <1.0 mmol/L men. [4] Body mass index ≥30 kg/m2 , [5] Waist circumference Men ≥102 cm women ≥88 cm.

Supplementary table 2: Odds ratios of cardiovascular disease primary prevention target achievement, adjusted for age, sex, education and current medication use. The Tromsø Study 2007-2016.

	Control of TC		Control of LDL		Control of hypertension		Control of smoking		Control of all targets	
	OR (95% CI)	P-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Demographics										
Men vs women[1]	1.92 (1.6,2.3)	<0.001	1.42 (1.1,1.6)	<0.001	1.10 (0.91.1.3)	0.231	1.19 (0.9,1.5)	0.153	1.77 (1.3,2.4)	0.001
Age ≥60 vs <60[2]	1.32 (1.1,1.6)	0.005	1.47 (1.2,1.8)	0.001	0.43 (0.4,0.5)	<0.001	1.84 (1.5,2.3)	<0.001	0.92 (0.7,1.2)	0.587
Higher vs lower education[3,4]	0.84 (0.7,1.0)	0.094	0.90 (0.7,1.1)	0.340	1.08 (0.9,1.3)	0.382	1.87 (1.4,2.4)	<0.001	1.02 (0.8,1.4)	0.920
Single/separated vs married/partner[5]	0.98 (0.8,1.2)	0.863	0.95 (0.8,1.2)	0.580	0.93 (0.8,1.1)	0.446	0.74 (0.6,0.9)	0.017	1.11 (0.8,1.5)	0.333
Risk factors at baseline										
Total CVD risk, mean[6], %	0.95 (0.9,0.9)	<0.001	0.96 (0.9,0.9)	0.001	0.95 (0.9,0.9)	<0.001	0.83 (0.8,0.9)	<0.001	0.89 (0.8,0.9)	<0.001
Total cholesterol mmol/L[5,7]	0.49 (0.4,0.5)	<0.001	0.59 (0.5,0.6)	<0.001	1.10 (1.0,1.2)	0.012	1.03 (0.9,1.2)	0.570	0.64 (0.6,0.7)	<0.001
LDL cholesterol mmol/L[5,7]	0.51 (0.5,0.6)	<0.001	0.49 (0.4,0.5)	<0.001	1.09 (1.0,1.2)	0.036	1.02 (0.9,1.2)	0.691	0.61 (0.5,0.7)	<0.001
Systolic blood pressure mmHg[5,8]	0.92 (0.9,0.9)	<0.001	0.93 (0.9,0.9)	0.002	0.65 (0.6,0.7)	<0.001	1.19 (1.1,1.3)	<0.001	0.78 (0.7,0.8)	<0.001
Diastolic blood pressure mmHg[5,8]	0.91 (0.8,1.0)	0.045	0.88 (0.8,0.9)	0.004	0.67 (0.6,0.7)	<0.001	1.25 (1.1,1.4)	<0.001	0.80 0.7,0.9)	0.001
Diabetes vs no diabetes[5]	3.48 (2.6,4.7)	<0.001	2.96 (2.2,3.9)	<0.001	1.23 (0.9,1.6)	0.152	1.18 (0.7,1.8)	0.435	2.58 (1.8,3.7)	<0.001
Smoking vs non-smoking[5]	0.91 (0.7,1.2)	0.453	1.02 (0.81.3)	0.838	1.37 (1.1,1.7)	0.004	--		0.45 (0.3,0.6)	<0.001
Baseline health factors										
General obesity vs overweight/normal weight[5,9]	1.16 (0.9,1,4)	0.140	0.91 (0.8,1.1)	0.417	1.18 (0.9,1.4)	0.075	1.46 (1.1,1.9)	0.009	1.23 (0.9,1.6)	0.157
Abdominal obesity vs normal WC[5,9]	1.15 (0.9,1.4)	0.156	0.92 (0.7,1.1)	0.425	1.15 (0.9,1.4)	0.108	1.46 (1.2,1.8)	0.002	1.22 (0.9,1.7)	0.168
Sedentary vs physical active at leisure time[5]	1.08 (0.9,1.4)	0.483	1.09 (0.9,1.4)	0.491	0.96 (0.8,1.2)	0.675	0.63 (0.5,0.8)	0.001	0.93 (0.7,1.3)	0.711
Poor health vs good health[5]	1.38 (1.1,1.7)	0.001	1.23 (1.0,1.5)	0.034	1.12 (0.9,1.3)	0.200	0.64 (0.5,0.8)	<0.001	1.11 (0.8,1.5)	0.430
Psychological distress vs no distress[5]	0.89 (0.7,1.2)	0.421	0.72 (0.5,0.9)	0.054	1.08 (0.8,1.4)	0.580	0.69 (0.5,1.0)	0.053	0.91 (0.6,1.5)	0.710
Current medication use										
Antihypertensives and/or lipid lowering drugs[10]	4.93 (3.8,6.3)	<0.001	5.65 (4.2,7.5)	<0.001	1.21 (1.0,1.5)	0.051	2.52 (1.9,3.2)	<0.001	8.64 (4.9,15.0)	<0.001
Antihypertensives only[10]	0.35 (0.3,0.4)	<0.001	0.24 (0.2,0.3)	<0.001	0.77 (0.6,0.9)	0.003	2.11 (1.6,2.8)	<0.001	0.34 (0.2,0.5)	<0.001
Lipid lowering drugs only[10]	2.04 (1.6,2.7)	<0.001	2.57 (2.0,3.4)	<0.001	1.78 (1.4,2.3)	<0.001	0.90 (0.6,1.3)	0.562	2.49 (1.8,3.5)	<0.001
Antihypertensives & lipid lowering drugs[10]	8.05 (6.5,9.9)	<0.001	8.98 (7.2,11.1)	<0.001	1.25 (1.0,1.5)	0.023	1.41 (1.1,1.2)	0.018	5.35 (3.9,7.0)	<0.001

Control of target: TC= Total cholesterol <5 mmol/L, LDL <3.0 (2.5 if diabetes) mmol/L, Hypertension BP <140/90 (<135/85 if diabetes) mmHg

[1]Adjusted for age, education, and current medication use, [2] Adjusted for sex, education, and current medication use, [3] Higher education: College/University < & ≥4 years, [4] Adjusted for age, sex and current medication use, [5] Adjusted for age, sex, education, and current medication use, [6] Total cardiovascular risk: NORRISK 2 score; 10-year risk of fatal and non-fatal myocardial infarction or stroke, [7] OR per one unit increase (one mmol/L) in TC and LDL cholesterol, [8] OR per 10-unit increase (10 mmHg) in systolic and diastolic blood pressure, [9] General obesity; Body Mass Index ≥30 kg/m2, Abdominal obesity; Waist circumference Men ≥102 cm women ≥88 cm, [10] Adjusted for age, sex, and education.

Appendix

The Tromsø Study ; List of links to web pages for invitation letters, information brochures and questionnaires.

All available from the Tromsø Study main web page: www.tromsoundersokelsen.no

Tromsø 6:

Invitation

https://uit.no/Content/100339/Invitasjon_deltakelse_fase_1_t6.pdf

Information brochure

https://uit.no/Content/100340/Forespoersel_om_deltakelse_t6.pdf

4 page initial questionnaire

https://uit.no/Content/100349/Q1_t6.pdf

First visit questionnaire

https://uit.no/Content/100351/Spoerreskjema_2_t6.pdf

Tromsø7

Invitation and information brochure

https://uit.no/Content/710341/cache=20203011123325/brosjyre.troms%C3%B87.pdf

4 page initial questionnaire

https://uit.no/Content/710342/cache=20203011123337/Q1%2BTroms%C3%B8%2B7.pdf

First visit questionnaire

https://uit.no/Content/710343/cache=20203011123350/Q2.troms%C3%B87.webside.oppdatert.sept2020.pdf

Simpler version of the first visit questionnaire:

https://uit.no/Content/710352/cache=20203011124130/Q2%2BTroms%C3%B87.pdf