Diet, weight change, coronary heart disease and death

The Hordaland Health Studies

Teresa Risan Haugsgjerd

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

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Teresa Risan Haugsgjerd Bergen, December 2020

"Don't listen to the person who has the answers; listen to the person who has the questions."

Albert Einstein

Abbreviations

Adequate intakes	AI
Body mass index	BMI
Cardiovascular disease	CVD
Cohort of Norway	CONOR
Confidence intervals	CIs
Coronary artery disease	CAD
Coronary heart disease	CHD
Energy percent	E%
European Food Safety Authority	EFSA
Food and Agriculture organization	FAO
Food frequency questionnaire	FFQ
Glycemic index	GI
Glycemic load	GL
Growth arrest-specific protein 6	Gas-6
Hazard Ratio	HR
High-density lipoprotein	HDL
Intermediate density lipoprotein	IDL
International Classification of Diseases	ICD

International normalization ratio	INR
Ischemic heart disease	IHD
Low-density lipoprotein	LDL
Matrix gla protein	MGP
Menadione, vitamin K3	K3
Menaquinone, vitamin K2	K2
Monounsaturated fatty acids	MUFA
Myocardial infarction	MI
Phylloquinone, vitamin K1	K1
Polyunsaturated fatty acids	PUFA
Randomized controlled trial	RCT
Risk ratio	RR
Saturated fatty acids	SFA
Small dense LDL	sdLDL
Standard deviation	SD
The Cardiovascular Disease in Norway Project	CVDNOR
The Hordaland Health Study	HUSK
The Hordaland Health Studies	HHS
Trans fatty acids	TFA
Very-low density lipoprotein	VLDL

Abstract

Background: While nutritional status is considered important in preventing coronary heart disease (CHD) and early mortality, there are numerous nutritional topics needing closer scrutiny. For example, it is unclear to what degree weight changes in older people are associated with mortality. Further, limiting intake of saturated fatty acids (SFA) often leads to increased intake of carbohydrates, and some types of carbohydrates have been shown to associate with increased risk of CHD. Further, studies suggest that cheese, a large contributor to SFA intake and vitamin K2 in the Nordic countries, associate with decreased risk of CHD.

Objectives: 1) To study the association between weight change and mortality in older individuals; 2) To evaluate the importance of the interplay between SFA and total carbohydrates, including food sources, when evaluating the association between SFA and CHD, and 3) to evaluate the association between dietary vitamin K with CHD in middle-aged adults.

Material and methods: Cohort study with participants from the Hordaland Health Study. In Paper I, 2935 men and women, age 71-74 years with weight measured both in 1992-93 and 1997-99 were followed for mortality through 2012. Multivariable Cox regression estimated Hazard ratios (HRs) and 95% confidence intervals (CIs) comparing individuals who lost (≥5%) or gained (≥5%) weight to those with stable weight (±<5% weight change). Cox regression with penalized spline was also used to evaluate the association between weight change (in kg) and mortality. Analyses adjusted for age, sex, physical activity, smoking, diabetes mellitus, hypertension, and previous myocardial infarction or stroke.

Papers II and III included 2995 and 2987 men and women, respectively, age 46-49 years at baseline in 1997-99. Participants were followed through 2009 to evaluate associations between intake of SFA, carbohydrates and vitamin K and incident CHD. Baseline diet was assessed by a past-year food frequency questionnaire. Energy- adjusted nutrient intakes were categorized into quartiles. Information on incident CHD events was obtained from the Cardiovascular Disease

in Norway (CVDNOR) Project. Multivariable Cox regression estimated HRs and 95% CIs with test for linear trends across quartiles. Analyses were adjusted for age, sex, energy intake, physical activity, smoking and education. Cox regression with penalized spline was used to evaluate the associations between the dietary predictors and incident CHD.

Results:

Paper 1

In the adjusted analyses, participants who lost ≥5% weight had an increased mortality risk (HR 1.59; 95% CI 1.35, 1.89) compared to those with stable weight. In contrast, those with a weight gain of ≥5% had a similar risk of CHD as those with a stable weight (HR 1.07; 95% CI 0.90, 1.28). Penalized spline analyses, however, identified that those who lost more than three kg or gained more than 12 kg had increased mortality risk.

Paper II

In the adjusted analyses, SFA associated with lower risk of CHD ($HR_{Quartile(Q)4vsQ1}$ 0.44; 95%CI 0.26, 0.76), p-trend 0.002). For carbohydrates, the opposite pattern was observed (HR_{Q4vsQ1} 2.10; 95%CI 1.22, 3.63, p-trend 0.003). SFA from cheese associated with lower CHD risk (HR_{Q4vsQ1} 0.44; 95%CI 0.24, 0.83, p-trend 0.006). A 5 energy percent (E%) substitution of carbohydrates with total fat, associated with lower CHD risk (HR 0.75; 95% CI 0.62, 0.90).

Paper III

In the adjusted analyses, there was no association between intake of vitamin K1 and CHD (HR_{Q4vsQ1} 0.92; 95%CI 0.54, 1.57, p-trend 0.64), while there was a lower risk of CHD associated with higher intake of vitamin K2 (HR_{Q4vsQ1} 0.52; 95% CI 0.29, 0.94, p-trend 0.03). Further adjustment for potential dietary confounders slightly attenuated the association for K2 (HR_{Q4vsQ1} 0.58; 95% CI 0.28, 1.19).

Conclusions and implications:

Even a minor weight loss of ≥5% or >3 kg was associated with increased risk of mortality in older people, whereas a weight gain had to be more substantial to increase mortality risk. Thus, weight should be routinely monitored in older adults.

A high intake of carbohydrates, reflecting low-fiber and relatively higher sucrose/fructose dietary sources, and a low intake of SFA were associated with higher CHD risk in the current study population. Substituting carbohydrates with total fat was associated with lower risk. Also, SFA from cheese was associated with lower risk of CHD. There is a need to clarify the relative health trade-offs between replacing carbohydrate intake with fat intake in study populations with diverse dietary habits and a wider range in carbohydrate and SFA intakes. In addition, results of our study suggest that dietary guidelines development and their communication to the public, especially regarding reductions in certain foods and nutrients need to consider the potential health impact of alternative sources of energy.

A higher intake of vitamin K2 was associated with lower risk of CHD, while there was no association between intake of vitamin K1 and CHD. Current dietary guidelines are based on insufficient knowledge with regard to vitamin K metabolism and the different characteristics of K1 and K2. Therefore, our results indicate a need for more studies on the association between K2 and CHD. In addition, more knowledge about the absorption, transport and bioactivity of K2 is warranted.

List of Publications

I. Haugsgjerd TR, Dierkes J, Vollset SE, Vinknes KJ, Nygård OK, Seifert R, Sulo G, Tell GS. *Association between weight change and mortality in community living older people followed for up to 14 years. The Hordaland Health Study (HUSK).* J Nutr Health Aging. 2017;21(8):909-917.

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1. Background

Life expectancy has increased in developed countries the last century.[1] In 2018, life expectancy in Norway was 81.0 and 84.5 years for men and women, respectively.[2] Due to longer life span and decreasing fertility rates,[3] the older population is the fastest growing age group in western societies and greater knowledge is required to improve the health and well-being of older individuals.

Paper I evaluated weight change in an older population while Papers II and III evaluated dietary characteristics in a middle-aged population. The health consequences of weight change in the elderly are complex as weight change also reflects underlying disease processes which are not as prevalent in younger populations. Therefore, Paper I focus on the elderly. For the dietary evaluations of Papers II and III, the focus was on a middle-aged population because previous literature has found that associations between diet and coronary heart disease (CHD) weaken with older age.[4] Also, improving dietary habits and health in midlife will influence health at older ages.[5] The period of middle-age begins between the ages of 35 - 45 years and end at 65 years, while the period of old age starts at the age of 65.[6]

1.1 Weight change in older people

Advancing age associates with decreases in fat free mass and increases in fat mass[7] both visceral, abdominal and intramuscular due to a decline in growth hormone and testosterone production.[8, 9] In both sexes, height decreases with age, and a reduction in height of 1 – 2 cm per decade after the age of 65 years is expected, due to changes of vertebral discs, as well as loss of muscle tone and bone mineral density.[7, 10] Also weight is often seen to decrease with age,[11] and reasons for weight loss in older people may be sarcopenia, cachexia and wasting. Sarcopenia consists of low muscle mass and poor physical performance [12] that may be due to chronic inflammation, atrophy of motor neurons or reduced protein intake. It may be age-related (primary) or functionally (secondary) when it is associated with sedentary lifestyle, malnutrition, organ failure and/or inflammatory disease.[13] Cachexia is loss of muscle

mass with or without loss of fat mass, triggered by an underlying illness.[12] It is defined as weight loss ≥5% during less than 12 months, and 3 or more of the following conditions: decreased muscle strength, fatigue, anorexia, low fat free mass, or abnormal laboratory tests such as increased inflammatory markers, anemia or low serum albumin.[14] Wasting is a result of fasting or malnutrition due to physiological and non-physiological causes.[15] Hence, weight loss in older people can result from natural aging processes, disease, or reduced food intake, and can either be intentional (dieting or/and increased physical activity), or unintentional (consuming less than the usual number of calories due to different reasons).[16] Unintentional weight loss occurs in 15-20% of people 65 years or older, and is clinically relevant if ≥5% of body weight is lost in six to 12 months.[17, 18] Causes can be organic or psychosocial, and the most common causes are malignancy, nonmalignant gastrointestinal disease, depression and dementia.[19] Also oral ulcers[18] and swallowing problems[20]may lead to unintentional weight loss.

Even though weight loss is seen to be common among older people due to several reasons, older people may also gain weight.[21]

1.1.1 Factors associated with weight change and mortality

Factors that are associated with both weight change and mortality include, among others, sex, physical activity, smoking habits, diabetes mellitus, myocardial infarction (MI), stroke and hypertension.

Body composition differs between sexes; men have more lean mass and women have more fat mass, and also changes in body composition with advancing age differ between men and women.[7, 11] Also, women have a longer life expectancy than men.[2] Physical activity can contribute to weight change[22] and has also been associated with decreased risk of mortality.[23] People who quit smoking typically gain weight,[24] while smoking cessation is likely to lead to reduced mortality.[25]

There are complex inter-relationships between changes in weight and chronic disease and mortality risks. Unexplained weight loss may be a symptom of diabetes mellitus, and diabetes mellitus increases mortality risk.[26] Further, reduced nutrient and energy intake before hospitalization has been found among patients hospitalized

for cardiovascular events such as MI and stroke,[27] which, in turn, increase risk of mortality.[26] In addition, overweight and obese persons with hypertension are counselled to change lifestyle which again may result in weight loss,[28] at the same time hypertension is clearly associated with mortality.[29]

Table 1. *Overview of current literature published 2000-2020 on the association between weight loss (WL) and weight gain (WG) and mortality in older people*

Author, year, country	**Sex, age**	**Exposure, Follow-up time**	**N**	**Main findings HR/RR (95% CI)**
Dey et al 2001 Sweden[30]	M & W 75-85y	WL & WG 10y	2628	M (WL 5–9.9%): 1.11 (0.77, 1.59) W (WL 5–9.9%): 1.33 (0.81, 2.16) M (WG ≥5%): 1.01 (0.72, 1.42) W (WG ≥5%): 1.43 (0.95, 2.17)
Newman et al 2001 USA[31]	M & W ≥65y	WL & WG ≥5% 4y	4714	WL: 1.66 (1.18, 2.33) WG: 0.86 (0.54, 1.36)
Wedick et al 2002 USA[32]	M & W ≥65y	WL ≥ 10 pounds 12y	597	M: 1.39 (P<0.05) W: 1.74 (P<0.01)
Wannamethee et al 2005 British[33]	M ≥65y	WL & WG 7y	2762	Intentional WL: Personal reasons: 0.73 (0.41, 1.30) Healthy reasons: 1.38 (0.90, 2.10) Unintentional WL: 1.66 (1.35, 2.04) WG: 0.92 (0.75, 1.13)
Knudtson et al 2005 USA[34]	M & W 65-86y	WL 10y	1989	M: 1.19 (1.06, 1.33) W: 1.23 (1.13, 1.35)
Amador et al 2006 Mexican American[35]	M & W ≥65y	WL & WG >5% 5y	1749	WL: 1.41 (1.03, 1.93) WG: 0.94 (0.64, 1.39)
Locher et al 2007 USA[36]	M & W ≥65y	WL >10 pounds 3y	983	Intentional: 0.62 (0.27, 1.42) Unintentional: 1.67 (1.14, 2.45)
Luchsinger et al 2008 USA[37]	M & W ≥65y	WL & WG >1kg/yr 7y	1113	WL: 1.5 (1.2, 1.9) WG: 1.1 (0.8, 1.5)
Arnold et al 2010 USA[38]	M & W ≥65y	WL & WG ≥5% 7y	3278	WL: 1.58 (1.33, 1.88) WG: 1.10 (0.89, 1.36)
Atlantis et al 2010 Australia[39]	M & W ≥65y	WL & WG 5kg 12y	986	Unintentional: WL: 0.46 (0.32, 0.66) WG: 0.78 (0.46, 1.32)
Lee et al 2011 USA[40]	M 65-93y	WL & WG >5% 9y	4331	WL:1.84 (1.50, 2.26) WG: 1.04 (0.71, 1.51)
De Hollander et al 2013 Europe[41]	M & W 70-77y	WL & WG 6y	1053	WL (≥3.2kg): 1.48 (0.99, 2.20) WL (3.2 - 1.0 kg): 1.25 (0.84, 1.88) WG (0.7–2.7 kg): 1.14 (0.76, 1.72) WG (≥2.8 kg): 0.94 (0.62, 1.41)
Murphy et al 2014 USA[42]	M & W 70-79y	WL & WG ≥5% 8y	1975	M (WL): 1.24 (0.92, 1.67) W (WL): 1.30 (0.92, 1.83) M (WG): 1.31 (0.91, 1.89) W (WG): 1.37 (0.90, 2.08)

Haugsgjerd et al 2017 Norway[43]	M & W 71-74y	WL & WG ≥5% 14y	2935	WL: 1.59 (1.35, 1.89) WG: 1.07 (0.90, 1.28)
Santanasto et al 2017 USA[44]	M & W 70-79y	WL per 4.9kg 12y	1803	M: 1.12 (1.02, 1.24) W: 1.27 (1.16, 1.40)
Mulligan et al 2018 Europe[45]	M & W ≥65y	WL & WG 15y	3329	WL (>5kg): 1.80 (1.48, 2.19) WL (>2.5–<5kg): 1.28 (1.10, 1.51) WG (>2.5–<5kg): 0.95 (0.83, 1.09) WG (>5–<10kg): 1.02 (0.84, 1.24)
Park et al 2018 USA[46]	M & W 65-75y	WL & WG 7.3y	63040	WL (>5–10kg): 1.65 (1.50, 1.82) WL (>2.5–5kg): 1.30 (1.18, 1.44) WG (>2.5–5kg): 0.94 (0.82, 1.07) WG (>5–10kg): 0.98 (0.84, 1.14)
LeBlanc et al 2018 USA[47]	W ≥65y	WL 5y	1323	WL (≤8.99kg): 1.22 (1.02, 1.47) WL (>8.99kg): 1.74 (1.37, 2.20)
Lee et al 2018 Taiwanese[48]	M &W ≥65y	WL & WG >5% 10y	627	WL: 2.3 (1.3, 4.1) WG: 0.8 (0.4, 1.8)
Nishida et al 2019 Japan[49]	M & W ≥65y	WL & WG 3y	1229	WL >4.8%: 2.85(1.12, 7.27) WG >3.1%: 2.71(0.95, 7.76)
Son et al 2020 Korea[50]	M & W ≥65y	WL & WG >5% 12y	1100256	WL: 1.68 (1.65, 1.72) WG: 1.10 (1.07, 1.13)

This literature review is restricted to epidemiological cohort studies published after year 2000, evaluating weight change in kilograms as exposure in community-living people at or above 65 years with a follow-up of at least 1 year. When more than one age cohort is evaluated and there are several weight change categories, only results from the oldest cohort and non-extreme weight change categories are reported. All results are from the fully adjusted models. The literature was identified through searches in PubMed, Web of Science and Embase. Search terms included "weight change", "weight gain", "weigh loss", "older people", "older adults", "the elderly", "mortality", "death", "cohort study" and "English language". In addition, an evaluation of studies included in relevant review and meta-analyses was made. The last search was performed on December 5th 2020. M indicates men; W, women; y, years; N, number included in the study population; HR, Hazard ratio; RR, Risk ratio; CI, Confidence interval; WL, weight loss; WG, weight gain; kg, kilograms.

1.1.2 **Weight change and mortality in older people**

Table 1 provides an overview of cohort studies evaluating weight change and mortality in older people. There seems to be an association between weight gain and mortality in older people, despite mixed results from cohort studies.[21, 30, 31, 33, 35, 37-42, 45, 46, 48-50] Son et al found a weight gain of >5% to be associated with increased risk of mortality,[50] and in several studies, weight gain seemed to be associated with increased risk of mortality, though not significantly.[30, 37, 38, 40, 42, 45, 49] Further, Bamia et al found that weight gain especially amongst those overweight/obese were associated with increased mortality when evaluating people ≥60 years at enrollment.[51]

In contrast, some studies also found weight gain to be inversely associated with total mortality, although not significantly.[31, 33, 35, 39, 41, 46, 48]

Weight loss in overweight and obese individuals improves health status by reducing hypertension, hypercholesterolemia, and insulin resistance,[28, 52, 53] but evidence that weight reduction lowers mortality is limited.[33, 36, 39] In older individuals, weight loss has been shown to associate with higher mortality across all body mass index (BMI) categories.[32, 51] However, the importance of whether the weight loss is unintentional or intentional is unclear.[31, 33, 36, 39] An association between weight loss and increased mortality has been found in a large number of studies.[21, 30-38, 40-42, 44-50]

Meta-analyses and reviews conducted in recent years of studies including people 60 years and above, concluded that weight gain, weight loss, and weight fluctuations are associated with higher mortality risk among adults ≥60 years.[21, 54] Further, a study including middle-aged people, concluded that advising overweight or obese individuals who are otherwise healthy to lose weight as a means of prolonging life is not recommended.[55]

1.2 Coronary heart disease

CHD is one of the diseases included in the definition of cardiovascular disease (CVD), together with stroke, congenital heart defects and peripheral artery disease. It is a non-communicable chronic disease resulting from genetic, physiological, environmental and behavioral factors. The leading metabolic risk factors globally are raised blood pressure, overweight/obesity and raised blood glucose.[26, 56]

Vascular calcification can be classified depending on its location within the arterial intima or media. Medial calcification mostly affects the peripheral arteries, while intimal calcification is the dominant type of calcification seen in coronary arteries,[57] and therefore also the type involved in coronary artery disease (CAD). CAD is the pathologic process affecting the coronary arteries (usually atherosclerosis) whilst CHD, also known as ischemic heart disease (IHD), includes diseases that occur mainly as a consequence of atherosclerosis. CHD is therefore mainly a result of CAD, however, a MI may also evolve without atherosclerosis.[58]

CHD includes stable and unstable angina, MI and sudden cardiac death, and also silent myocardial ischemia, that is myocardial ischemia in the absence of clinical symptoms.[59, 60]

1.2.1 Lipids, lipoproteins and coronary atherosclerosis

Unmodifiable risk factors for atherosclerosis are age, sex, race and family history (genetics), whereas lipid concentrations, smoking habits, diabetes mellitus, obesity and hypertension may be modified.[61]

Coronary atherosclerosis is an inflammatory process characterized by accumulation of lipids, macrophages and smooth muscle cells in intimal plaques in the large and medium-sized epicardial coronary arteries. The plaque lays on the arterial wall and may become unstable, undergo thrombosis, and result in an obstruction.[62]

The various lipids and lipoproteins have different roles when it comes to accumulation in the arterial wall. High low-density lipoprotein (LDL) cholesterol increases risk of atherosclerosis. However, unmodified LDL particles are, to only a small extent, taken up in the artery wall; in contrast to modified LDL which are incorportated.[62] Modified LDL has an important function in the development of endothelial dysfunction, an early marker of atherosclerosis.[62, 63] Further, small dense LDL (sdLDL) are less easily cleared from the circulation due to reduced receptor-mediated uptake, and they also have higher susceptibility to oxidation compared to unmodified LDL.[64] High-density lipoprotein (HDL) cholesterol performs reverse cholesterol transport by stimulating the removal of cholesterol from cells and delivering it to the liver where some may be secreted in bile and excreted.[65] Triglycerides are carried primarily within large lipoproteins, chylomicrons, and very-low density lipoproteins (VLDL), which are also rich in cholesterol and like LDL can stimulate atherosclerosis.[66] However, in hypertriglyceridemia, higher CHD risk seems to be mainly due to reduced HDL cholesterol, and triglyceride-rich particles are weakly independently associated with CHD risk.[67]

Atherogenic dyslipidemia associated with atherosclerosis, comprises increased blood concentrations of sdLDL cholesterol, decreased HDL cholesterol and increased triglycerides.[68] Further, the combination of high serum cholesterol and low HDL

cholesterol is strongly associated with atherosclerosis, whereas a high HDL cholesterol and a low LDL:HDL cholesterol ratio reduce risk of atherosclerosis.[69]

A high intake of carbohydrates increases hepatic triglycerides that drives the secretion of larger VLDL, enriched with triglycerides. These particles are lipolyzed to remnant lipoproteins that are then catabolized to sdLDL particles (**Figure 1**).[70]

Saturated fatty acids (SFA) increase plasma concentrations of larger LDL particles, both by reducing their plasma clearance through suppression of LDL receptor activity, and by influencing the LDL production rate.[64, 70] However, SFA with <12 carbon atoms are thought not to increase cholesterol concentrations,[71] while the strength of the LDL-raising effects of the longer SFAs are as follows: lauric acid (C12:0) > myristic acid (C14:0) > palmitic acid (C16:0). Lauric acid may also increase HDL cholesterol. Stearic acid (C18:0) mostly has a neutral effect on lipid and lipoprotein profiles.[72]

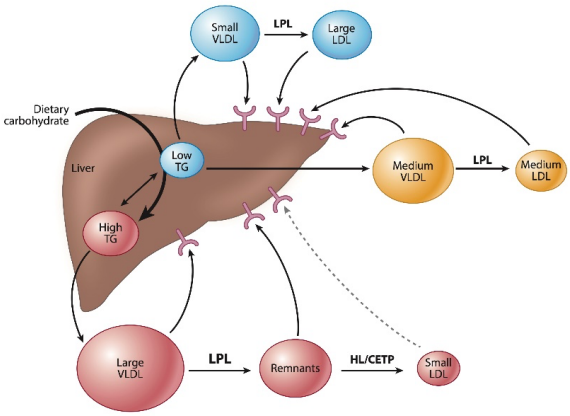

Figure 1. *Pathway of lipoprotein metabolism after intake of carbohydrates. Reprinted with permission from The Annual Review of Nutrition*[70]

High plasma lipoprotein(a) concentrations can occur in patients with otherwise normal lipid levels and is a genetic risk factor for CHD.[73] Lipoprotein(a) concentrations have been thought to be only minimally altered by diet, however, a defined plant-based diet has shown to substantially reduce the concentration of lipoprotein(a).[74] When effect of SFA replacement on lipoprotein(a) was evaluated in a recent review, results were heterogeneous, although lipoprotein(a) often increased when SFA were replaced by other macronutrients.[75]

Apolipoprotein A1 represents the major protein in HDL and is the main acceptor of cholesterol when HDL transports cholesterol from the tissue to the liver.[76]

Non-HDL cholesterol is a measure of cholesterol content of VLDL, intermediate density lipoprotein (IDL), LDL, chylomicron remnants and

lipoprotein(a).[77] Apolipoprotein B is the major structural protein in VLDL, IDL, LDL and lipoprotein(a). [78]

A cross-sectional Swedish population-based study that examined the associations between diet and apolipoprotein concentrations found that intake of sucrose and food products containing added sugar was negatively correlated with apolipoprotein A1 concentrations and positively correlated with apolipoprotein B concentrations.[76] The intake of fermented dairy products was positively correlated with apolipoprotein A1 concentrations.[76] Recent research suggests that non-HDL cholesterol and apolipoprotein B are superior to LDL cholesterol in predicting coronary atherosclerosis.[78, 79]

1.2.2 Prevention of coronary heart disease

CHD mortality has declined in western countries over the last decades,[80] but CHD is still a major contributor to deaths in people >35 years.[81, 82] Norway has had a decrease in death rates due to CHD of the last ten years, and the decrease appears to be continuing.[2] Also, the incidence of acute MI decreased from 2001 to 2014, including both fatal and nonfatal events.[83] However, despite falling CHD rates, the Global Burden of Disease Study report that CHD was the leading cause of years of life lost in 2017; the global rates of CHD increased for the first time since the 1970s.[26]

The IMPACT model can be used to estimate the proportion of the observed change in mortality that can be attributed to either treatment or risk factor changes and has been used to explore the contributions of changes in risk factors and treatment in >15 countries. The model estimated that among different countries about 40-75% of the CHD mortality fall could be attributed to changes in risk factors and the remaining 25-60% to advances in treatment.[84] When it comes to the disease burden of CHD, most of it can be attributed to lifestyle factors such as smoking, unhealthy diet, alcohol abuse and physical inactivity.[82, 84]

1.2.3 Factors associated with diet and coronary heart disease

In Papers II and III, focus is on associations between diet and CHD. However, there are several factors that may influence both diet and risk of CHD. Among these are sex, physical activity, smoking habits, socioeconomic status, and family history of

CHD. Diet has shown to differ between men and women,[85] and male sex is associated with higher risk of CHD.[83] As people who perform physical activity need more energy (calories), physical activity influence the diet of people,[86] at the same time a high level of physical activity is associated with decreased risk of CHD.[82] Researchers have found that smoking habits may influence diet,[87] at the same time, smoking is also clearly associated with risk of CHD.[82] Education as a measure of socioeconomic status is associated with dietary patterns,[88] and higher education is associated with decreased CHD risk.[89] Further, family history of diseases have been found to be associated with a healthy diet,[90] but a family history of CHD is also associated with risk of CHD.[91]

1.2.4 **Diet**

The Global Burden of Diseases, Injuries, and Risk Factors Study quantified the impact of poor dietary habits on non-communicable disease mortality in 2017 and found that approximately 11 million deaths were attributable to dietary risk factors.[92] Dietary habits may influence risk of CHD through adverse effects on serum lipids and lipoproteins, blood pressure, body weight and insulin sensitivity.[93]

Carbohydrates

In Norway, carbohydrates are recommended to make up 45 – 60 energy percent (E%) of the diet.[94] Carbohydrates are composed of carbon, hydrogen and oxygen, with the main carbohydrates being monosaccharides, disaccharides, oligosaccharides, and polysaccharides.[95] Monosaccharides as glucose, galactose, and fructose have three to seven carbons. Disaccharides as sucrose, lactose, and maltose are formed by combining monosaccharides.[95] Oligosaccharides contains three to ten monosaccharide units, while polysaccharides constitute >10 monosaccharide units. Starch comprises amylose that is <1% branched and amylopectin that is highly branched. Dietary fiber are intact plant components not digestible by gastrointestinal enzymes.[95]

Carbohydrates are digested into monosaccharides by α-amylase and brush-border digestive enzymes.[95] Once digested, glucose is absorbed across the intestinal cell and transferred to the liver. The liver removes approximately 50% of glucose for

oxidation and storage as glycogen. After leaving the liver, glucose enters the systemic circulation and is available for insulin-dependent uptake by peripheral tissue.[95] Blood glucose concentration depends on the amount and digestibility of carbohydrate, absorption and degree of liver uptake, insulin secretion, and sensitivity of peripheral tissues to insulin action.[95]

Carbohydrates' primary role is to maintain blood glucose concentrations between 3.5-8.0mmol/L between feedings in healthy individuals.[61] High intake of carbohydrates releases insulin for glucose uptake and subsequent synthesis of glycogen and fat, in order to get blood glucose to drop to a normal range. It takes approximately two hours after a meal before the intestinal absorption is complete.[61]

Parameters of carbohydrate quality are glycemic index (GI), glycemic load (GL) and fiber content. GI is used to rank carbohydrates by their ability to raise blood glucose levels as compared with a reference food where portions of both the reference foods and test foods contain 25 or 50g available carbohydrate.[96] The GL of a food is the GI of the carbohydrate divided by 100 and multiplied by its amount of available carbohydrate content in grams.[96] The first GI table was published in 1995 and contained >750 different types of foods [96]. However, GI has limitations: 1) there are low correlations between GI values and fiber content of foods,[96] 2) values vary for similar foods,[96] 3) foods high in fat and protein do not have GI values, 4) carbohydrates increase plasma triglycerides, independent of the GI value,[97] and 5) Nordic food items lack reliable GI values.[98] A study in outpatients with type 1 diabetes mellitus showed that bread and pasta contribute most to the overall dietary GI [99] and Norwegians consume large amounts of bread [100, 101] with medium to high GI.[102]

Fatty acids

In Norway, fat are recommended to make up 25 – 40 E% of the diet and SFA <10E% of the diet.[94] Fatty acids are classified according to the number of carbons, the number of double bonds, and the position of the double bonds in the chain.[95] Short-chain-fatty-acids have 4 - 6 carbons, medium-chain fatty acids have 8 - 14, and long-chain fatty acids have ≥16 carbons. In SFAs, all carbon binding sites not linked to another carbon are linked to hydrogen, while in monounsaturated fatty acid (MUFA)

one double bond forms between carbons, and in polyunsaturated fatty acid (PUFA) two or more double bonds form between carbons.[95] Hydrogen can be added both in the cis position that is when two carbons bind a hydrogen on the same side of the bond, and in the trans position, that is when two carbons bind a hydrogen on opposite sides of the double bond. While the cis double bonds make the fatty acids to pack loosely, fatty acids with trans double bonds is packed tightly into the membrane.[95]

Natural trans fatty acids (TFA) are formed by bio-hydrogenation in the rumen of ruminant animals (e.g., cattle, sheep, and goats), while industrial TFA are formed by hydrogenation of vegetable and marine oils.[103] Already in the 1950s, Ancel Keys speculated that TFA were associated with heart disease.[104] However it was first in the 1990s that experimental evidence found that TFAs may increase risk of CHD [105] through raised LDL cholesterol, apolipoprotein B and fasting triglyceride levels and decreased HDL cholesterol.[106] Food industry have used industrial TFA in processed foods for decades, and especially partially hydrogenated fish oil was used in Norway.[107] TFA from partially hydrogenated fish oil increased LDL cholesterol and reduced HDL cholesterol the most when compared with TFA from partially hydrogenated soybean oil and with butter.[108] Currently, the use of partially hydrogenated fish oils has been reduced or discontinued in industrialized countries,[106] but emerging evidence suggests that ruminant TFA may have similar adverse effects on blood lipids as partially hydrogenated oils.[109]

Fat allows digestion, absorption, and transport of essential nutrients, it promotes digestion by decreasing gastric secretion, slowing gastric emptying and stimulating biliary and pancreatic flow, and it gives textural properties to foods.[95]

Shift from intake of fat to intake of carbohydrates

In Finland, CVD mortality rates for middle-aged men were the highest in the world in the late 1960s.[110] The Finnish diet has traditionally been high in SFA, but underwent major changes between 1982 to 2007 due to recommendations based on the assumed association between fat and serum cholesterol.[111] Consumption of high-fat milk products and butter fat decreased by 86% and 67% respectively. Furthermore, since the early 1980s the annual consumption of vegetables and fruit and berries increased

considerably.[112] The decreased intake of SFA are reported to explain 41% and 47% of the decrease in total cholesterol between 1982 to 2007 in women and men in Finland, respectively.[111]

Similarly as in Finland, the US population was recommended to reduce fat intake in order to lower the incidence of CVD. In the US, fats were replaced principally with carbohydrates,[71] and also in Finland the intake of sucrose/fructose carbohydrate sources increased between 1970 and 2000.[112] In Norway, a decreased consumption of dietary fats may explain a large part of the changes in mortality from CHD between 1960 and 1992, although this change was smaller than predicted in Finland and the US.[113] The decrease in intake of total fat and SFA was followed by an increased intake of carbohydrate sources rich in sucrose and fructose also in Norway.[113, 114] Further, in Norway there has been a strong shift in fat supply from milk and butter to cheese, especially over the last decades.[114]

Table 2. *Overview of current literature published 2000-2020 on the associations between dietary saturated fatty acids / carbohydrates with coronary heart disease.*

Author, year, country	**Sex, age**	**Exposure, Follow-up time**	**Event**	**N**	**Main findings HR/RR (95% CIs)**
Liu et al 2000 USA[115]	W 38-63y	CH 10y	CHD	75521	Q5vs.Q1: 1.23 (0.86, 1.75)
Jakobsen et al 2004 Denmark[4]	W & M 30 - <60y	SFA for CH and SFA 16y	CHD	3686	$W_{per5E\%forCH}$: 2.68 (1.40, 5.12) $W_{per5E\%}$: 2.48 (1.33, 4.65) $M_{per5E\%forCH}$: 1.29 (0.87, 1.91) $M_{per5E\%}$: 1.29 (0.92, 1.80)
Oh et al 2005 USA[116]	W 30-55y	SFA 20y	CHD	78778	Q5vs.Q1: 0.97 (0.73, 1.27)
Xu et al 2006 USA[117]	M & W 45-74y	SFA 7y	CHD	2938	Q4vs.Q1: 1.11 (0.82, 1.51)
Leosdottir et al 2007 Sweden[118]	M & W ≈59y	SFA 8.4y	Acute coronary events	28098	$W_{Q4vs.Q1}$: 0.81 (0.53, 1.24) $M_{Q4vs.Q1}$: 1.02 (0.76, 1.37)
Jakobsen et al 2009 USA/ Europe[119]	M & W ≈ 30-80y	CH for SFA 4-10y	CHD	344696	Per 5E%: 1.07 (1.01, 1.14)
Sieri et al 2010 Italy[120]	M & W 35-74y	CH 7,9y	CHD	47749	$W_{Q4vs.Q1}$: 2.00 (1.16, 3.43) $M_{Q4vs.Q1}$: 0.91 (0.64, 1.30)
Jakobsen et al 2010 Denmark[121]	M & W 50-64	CH for SFA12y	MI	53644	Per 5E%: 1.04 (0.92, 1.17)
Burger et al 2011 The Netherlands[122]	M & W 21-64y	CH 11.9y	CHD	19608	W_{perSD}: 1.04 (0.82, 1.33) M_{perSD}: 1.23 (1.04, 1.46)
Wallström et al 2012 Sweden[123]	M & W 44-73y	SFA & CH 13.5y	Coronary event	20674	CH: $W_{Q5vs.Q1}$: 1.17 (0.81, 1.68) $M_{Q5vs.Q1}$: 1.21 (0.92, 1.59) SFA: $W_{Q5vs.Q1}$: 0.67 (0.46, 0.97) $M_{Q5vs.Q1}$: 0.86 (0.66, 1.13)
Dilis et al 2012 Greece[124]	M & W 20 – 86y	SFA 10y	CHD	23929	Per SD: 0.93 (0.73, 1.20)
Yamagishi et al 2013 Japan[125]	M & W 45-74y	SFA 11.1y	MI	81931	Q5vs.Q1:1.39 (0.93, 2.08)
Similä et al 2013 Finland[126]	M 50-69y	CH for SFA + TFA 19y	CHD	21955	Per 2E%: 0.97 (0.94, 0.99)
Yu et al 2013 China[127]	M & W 40-74y	CH W:9.8y & M:5.4y	CHD	117366	Q4vs.Q1: 2.88 (1.44, 5.78)
Virtanen et al 2014 Finland[128]	M 42-60y	SFA 21.4y	CHD	1981	$Fatal_{Q4vs.Q1}$: 0.88 (0.48, 1.62) $Non\text{-}fatal_{Q4vs.Q1}$: 1.05 (0.70, 1.57)

Li et al 2015 USA[129]	M & W 30-75y	SFA & CH 24 - 30y	CHD	127536	$SFA_{Q5vs.Q1}$: 0.93 (0.82, 1.05) $CH_{Q5vs.Q1}$: 1.04 (0.94, 1.14)
Praagman et al 2016 The Netherlands[130]	M & W ≥55y	SFA & CH for SFA 16.3y	CHD	4722	$SFA_{per5E\%}$: 1.13 (0.94, 1.36) Per 5E%: 0.90 (0.80, 1.02)
Praagman et al 2016 The Netherlands[131]	M & W 20-70y	SFA & CH for SFA 12y	IHD	35597	$SFA_{per5E\%}$: 0.83 (0.74, 0.93) Per 5E%: 1.23 (1.09, 1.40)
Dehghan et al 2017 Five Continents[132]	M & W 35-70y	SFA & CH 7.4y	MI	135335	$SFA_{Q5vs.Q1}$: 1.17 (0.94, 1.45) $CH_{Q5vs.Q1}$: 0.90 (0.73, 1.10)
Sluijs et al 2017 The Netherlands[133]	M & W 20-70y	SFA 15y	CHD	36520	Q4vs.Q1: 0.96 (0.82, 1.12)
AlEssa et al 2018 USA[134]	M & W 30-75y	CH 27y	CHD	117885	Q5vs.Q1: 1.04 (0.96, 1.14)
Haugsgjerd et al 2020 Norway[135]	M & W 46 – 49y	SFA & CH	CHD	2995	$SFA_{Q4vs.Q1}$: 0.44 (0.26, 0.76) $CH_{Q4vs.Q1}$: 2.10 (1.22, 3.63)
Sieri et al 2020 Europe[136]	M & W 35-70y	CH 12,8y	CHD	338325	Q5vs.Q1: 1.15 (1.00, 1.32)

The literature review is restricted to epidemiological cohort studies published after year 2000, evaluating the association between total saturated fatty acids and/or carbohydrates with CHD. Studies with an exclusively older population and studies only evaluating fatal CHD events or CVD were excluded. In studies reporting estimates both for the middle-aged and the older population, only estimates for the middle-aged population are reported. When studies have evaluated different carbohydrate quality as exposure, only results for total carbohydrates are included. All results are from the fully adjusted models. The literature was identified through search in PubMed, Web of Science and Embase. Search terms included "SFA", "saturated fatty acids", "fat", "carbohydrates", "dietary", "intake", "CHD" "coronary heart disease", "middle-aged", "cohort study" and "English language". In addition, an evaluation of studies included in relevant review and meta-analyses was made. The last search was performed 5th of December 2020. MI indicates myocardial infarction; CHD, coronary heart disease; IHD, ischemic heart disease; M, men; W, women; y, years; N, number included in the study population; HR, Hazard ratio; RR, Risk ratio; CI, Confidence interval; SFA, saturated fatty acid; CH, carbohydrates; Q4, quartile; Q5, quintile; SD, standard deviation; E%, energy percent.

Intake of saturated fatty acids and coronary heart disease

Dietary SFA were first linked to increased CHD risk in the Seven Countries Study.[137, 138] Keys et al. related the mean intake of dietary factors from 16 populations in seven countries to CHD mortality, and found that death rates were positively related to the average percentage of dietary energy from SFA.[137]

Possible positive effects of SFA substitution scenarios on CHD risk factors other than lipids and lipoproteins are unclear.[70, 139]

A Cochrane review including 15 randomized controlled trials (RCTs) that assessed the effect of reducing SFA on mortality and cardiovascular morbidity reported no clear reduction in total MI or total CHD events (Relative Risk (RR) 0.83; 95% Confidence interval (CI) 0.68, 1.01) when reducing dietary SFA.[140] Further, a recent review evaluating the efficacy of dietary interventions for CVD prevention concluded that the certainty of evidence for an effect of reduced SFA intake was low for MI and very low for CHD.[141] On the other hand, a recently published prospective cohort study assessing dietary fat intake in relation to total and cause-specific mortality found a positive association between intake of SFA and CVD mortality (Hazard Ratio (HR) 1.07; 95% CI 1.05, 1.09) when 1 Standard deviation (SD) increment in SFA was substituted for carbohydrates.[142]

Results from cohort studies evaluating the association between SFA and CHD are diverse, as shown in **Table 2**. In a study by Jakobsen et al, of 3686 Danish men and women, a strong positive association between SFA and CHD was found only among younger women (HR 2.48; 95% CI 1.33, 4.65).[4] On the other hand, in a cohort study by Praagman et al a reduced risk of IHD with increased intake of SFA was found (HR 0.83; 95% CI 0.74, 0.93).[131] Similar results have been reported among women in a cohort study by Wallström et al (HR 0.67; 95% CI 0.46, 0.97).[123]

Meta-analyses of prospective cohort studies have not shown a clear association between intake of SFA and CHD.[143-145] Siri-Tarino et al found no association between SFA intake and risk of CHD (RR 1.07; 95% CI 0.96, 1.19).[143] Further, meta-analyses by Chowdhury et al, that included four additional studies [144] as well as by de Souza et al, with 12 studies,[145] observed no association between SFA intake and risk of CHD. However, a recent published meta-analysis of 29 prospective cohort studies

evaluating the association between dietary fat and all-cause and cause-specific mortality found a positive association between SFA intake and CHD mortality (HR 1.10; 95% CI 1.01, 1.21).[146] Also, Wang et al, found that the proportional attributable CHD deaths (percent of total CHD deaths) due to higher SFA intake (>10E%) in Western Europe was 4.5 (uncertainly interval 4.3, 4.8).[147]

A recent paper summarizing the debate around SFA and CVD, briefly described topics of agreement, disagreement and research needed, stated that *"Advice to maximally reduce SFAs can have unintended consequences if implementation is done inappropriately with respect to the nutrients and foods that are substituted."*[139]

Intake of carbohydrates and coronary heart disease

Seidelmann et al recently published a large prospective cohort study and meta-analysis which found that both high and low percentages of carbohydrates in diets to be associated with increased mortality, with lowest risk observed at 50-55 E% carbohydrate intake.[148] However, sources of carbohydrates are diverse, and high-carbohydrate foods are heterogenous in their associations with CHD. Higher intake of carbohydrates at the expense of SFA have been positively associated with the prevalence of atherogenic dyslipidemia.[149] Sugar, also from fruit, contributes to atherogenic dyslipidemia.[70, 150] However, Bhupathiraju et al found that those in the highest quintile of fruit intake had lower risk of CHD (RR 0.88; 95% CI 0.80, 0.96).[151] In contrast, there are several examples of studies that have found a positive association between sugar containing products and CHD events.[152]

RCTs have shown that increased consumption of whole grains high in fiber associate with a decrease in blood pressure, [153] improved lipid profiles,[154] and an increase in insulin sensitivity.[155] Further, Barret et al recently published a review of observational studies reporting whole grain and cereal fibre or bran intake in association with any CVD-related outcome, concluding that intake of whole grain, cereal fibre and bran were similarly associated with lower risk of CVD-related outcomes.[156] On the other hand, a Cochrane review including 21 randomized studies evaluating low GI diets for the prevention of CVD, concluded that there was insufficient evidence from RCTs to recommend consumption of low GI diets for the

purpose of improving blood lipids or blood pressure.[157] Ho et al investigated the nonlinear associations between macronutrient intake and incident CVD, and found a positive association between intake of sugar and CVD, while dietary fiber intake was weakly inversely related to incident CVD.[158]

Several cohort studies have evaluated the association between intake of carbohydrates and CHD (**Table 2**). In a pooled analysis of 11 cohort studies, Jakobsen et al reported that replacement of 5E% from SFA with carbohydrates was associated with a higher risk of coronary events (HR 1.07; 95% CI 1.01, 1.14).[119] In a later study by Jakobsen et al, including 53644 men and women, and considering the carbohydrate quality, they found that only when substituting SFAs with high GI carbohydrates it was associated with increased risk of MI (HR 1.33; 95% CI 1.08, 1.64), while the association was opposite when substituting SFAs with whole grains (HR 0.88; 95% CI 0.72, 1.07).[121] The same associations were also found in a study by Li et al. They found that replacing 5E% from SFA with carbohydrates from whole grains was associated with a 9% lower risk of CHD, while when replacing it with carbohydrates from refined starches/added sugars there seemed to be a weak increased risk of CHD.[129] This association was not replicated in a later study. However, this study combined SFA and TFA in one category, which may have influenced the results.[126] A Food and Agriculture Organization (FAO) report found that replacement of fat with refined carbohydrates may increase risk of the metabolic syndrome, but not CHD,[159] and the Cochrane study by Hooper et al, including RCTs, found that replacement of SFA with carbohydrates was not associated with a decreased risk of neither total MI (RR 0.96; 95% CI 0.86, 1.06) nor total CHD events (RR 0.93; 95% CI 0.78, 1.11). [140]

One of the conclusions of the American Heart Association's Presidential Advisory on dietary fats and CVD published in 2017 was that a dietary strategy of reducing intake of total fat, including SFA, and replacing it mainly with unspecified carbohydrates does not prevent CVD.[160] Also, a systematic review of the effect of dietary SFA on heart disease concluded that reducing SFA and replacing it with carbohydrates will not lower CHD events, while replacing it with PUFA, MUFA or high-quality carbohydrates will lower CHD events.[161]

Shift from focus on single nutrients to foods and dietary patterns

In recent years, dietary guidelines as well as research, to a certain degree, have changed their focus from single nutrients to foods and dietary patterns in order to make recommendations more relevant to consumers. Also, there has been greater awareness of nutrient and food matrix interactions which further supports the need for shifting focus from individual nutrients to dietary patterns.[162]

Bechthold et al conducted a systematic review and dose-response meta-analysis of prospective studies evaluating the associations between food groups and risk of CHD.[163] Regarding high-carbohydrate foods, they found an inverse association between consumption of whole grains, vegetables and fruits with CHD risk, while there was a positive association between consumption of sugar-sweetened beverages and CHD risk.[163] They found a positive association between red meat and processed meat, high in SFAs, with CHD risk.[163]

Kwok et al summarised the highest level of evidence and ranked the risk associated with each individual component of diet within its food group and found that among carbohydrates and SFA sources, grains and vegetables appeared to be beneficial for CVD, while processed meat and canned fruit appeared to be harmful.[164] Intake of cheese has also been found to be inversely associated with CHD.[165]

Vitamin K

Forms of vitamin K

Vitamin K appears as phylloquinone, also known as vitamin K1 (K1), menaquinone (MK), also known as vitamin K2 (K2), and menadione, also known as vitamin K3 (K3). All vitamin K forms have a 2-methyl-1,4-napthoquinone ring but differ in whether they have a side chain and also in the structures of the side chain.[166] K1 has a side chain of isoprenoid residues were three are saturated, while K2 has a 3-substituted lipophilic side chain and side chains with mostly unsaturated isoprene residues (**Figure 2**). The number of isoprenoid units, and the degree of saturation, gives rise to the MKs nomenclature. K3 constitutes of the 2-methyl-1,4-napthoquinone ring only.[166]

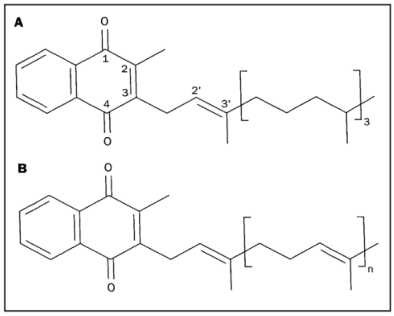

Figure 2. *Chemical structure of vitamin K1 (A) and vitamin K2 (B). Reprinted with permission from The Lancet.*[166]

Mechanisms

The vitamin K cycle is essential for the posttranslational carboxylation of glutamic acid residues (Glu) in proteins to form carboxyglutamate residues (Gla) by the enzyme ɣ-glutamyl carboxylase.[167] The active cofactor form of vitamin K required by the enzyme is the reduced form vitamin K quinol (KH_2). During carboxylation, the carboxylated Gla proteins are secreted into the circulation and KH_2 becomes oxidized to vitamin K epoxide. This epoxide metabolite is reduced to vitamin K quinone by the enzyme VKOR. Vitamin K quinone is then further reduced to KH_2 by a vitamin K reductase activity to complete the cycle (**Figure 3**).[168]

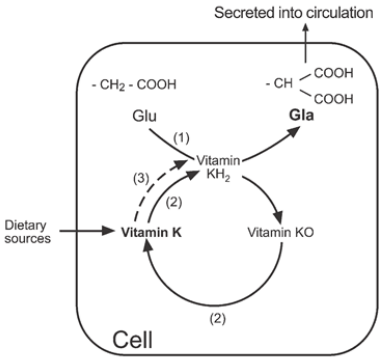

Figure 3. *Metabolism of vitamin K via the vitamin K-epoxide cycle. Reprinted with permission from Journal of lipid research.* [168]

Vitamin K dependent Gla proteins include, but are not limited to, seven involved in blood coagulation, osteocalcin in bone, matrix Gla protein (MGP) mainly in cartilage and vessel walls and growth arrest-specific protein 6 (Gas-6) in cell proliferation.[169] Further, clinical studies have reported several properties of vitamin K, including having antioxidant activity.[170] While K1 preferentially assists carboxylation of clotting factors in the liver, long chain K2 are available for extra-hepatic tissues.[171] Together, MGP and Gas-6 perform local vascular regulation, and a failure of these mechanisms might lead to vascular calcification.[167] Due to the mechanisms of the vitamin K dependent proteins, vitamin K is assumed to inhibit the development of atherosclerosis.

Warfarin is used to treat atrial fibrillation, venous thromboembolism, and valvular stenosis,[172] however, it disrupts the vitamin K cycle and may increase risk for vascular calcification.[168]

Sources of vitamin K

K1 is found in green, leafy vegetables, including kale, broccoli and spinach, and also in oils, such as rapeseed, sunflower and olive oils.[173] K2 is mainly found in animal products such as meat and dairy products.[173] However, K1 is also converted into MK-4, probably in the intestine, and it accumulates in extrahepatic tissues.[174] It was previously assumed that much of the daily requirement for vitamin K was supplied from production of K2 in the colon, while today we know that the absorption from colon is probably low.[175] K1 constitutes most of the vitamin K intake, while 10-25% seems to be provided by K2, primarily from dairy sources. [173] Still, the contribution of K2 to vitamin K status is at least equal to that of K1, due to differences in bioavailability.[173, 176] K3 is a synthetic form of vitamin K, but natural occurrence in staphylococcus aureus has been reported, and it seems to also be a biosynthetic precursors of other forms of vitamin K.[177]

Vitamin K and fat contents in dairy products are proportional, and MK9-11 accounts for approximately 90% of vitamin K in dairy foods.[178] Vitamin K content of cheeses ranged from 40μg/100g to ≤850μg/100g in a study by Fu et al.[178] Lactic acid bacteria used as starters in dairy and fermented food include a variety of bacterial

strains. The specific strains used and production conditions during fermentation, such as pH, temperature and duration affect the concentrations and forms of K2 in food products.[175, 179] Presence of K2 in nonfermented products may come from the microbial content of the ruminant digestive system, but contents in meat and fish are low.[173, 179]

Recommended intake

Guidelines on vitamin K intake differs globally, are mainly given for intake of K1 and is based on information about daily intake of K1 in healthy individuals and the requirement in order to achieve proper blood coagulation.[180-182] The European Food Safety Authorities (EFSA) has set Adequate Intakes (AI) to be 1μg K1 /kg body weight per day giving the recommended intakes of 90 and 120μg/day for women and men, respectively,[181] while the World Health Organization (WHO) and the FAO recommend a dosage of 65μg/d for men and 55μg/d for women.[180] The Nordic Nutrition Recommendations 2012 gives only a provisional recommendation of 1μg of vitamin K/kg body weight per day for both children and adults.[182]

Vitamin K deficiency is characterized by a bleeding tendency due to impaired blood coagulation.[181] Clinically indicated use of vitamin K is a prophylactic against vitamin K deficiency bleeding in neonates,[183] as an antagonist in patients on vitamin K antagonist treatment prior to surgery or when international normalization ratio (INR) values are high and give prolonged bleeding.[184, 185] However, the triage theory that when the availability of a micronutrient is inadequate, there may be compensatory mechanisms protecting short-term survival,[169, 186] may apply for vitamin K. The recommended intake may not be sufficient for optimal function of all the vitamin K dependent proteins.[169]

Table 3. *Overview of current literature published 2000-2020 on the association between dietary vitamin K with coronary heart disease and cardiovascular disease mortality.*

Author, year, country	**Sex, age**	**Exposure, Follow-up time**	**Event**	**N**	**Main findings HR/RR (95% CI)**
Geleijnse et al 2004 The Netherlands[187]	M & W ≥55y	K1 & K2 7.2y	CHD	4807	$K1_{T3vs.T1}$: 0.89 (0.63, 1.25) $K2_{T3vs.T1}$: 0.59 (0.40, 0.86)
Erkkila et al 2005 USA[188]	W 38-65y	K1 16y	CHD	72 874	Q5vs.Q1: 0.84 (0.71, 1.00)
Erkkila et al 2007 USA[189]	M 40-75y	K1 14y	CHD	40 087	Q5vs.Q1: 0.91 (0.77, 1.06)
Gast et al 2009 The Netherlands[190]	W 49-70y	K1 & K2 8.1y	CHD	16 057	$K1_{per10\mu g}$: 1.00 (1.00, 1.02) $K2_{per10\mu g}$: 0.91 (0.85, 1.00)
Juanola-Falgarona et al 2014 Spain[191]	M & W 55-80y	K1 & K2 4.8y	Fatal CVD	7216	$K1_{Q4vs.Q1}$: 0.63 (0.31, 1.28) $K2_{Q4vs.Q1}$: 1.18 (0.60, 2.34) $K1_{increase\ during\ follow\text{-}up}$: 0.52 (0.31, 0.86) $K2_{increase\ during\ follow\text{-}up}$: 0.76 (0.44, 1.29)
Zwakenberg et al 2017 The Netherlands[192]	M & W 20-70y	K1 & K2 16.8y	Fatal CHD	33 289	$K1_{Q4vs.Q1}$: 0.85 (0.59, 1.24) $K2_{Q4vs.Q1}$: 0.77 (0.47, 1.26)
Haugsgjerd et al 2020 Norway[193]	M & W 46-49y	K1 & K2 11y	CHD	2987	$K1_{Q4vs.Q1}$: 0.69 (0.38, 1.27) $K2_{Q4vs.Q1}$: 0.58 (0.28, 1.19)

Due to few publications in the field, the literature review includes cohort studies published after year 2000 evaluating the association between vitamin K with total CHD, CHD mortality and CVD mortality. All results are from the fully adjusted models. The literature was identified through search in PubMed, Web of Science and Embase. Search terms included "vitamin K", "vitamin K1", "phylloquinone", "vitamin K2", "menaquinone" "coronary heart disease", "CHD", "cardiovascular disease", "CVD", "middle-aged", "cohort study" and "English language". In addition, an evaluation of studies included in relevant review and meta-analyses was made. The last search was performed 5th of December 2020. CHD indicates coronary heart disease; CVD, cardiovascular disease; M, men; W, women; y, years; N, number included in the study population; HR, Hazard ratio; RR, Relative risk, CI, confidence interval; K1, vitamin K1; K2, vitamin K2; T3, tertile; Q4, quartile; Q5, quintile.

Vitamin K and coronary heart disease

Few cohort studies have investigated the association between dietary vitamin K and incident CHD, therefore studies with CVD as the event will also be evaluated here (**Table 3**). Geleijnse et al examined whether dietary K1 and K2 were related to aortic calcification and CHD in the Rotterdam Study.[187] They found that dietary K2 was

associated with reduced risk of incident CHD (RR 0.59; 95% CI 0.40, 0.86) in a model adjusted for age, sex, total energy intake, BMI, smoking, diabetes mellitus, education and dietary factors, while K1 was not associated with incident CHD.[187] Gast et al examined the relationship between dietary K1 and K2, and its subtypes, and incident CHD and found an inverse association between K2 and risk of CHD with a HR of 0.91 (95% CI 0.85, 1.00) per 10µg/d vitamin K2 intake.[190] Erkkila et al examined the feasibility of using K1 as a marker of CHD risk in women and found that after adjustment for age, lifestyle factors and dietary factors and comparing the highest with the lowest intake quintile, there was a reduced risk of CHD (RR 0.84; 95% CI 0.71, 1.00). However, they concluded that dietary and lifestyle patterns associated with K1 intake might account for all or part of the association.[188] Later, when Erkkila et al examined the association between dietary K1 and risk of CHD in men, they found that in the model adjusted for age, BMI, smoking, history of elevated blood pressure and serum cholesterol, diabetes mellitus, parental history of MI, physical activity, aspirin use, alcohol intake, use of multivitamin supplements, energy intake and dietary factors, RR of total CHD events when comparing the fifth with the first quintile was 0.91 (95% CI 0.77, 1.06).[189] Zwakenberg et al.found that only high intakes of long chain K2 were borderline associated with lower CHD mortality with a HR per 10µg/d of 0.86 (95% CI 0.74, 1.00).[192] Juanola-Falgarona et al studied the association between dietary K1 and K2 with mortality in a cohort with high CVD risk, and found that only increased intake of K1 during follow-up was associated with a reduced risk of CVD mortality (HR 0.52; 95% CI 0.31, 0.86).[191]

A review from 2012 concluded that based on observational studies of dietary vitamin K, intake of K2 may be more likely to protect against vascular calcification than K1.[194] However, there is evidence that K1 supplementation is of importance to vascular calcification.[195] In 2018, Zhang et al performed a meta-analyses on the association between intake of K1 and K2 with CVD mortality, concluding that neither were associated with CVD mortality.[196] In 2019 Chen et al performed a meta-analyses on the association between vitamin K and CVD events and all-cause mortality. They found an inverse association of both vitamin K1 and K2 with total CHD.[197] However, both meta-analyses included few studies (≤ 4 studies).[196, 197]

2. Study rationale and aims

In Paper I the aim was to investigate the effect of weight change on risk of mortality in community-dwelling older people, whose weight and height were measured in their mid-sixties and again in their early seventies, with subsequent 14 years follow-up with regard to mortality.

In Paper II the aim was to evaluate associations and possible interplay of carbohydrate and SFA intakes with incident CHD events in a sample of middle-age community-dwelling adults.

In Paper III the aim was to evaluate associations between intake of vitamins K1 and K2 and incident CHD events among middle-age community-dwelling adults.

3. Material and methods

3.1 Data sources

3.1.1 The Hordaland Health Studies (HHS)

The Hordaland Health Studies (HHS) (https://husk-en.w.uib.no/) were conducted in 1992-93 (The Hordaland Homocysteine Study) and in 1997-99 (The Hordaland Health Study, HUSK). Both surveys were conducted as a joint project between the University of Bergen, the Norwegian Health Screening Service (SHUS) (now part of the Norwegian Institute of Public Health) and the Municipal Health Service in Hordaland.[198] The Hordaland Health Study is included in Cohort of Norway (CONOR).[199] CONOR is a multipurpose study, with the aim to study aetiological factors for a range of diseases, and also to describe Norwegian men and women in terms of distribution of exposures and health status according to time, place and socio-economic factors.[199]

About 7,000 of those who participated in the 1992-93 survey also participated in 1997-99.[198] Participants included in this project, from The Hordaland Health Study, included 2.291 men and 2.558 women born 1950-51 and 1.868 men and 2.470 women born 1925-27 who had also participated in the study in 1992-93. Participation rates in these groups in 1997-99 were 73 %, 81 %, 79 %, and 76 %, respectively.[200] Baseline measurements in 1997-99 included height, weight, waist and hip circumferences, blood pressure, heart rate, non-fasting analyses of serum total cholesterol, HDL cholesterol, triglycerides, and glucose. Self-administered questionnaires provided information on various health behaviors including physical activity and smoking habits. Serum lipids were analyzed at the Department of Clinical Chemistry, Ullevål Hospital, Oslo using a Hitachi 911 analyzer. This analyzer came with adapted reagents and measurement methods from the company Boehringer Mannheim FRG (now: Roche, Basel, Switzerland).[201] Cholesterol and triglycerides were measured by enzymatic methods. HDL cholesterol was measured by a direct, enzymatic inhibition method.[200]

3.1.2 The National Population Register

The National Population Register (https://www.skatteetaten.no/en/person/national-registry) contains information of everyone who resides or have resided in Norway, and includes information on, among others, vital status (alive, emigrated, or dead).[202] The unique 11-digit personal identification number assigned to all Norwegian residents facilitates linkage between HUSK and The National Population Register.

3.1.3 The Cardiovascular Disease in Norway 1994-2009 Database

As described on https://cvdnor.w.uib.no/: The Cardiovascular Disease in Norway (CVDNOR) project was established as a collaborative research project between the University of Bergen and the Norwegian Knowledge Centre for the Health Services (now part of the Norwegian Institute of public Health).[203, 204] Information on hospital stays with a CVD-related diagnosis (International Classification of Diseases (ICD)9: 390-459, ICD10: I00-99, G45), diabetes mellitus (ICD9: 250, ICD10: E10-14) or congenital malformations of the circulatory system (ICD9: 745-747, ICD10: Q20-28) (either primary or secondary diagnoses) were retrieved from the electronic Patient Administrative Systems (PAS) of all Norwegian somatic hospitals during 1994-2009, using a semi-automatic program named FS (Forskning i Sykehus [English: Research in hospitals]) established by Tomislav Dimoski. In addition, all related diagnostic and interventional procedures performed during the hospitalization were obtained.[204]

From the CVDNOR project we received information on patient`s age at hospitalization, sex, municipality of residence, time and date of hospitalization and discharge, hospital, department and ward codes, main and secondary diagnosis (≤ 20), medical procedures (≤30) performed during the hospital stay, and information about whether the hospitalization was acute or elective. Hospitalizations less than 24 hours apart were merged and counted as one.[204]

3.1.4 The Norwegian Cause of Death Registry

The Cause of Death Registry (https://www.fhi.no/en/hn/health-registries/cause-of-death-registry/), established in 1951, covers all deaths in Norway.[205] Deaths are reported by physicians who are required to complete a death certificate. The official

cause of death statistics are prepared in accordance with the ICD, and the 10th revision of ICD was implemented in Norway in 1996.[205, 206]

From The Cause of Death Registry we received information on the time of death (date), age at death, underlying cause of death, municipality code for residency at the time of death, place of death (hospital/institution/during transport/outside institution), municipality code for place of death and basis for the diagnosis.

3.2 Study design

The study design in Papers I-III was community-based cohort studies. The follow-up period started in 1997-99 in all three studies, but ended in 2012 in study I, and in 2009 in study II and III.

3.3 Definition of exposures, endpoints and covariates

3.3.1 **Exposures**

In Paper I, exposure included change in weight between 1992-93 and 1997-99. Weight was measured both in 1992-93 and 1997-99, wearing light clothes without shoes to the nearest half-kg on a calibrated scale.[207] Weight change has been evaluated both as change in BMI and change in weight in previous studies.[21] Since weight change in kg tend to capture increases in fat mass more precisely than BMI change,[208] and since it also is a more intuitive concept that more easily can be communicated in recommendations,[209] weight change in kg were used in this project. Change in weight between the first and second measurements was categorized into loss (≥5%), stable (±<5%), and gain (≥5%).

As described in Papers II and III, exposures were obtained using a 169-item past-year semi-quantitative Food Frequency Questionnaire (FFQ), a modified version of a previously described FFQ,[210] completed by 87% of the participants.[200] FFQ provides time-integrated data that in these two papers represented usual intake the past year. It is the most affordable and easily administered diet assessment method, with the lowest respondent burden. The FFQ was handed out on the day of the health

examination, filled out at home, and returned by mail to the HUSK project center. It includes frequency alternatives (from once a month to several times per day), the number of units eaten and portion sizes (e.g., slices, glasses, spoons) to capture the habitual diet during the past year. The information is presented as individual food or beverage items, food groups and nutrients. Daily nutrient intakes were computed from a database and software system developed at the Department of Nutrition, University of Oslo (Kostberegningssystemet, version 3.2). The nutrient database is primarily based on the official Norwegian food composition table [211], and in Paper II, exposures were the total dietary amount of SFA and carbohydrates, as well as intake of SFA and carbohydrates from different food items. All are expressed as E%. We also evaluated SFA after excluding the contribution from cheese for their associations with incident CHD.

As described in Paper III dietary data from other sources in addition to the Norwegian food composition tables were needed, and information on vitamin K primarily came from available literature from other countries.[173] Data for K1 also came from public authorities in Finland,[212] Sweden[213] and USA.[214] For some food products, analyses had been performed using high performance liquid chromatography of fermented foods.[215] K2 was evaluated with no distinction between the different menaquinones. Vitamin K intake reflects dietary sources only. Both energy-adjusted residuals and actual intake of K1 and K2 were used as the final exposure.

3.3.2 Endpoints

In Paper I endpoints were all-cause mortality, obtained by linkage to the National Population Register. Participants were followed from baseline through 31.12.2012 for death events (**Figure 4**). There were 1159 events during follow-up.
In Papers II and III, endpoints were incident (first time) hospitalization with CHD (ICD9 codes 410-414, ICD10 codes I20-I25) as primary or secondary diagnosis or death with CHD as the underlying cause of death. Participants were followed from baseline through 31.12.2009 for CHD events through the CVDNOR (www.cvdnor.no)[203, 216] project and The Cause of Death Registry (**Figure**

4). There were 107 non-fatal and 5 fatal episodes; 41 participants experienced a MI and 71 participants experienced stabile/unstable angina pectoris.

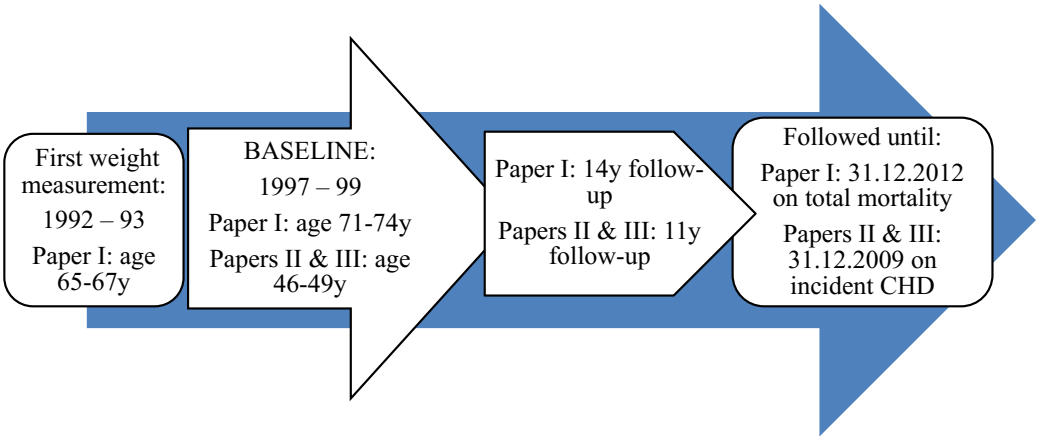

Figure 4. *Overview of follow-up and age at baseline in all three papers.*

3.3.4 **Potential covariates**

Covariates are variables that are included in statistical models to adjust for potential confounding and to produce more precise effect estimates.[217]

A simple definition of confounding is defined as the confusion of effects, and indicates that the effect of the exposure is mixed with the effect of another variable (**Figure 5**).[218]

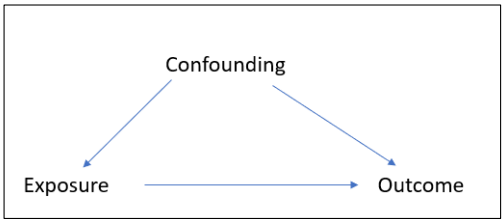

Figure 5. *Confounding*

A mediator, also called an intermediate variable, is a variable that occurs in a causal pathway from an exposure to an outcome (**Figure 6**).[219]

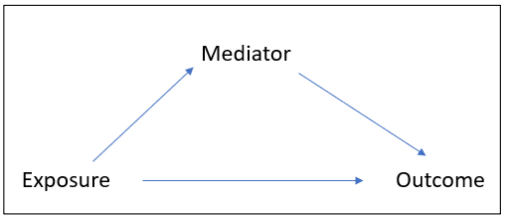

Figure 6. *Mediator*

Paper I	**Mediators** → BMI* **Confounders** → age, sex, physical activity, smoking habits, self-reported diabetes mellitus, self-reported use of medication for hypertension, previous MI or/and stroke, education*
Paper II	**Mediators** → LDL cholesterol*, HDL cholesterol*, triglycerides*, glucose*, systolic blood pressure*, diastolic blood pressure*, BMI*, hypertension*, diabetes mellitus*, statins*, oral hypoglycemics*, insulin*, anti-hypertensive medications* **Confounders** → age, sex, total energy intake, physical activity and smoking habits, education* and family history of MI* **Dietary confounders** → energy adjusted intake of alcohol*, fiber from bread, fruit and vegetables*, cholesterol*, PUFA* and protein*
Paper III	**Mediators** → BMI*, diabetes mellitus*, hypertension*, serum total cholesterol* and statin use* **Confounders** → age, sex, total energy intake, physical activity, smoking habits, education, family history of MI* **Dietary confounders** → energy adjusted intake of fiber, folate, SFA and calcium, alcohol*

Figure 7. *Overview of mediators and confounders in the three papers*
*Covariates not adjusted for in the main analyses.

In Paper I, covariates for which we had data that, based on *a priori* knowledge, were suspected to be confounders and were found to modify the association between weight change and total mortality were included in the multivariable models (**Figure 7**).

In nutritional epidemiology, methods for selection of covariates are non-consistent.[217] In Papers II and III, the included covariates were *a priori* determined to be potential confounders and were found to modify the association of the nutrients of interest with CHD (**Figure 7**). In Papers II and III, intermediate variables adjusted for in previous studies[143-145, 196] were also evaluated to determine consistency in results. We did not intend to include these analyses as main analyses, however, in Paper II, they are attached as supplementary analyses in order to make the results easier to compare to results from previous research in the field. Selecting covariates based on whether it modifies the association between exposure and outcome may ignore theoretical and empirical understanding of important confounders and this relies heavily on the available data.[217, 220] However, only covariates we considered as potential confounders were included in the primary models. Further, some explanatory variables such as age and sex were included in the analyses even if they did not have any considerable influence on the association under evaluation.

When evaluating the number of covariates, we also found it of importance to bear in mind that including too many covariates may lead to data sparsity in which there are too few subjects at crucial combinations of covariates, with consequent inflation of effect estimates.[221] In addition, selecting factors highly predictive of the exposure can produce multicollinearity, and thus unnecessarily wide CIs and potentially inflated effect estimates.[220, 222] We found it of particular importance to bear this in mind when we evaluated dietary covariates.

Information collected at the baseline health examination

Height, weight, waist and hip circumferences, blood pressure, and heart rate were measured. Further, blood samples for analyses of serum total cholesterol, HDL

cholesterol, triglycerides, and glucose were collected.[200, 207] The Friedewald equation was used for calculation of LDL-cholesterol.[78]

Information from self-administered questionnaires

Myocardial infarction or/and stroke

Information on whether participants had experienced a previous MI or/and stroke came from self-administered questionnaires both in 1992-93 and 1997-99.[198] Information on a history of MI and stroke were combined, such that all who answered yes at first and/or second survey to either of the two questions were classified as having had an MI or/and stroke.

Diabetes mellitus

In Paper I participants were classified as having diabetes mellitus if they answered yes at the first measurement in 1992-93 and/or second measurement in 1997-99.
In Papers II and III participants taking diabetes medications or reported having been diagnosed with diabetes mellitus were defined as having diabetes mellitus. Also, participants with a serum glucose level >7mmol/L who had not eaten a meal during the last 8 hours, or with a glucose level >11.1mmol/L and less than 8 hours since their last meal, were defined as having diabetes mellitus.

Hypertension

In Paper I participants were classified as having hypertension if they reported taking blood pressure medication. In Papers II and III, hypertension was defined as present if the mean of at least two consecutive measurements of systolic blood pressure was ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or if they reported to use hypertension medication.

Physical activity

Physical activity was self-reported, using two questions, one where participants reported how many times per week they performed light physical activity and one were they reported how many times per week they performed vigorous physical activity. These two questions, which are included in the CONOR questionnaire on health behaviours, were used to make one variable on physical activity, categorized in none/light physical activity and moderate/vigorous physical activity. In Paper I, those who answered that they performed vigorous physical activity one hour or more per week were categorized in the group moderate/vigorous, all other were categorized in the group none/light physical activity. In Papers II and III, only the question on past-year vigorous physical activity (none, < 1h/week, 1-2 h/week, or ≥3 h/week) was used, and this variable was treated as a categorical variable with none as the reference.

Education

Highest level of education was included as a categorical variable including the categories primary school (≤10 years), high school or vocational school, and any college or university. Primary school (≤10 years) was used as the reference category.

Smoking habits

Participants were categorized into never smokers, former smokers and current smokers based on their answers on three questions: *"Do you smoke cigarettes, cigars, cigarillos/pipe?"* answered both in 1992-93 and 1997-99, and the questions *"Never smoked daily?"* and *"Number of years since you stopped smoking daily?"* answered only in 1997-99. The category with non-smokers was used as the reference.

Family history of myocardial infarction

Information on family history of MI came from the question *"Has one or more of your parents/siblings had a MI before they turned 60 years old?"* answered in 1997-99.

3.4 Statistical methods

The Cox proportional hazard regression model is a regression model for analyses of survival data and was used in all three papers. Both survival analyses in general and Cox proportional hazard regression will be described below.

Survival analyses

Survival analysis methods are used when we are interested in the time until an event of interest occurs. The event could for instance be death or an incident case of CHD. A key feature of 'survival-time' data is the presence of 'censored' observations. An observation is censored if we do not observe the event of interest for an individual during the follow-up time in the study. For most of the individuals this occurs because the study is ended before everybody has experienced the event, but censoring can also occur if the person is lost to follow-up (e.g withdrawal from a study, emigration, death from other causes than the event of interest). For censored observations we do not know the exact time until the event occurs, we only know that the person was event-free at least until the time of censoring. Statistical methods within survival analysis takes censoring into account.[223]

The Kaplan Meier survivor estimate of the survivor function S(t) gives the probability of survival (not experiencing the event of interest) up to and after time t, and include information from both censored and uncensored observations.[223]

$S(t) = P(T \geq t) \rightarrow$ P = probability, T = time of event of interest, t = some time point.

The survival function is thus the probability that the time of an event is later than some specified time, t.[223]

The estimated survivor function can be presented graphically as a Kaplan Meier survival curve with S(t) versus t or as a failure curve with 1- S(t) versus t. The hazard function h(t) gives the probability that the event will occur in a small interval after a specified time t, given that an individual has survived up to time t. It is a rate, thus the values range between zero and infinity.[223]

Cox proportional hazard regression analyses

Cox proportional hazard regression models the hazard ratio (HR) as a function of one or more covariates:

$h(t) = h_0(t) \times \exp(\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p)$

Function $h_0(t)$ is the baseline hazard functions (i.e the hazard function if all covariates are zero) and is only dependent on time. The exponential part (exp) depends on the values of the covariates and regression coefficients. The exponentiate of the estimated regression coefficient for a given covariate is interpreted as a HR, that is the ratio of the hazard rate for those who e.g. experience exposure and hazard rate of those who did not experience exposure.[223] In the papers of the thesis, it is the hazard rate of those who lose or increase in weight to hazard rate of those with stable weight in Paper I and hazard rate of those with the higher intake of the specific nutrient to hazard rate of those with the lowest intake of the specific nutrient in Papers II and III. The model is semi-parametric, meaning that the model has both parametric and non-parametric components.[223]

Cox proportional hazard regression analyses were conducted in all three papers, estimating HRs and 95% CIs for each study outcome (Paper I: total mortality; Papers II and III: incident CHD), comparing participants with different weight change status (Paper I) and nutrient intake (Papers II and III).

Proportional hazard assumption

A Cox regression is done on the assumption that the HR between two or more groups are constant at all times t, $H(t)/H_0(t)=h(t)/h_0(t)=\text{constant}=HR$. This does not mean that the hazard rate cannot change over time, but the relationship must be constant. This was checked by evaluating log-(log) survival plots for all relevant variables and by performing the Schoenfeld test.[223]

Multivariable analyses

Multivariable analysis makes it possible to address whether an observed association between the specific exposure and event is merely secondary to its correlation with

other, causal factors (confounders).[224] The HR for a specific variable in a multivariable Cox regression is adjusted for all other covariates in the model and can be interpreted as the ratio of hazard between different levels of exposure when all other covariates in the model are kept constant. In all three papers, multivariable analyses were performed. Only possible confounders were included as covariates in our main analyses. In supplementary analyses in Paper II, intermediate variables were adjusted for as this have been done in previous studies in this field, and it is useful in order to compare with previous results.

Effect modification

We investigated possible effect modifications, which can be done in two different ways. One method is by adding an interaction term in the cox regression analysis, and comparing a model with an interaction term with a model without an interaction term using likelihood-ratio test, while the second method is to see whether the effect of exposure varies in strata of the covariate.[225]

Penalized splines

When modelling continuous variables with standard Cox regression we assume a linear association between log(hazard) and the variable, which may not always be true. One way of allowing for non-linear associations is to model the variable with smoothing splines. Penalized spline is a variant of smoothing spline with more flexible choice of bases, knots and penalties. Penalized splines combine the flexibility of non-parametric methods with stability and simplicity of parametric smoothers. The estimated smooth function can thus be used to plot the relative hazard of the desired endpoint against the explanatory variable, and non-linear relationships can thus be investigated visually.[226] In all three papers, Cox regression with penalized splines were used to illustrate the functional form of exposure estimated by a smoothing spline, in which the estimated smooth function were used to plot the relative hazard of event against exposure as a continuous variable.[226]

Missing data

Missing data on covariates were handled with listwise deletion in analyses included in the main manuscript in all three papers. When performing listwise deletion, also called complete case analysis, only subjects with complete data are included in the analysis.[227] Therefore, multivariable-adjusted analyses in Paper I included 2330 participants and 895 events, in Paper II 2820 participants and 105 CHD events, and in Paper III 2792 participants and 100 CHD events.

However, in supplementary analyses in Paper III, missing values for physical activity, smoking and education were imputed using ordinal logistic regression as the imputation model in MICE (multiple imputation using chained equation) with 20 imputations.[228] This is a repetitive method for data with several variables with missing values in a non-monotone pattern.[228] The key concept of multiple imputation is to use the distribution of the observed data to estimate a set of plausible values for the missing data.[228] As described in Paper III, all variables in the Cox regression models were included as imputation variables together with total cholesterol, HDL cholesterol, triglycerides and BMI as auxiliary variables due to their correlation with physical activity, smoking and education.

3.4.1 Overview of materials and methods in all three papers

	Paper I – weight change in older people and its association with total death	Paper II – Carbohydrates and SFA and its association with CHD	Paper III – Vitamin K and its association with CHD
Main aim	To evaluate the importance of weight change with regard to mortality in older people	To evaluate associations and possible interplay of carbohydrate and SFA intakes with CHD	To evaluate the association between intake of both K1 and K2 with CHD
Study design	Cohort study	Cohort study	Cohort study
Study population	2935 men and women, age 71-74y	2995 men and women, age 46-49 y	2987 men and women, age 46-49 y
Observation period	Time from 1997-99 until death or 31.12.2009.	Time from 1997-99 until CHD, death from other causes, emigration, or 31.12.2009.	Time from 1997-99 until CHD, death from other causes, emigration, or 31.12.2009.
Statistical methods	Kaplan-Meier failure curves*, Cox proportional hazard regression, Cox regression with penalized spline.	Cox proportional hazard regression, Cox regression with penalized spline.	Cox proportional hazard regression, Cox regression with penalized spline.
Confounders	Age, sex, physical activity, smoking, diabetes mellitus, hypertension, and previous myocardial infarction or stroke.	Age, sex, energy intake, physical activity and smoking	Age, sex, energy intake, physical activity, smoking and education. K1 was adjusted additionally for fiber and folate; K2 was adjusted for SFA and calcium.

*Figure 1 in Paper I should have been labeled Kaplan-Meier failure curves instead of Kaplan-Meier cumulative hazard curves.

Paper I *Association between weight change and mortality in community living older people followed for up to 14 years. The Hordaland Health Study (HUSK)*

In Paper I we excluded from the analyses six participants who emigrated after the second measurement, and 369 participants diagnosed with cancer before or between the surveys in 1992-93 and 1997-99 (information obtained by linkage to the Norwegian Cancer Registry).

Follow-up time was defined as time from baseline in 1997-99 until they experienced death or at 31.12.2012, whichever occurred first.
Kaplan-Meier failure curves were used to estimate hazard rates and multivariable Cox proportional hazard regressions estimated HR with 95% CIs for weight change in categories (%). Cox regression with penalized spline was used to evaluate the association between weight change (in kg) and mortality.

In supplementary analysis, Chi-square analyses or t-tests were applied to determine whether the survivors and non-survivors in the different weight change groups differed significantly on any of the baseline characteristics. Further, in order to eliminate early deaths that could be attributed to clinical or subclinical disease, two sensitivity analyses were performed after excluding persons who 1) died within two years after baseline (n=69), and 2) persons who were diagnosed with cancer within two years after baseline (n=136). In addition to percent weight change we also examined different measures of weight change, e.g. ± 3 kg and ±2 kg weight change. In addition, ± ≥ 5% changes in BMI were examined.

Paper II *Intake of carbohydrates and saturated fatty acids and risk of coronary heart disease in middle-age adults. The Hordaland Health Study (HUSK)*

In Paper II we excluded from the analyses 22 men and 5 women who reported prior CHD, and 4 men and 19 women due to missing information on prior CHD. Further, we excluded 27 men and 35 women who reported extreme energy intakes (below the 1st percentile; or above the 99th percentile).

The nutrient density method was used to adjust the exposures (nutrients) for total energy, giving the exposure as E% intake from the specific nutrient.

$$E\% = \frac{Energy\ intake\ from\ the\ specific\ nutrient}{\text{Total energy intake}}\ X\ 100$$

The coefficients for the nutrient density term represents the relation of the nutrient composition of the diet with disease since by adjusting the nutrient for energy, we separates the variation in nutrient intake due only to the nutrient composition of the diet from the complete variation in nutrient intake, which is due both to composition and overall consumption of food.[86] Energy adjusted nutrients are uncorrelated with total energy intake. Further, additional adjustment for total energy intake as a covariate can reduce measurement error (and width of confidence limits). This is because both specific nutrients and total energy are calculated from the same foods, and the effects of overreporting and underreporting will therefore apply to both variables, and an adjustment for total energy will tend to "cancel" these errors.[86] Also, when total energy intake is anticipated to be associated with the outcome as in these papers where incident CHD was the outcome, total energy should be included in the model in addition to the energy adjusted nutrient.[86]

Follow-up time was defined as time from baseline in 1997-99 until they experienced CHD, death from other causes, emigration, or at 31.12.2009, whichever occurred first. Multivariable Cox proportional hazard regression estimated HRs with 95% CIs for quartiles of SFA and carbohydrate intake, and also for continuous variables (per 2E%). Test for linear trends across quartiles was also performed. Cox regression with penalized spline was used to evaluate the association between SFA, carbohydrates and SFA minus SFA from cheese (in E%) and CHD.

When evaluating the association between higher or lower intake of energy adjusted nutrients with an endpoint, the higher or lower intake of an energy containing nutrient can only be accomplished by the exchange of other dietary variables. In substitution models, one dietary variable is replaced by another dietary variable, taking energy as the common unit across the dietary factors.[229, 230] We therefore used theoretical substitution analyses to model the substitution of carbohydrates with other nutrients. Variables for the E% (per 5E% unit increments) of all macronutrients except carbohydrates (SFA, MUFA, PUFA, protein and

alcohol) were included in a Cox model with adjustment for total energy intake, age, sex, physical activity and smoking habits. The HR for "the nutrient of interest" is then interpreted as the change in estimated risk for each 5E% unit increase in "the nutrient of interest" while holding all other variables in the model constant but allowing for concomitant decreases in carbohydrate intake as all sources of macronutrients sum to 100% of energy intake. A key assumption for any substitution analysis is that the total consumption of different nutrients under substitution is known and constrained to a certain level for each individual since the effect has to be assessed on the basis of equal amount of replacement.[231]

Supplementary analyses evaluated models adjusted for age, sex and energy intake, with additional adjustments for HDL cholesterol, LDL cholesterol, triglycerides, glucose, systolic blood pressure, diastolic blood pressure, and BMI; and with additional adjustments for diabetes mellitus, hypertension, family history of MI, statins, oral hypoglycemics (including metformin) and insulin, and anti-hypertensive medications; and additional adjustments for smoking, physical activity, alcohol consumption in E%, and education. In additional supplementary analyses, we stratified intake of SFA on smoking habits and we also evaluated associations between carbohydrates and SFA from other specific food groups and CHD risk. Also, sensitivity analyses were conducted where we excluded the first 2 years of observation following the baseline assessment in all of the above analyses.

Further, adjustment for energy-adjusted nutrients were performed but not included in the final models. In carbohydrate analyses adjustment for fiber from bread, fruit and vegetables were evaluated, while in SFA analyses adjustment for intake of cholesterol, PUFA and protein were evaluated. Due to the relatively few events, multivariable analyses with dietary factors were performed by including standard nondietary risk factors with two dietary factors at a time. This made it possible to evaluate whether they have no independent association with CHD and that the association with the primary nutrient remains.[224]

Paper III *Dietary vitamin K and risk of coronary heart disease in the prospective Hordaland Health Study*

In Paper III we excluded from the analyses 27 men and 35 women who reported extreme energy intakes (below the 1st percentile: or above the 99th percentile). Further, we excluded 22 men and 5 women who had prior CHD. Additionally, 4 men and 19 women with missing information on self-reported MI from the Homocysteine Study (1992-93) were excluded. Further, we excluded one man and one woman who reported use of Warfarin and 2 men and 4 women with missing measurement on dietary vitamin K intake.
Even though vitamin K does not contribute with energy, it is correlated with total energy intake. The spearman correlation coefficients between total energy intake and total vitamin K, vitamin K1 and vitamin K2 were 0.47, 0.43 and 0.59, respectively. We therefore decided to use energy-adjusted residuals as exposure in the main analyses. Energy-adjusted residuals were obtained from linear regression models with total energy intake as independent variable and K1 or K2 as dependent variables. Residuals were then categorized into sex-specific quartiles.

The residuals measure the difference between actual intake and expected intake predicted by total energy intake and thereby provides an assessment of K1 and K2 intake relative to energy consumed. The residuals will have a mean of zero and includes negative values (**Figure 8**).[86]

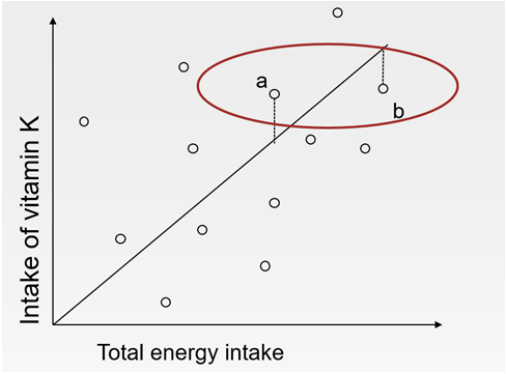

Figure 8. *Nutrient residuals.*
Person a and b have almost the same intake of vitamin K, but due to differences in total energy intake, person a will have a positive value, while person b will have a negative value and person a will therefore be in a higher intake quartile, as vitamin K will make up a larger part of this persons diet.[86]

One possible caveat with nutrient residuals is that they assume that a given residual indicates the same effect across the spectrum of energy intakes (i.e., from small to large body sizes requiring greater energy intake). Willett emphasized, however, that among specific age-sex groups variations in body size and total energy are not large.[86] In this paper, the age range was narrow, and sex-specific quartiles were used, so this is not a major issue.

The coefficient and the standard error from the residual model in continuous analysis is identical to that from the standard multivariable model where only total energy intake is included.[86] In conducting categorical analyses, however, the interchangeability of the two methods does not apply, and statistical power will be higher with the residual method. The range in unadjusted vitamin K intake will be wider than for energy-adjusted vitamin K intake, and due to the collinearity between vitamin K and total energy intake, the CIs will be wider.[86]

Follow-up time was defined as time from baseline in 1997-99 until they experienced CHD, death from other causes, emigration, or at 31.12.2009, whichever occurred first. Multivariable Cox proportional hazard regression estimated HRs and 95% CIs for quartiles of both sex-specific energy-adjusted and absolute intake of K1 and K2. K1 and K2 were also evaluated per 10µg increments. Test for linear trends across quartiles was performed by using the median residuals for each quartile group as a continuous independent variable in the regression models.

In Cox regression with penalized spline the functional form of the association between absolute K2 intake and risk of CHD was estimated by smoothing splines, in which the estimated smooth functions were used to plot the relative hazards of CHD.

Data packages

In Paper I, statistical analyses were performed using STATA version 14 (Stata Corp. LP. College Station, TX), SPSS, version 21 (IBM SPSS, Armonk, NY:IBM) and R version 3.1.0 (https://www.r-project.org/), The R Foundation for Statistical Computing, Vienna, Austria. In Papers II and III, statistical analyses were performed using Stata version 15 (Stata Corp LP, College Station, TX) and R version 3.4.0 (https://www.r-project.org/), The R Foundation for Statistical Computing, Vienna, Austria.

In all three papers, a two-sided p-value <0.05 was considered statistically significant.

3.5 Ethical considerations/approval

The HUSK study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The Regional Committee for Medical Research Ethics (REC number: 14580) approved the study protocol. HUSK is registered in ClinicalTrials.gov (Clinical trial number: NCT03013725).

4. Results

4.1 Summary of results in Paper I

We followed 2935 men and women from 1997-99 through 2012, giving a median follow-up of 13 years and the average age at start of follow-up was 72.4 years.

During follow-up, 648 men and 511 women died. Compared to the stable-weight groups, Kaplan-Meier failure curve for the weight loss groups increased more rapidly for both sexes. The curves for the weight stable and weight gain groups followed each other closely the first few years, especially among women. The Log rank test showed significant differences in hazard between the three weight change groups in both sexes.

In the Cox proportional hazard regression model adjusted for age, sex, smoking, physical activity, MI and/or stroke, diabetes mellitus and being under treatment for hypertension, the HR was 1.59 (95% CI 1.35, 1.89, $p<0.001$) when comparing the weight loss group to the weight stable group. The excess mortality risk associated with weight loss was similar in men and women in the fully adjusted model. When evaluating weight gain in the fully adjusted model, weight gain was not associated with increased mortality risk, when compared to the weight stable group, HR 1.07 (95% CI 0.90, 1.28, $p=0.453$). Also when stratifying for sex, there were no associations between weight gain and mortality in the fully adjusted models.
When stratifying weight change by BMI categories (<25 kg/m^2, 25-29.9 kg/m^2, and ≥30 kg/m^2), the fully adjusted model showed that increased risk of mortality associated with weight loss persisted in participants with a BMI of <25 kg/m^2 and 25-29.9 kg/m^2, but not in participants with a BMI of ≥30 kg/m^2. The total group with weight gain did not have increased risk of mortality compared to stable weight also when stratified by BMI. The multivariable adjusted Cox regression with penalized spline of the relationship between weight change and mortality illustrated that both major weight gain and minor weight loss was associated with increased mortality in comparison with stable weight.

4.2 Summary of results in Paper II

We examined 1282 men and 1713 women from 1997-99 through 2009, providing a mean follow-up time of 10.8 years, and 112 incident CHD events. Median baseline age was 48 years.

Higher intake of carbohydrates was associated with higher risk of CHD when adjusted for age, sex, energy intake, smoking habits and physical activity and comparing the fourth to the first intake quartile (HR 2.10; 95% CI 1.22, 3.63, p-trend 0.003). Also, continuous analyses (per 2E%) showed higher risk of CHD with higher intake of carbohydrates (HR 1.12; 95% CI 1.05, 1.20) in the fully adjusted model. Plotting the data with multivariable adjustments indicated a linear relationship.

A high intake of SFA was associated with lower risk of CHD in the model adjusted for age, sex, energy intake, smoking habits and physical activity when comparing the fourth to the first quartile (HR 0.44; 95% CI 0.26, 0.76, p-trend 0.002). Also, continuous analyses (per 2E%) showed lower risk of CHD with higher intake of SFA (HR 0.78; 95% CI 0.66, 0.92) in the fully adjusted model. When plotting the data and performing multivariable adjustments, lower risk of CHD with a higher intake of SFA were illustrated until an intake of about 13E%, after which the curve levelled off. When examining the association between SFA from various food items, only SFA from cheese was significantly associated with a lower risk of CHD.

We further evaluated the association between SFA and CHD after excluding the SFA contribution from cheese and found that intake of SFA after exclusion of cheese was associated with lower risk of CHD when comparing the fourth to the first quartile (HR 0.58; 95% CI 0.34, 0.98, p-trend 0.030), after adjustment for age, sex, energy intake, physical activity and smoking habits. Results from the continuous analyses (per 2E%) were in the same direction as the quartile analyses, but we observed deviations from linearity in the association between SFA intake and CHD risk after excluding SFA from cheese.

Substitution of 5% of total energy intake from carbohydrates with SFA was associated with lower risk of CHD (HR 0.74; 95% CI 0.40, 1.36) in the fully adjusted

model. A substitution of carbohydrates with total fat was also associated with lower risk of CHD (HR 0.75; 95% CI 0.62, 0.90).

4.3 Summary of results in Paper III

We followed 1279 men and 1708 women from 1997-99 through 2009, resulting in a mean follow-up time of 10.8 years and 112 incident CHD events. Median baseline age was 48 years.

When adjusting for age, sex, total energy intake, physical activity, smoking habits and education, and comparing the fourth to the first quartile of K1 intake, there was no association between intake of K1 and CHD (HR 0.92; 95% CI 0.54, 1.57, p-trend 0.64). Results were similar when evaluating energy-adjusted K1 intake as a continuous variable (per 10µg increase). Additional adjustments for energy-adjusted fiber and folate did not materially change the results. Results were consistent with the above analyses when evaluating sex-specific quartiles of absolute K1.

When adjusting for age, sex, total energy intake, physical activity, smoking habits, and education and comparing the fourth to the first quartile, higher K2 intake was associated with lower risk of CHD (HR 0.52; 95% CI 0.29, 0.94, p-trend 0.03). Consistency in results were observed in analyses of K2 intake as a continuous variable (per 10µg increase). Additional adjustments for energy-adjusted SFA and calcium attenuated the risk estimates for the association between K2 intake and CHD (HR 0.58; 95% CI 0.28, 1.19, p-trend 0.16).

When evaluating sex-specific absolute K2 intake, HRs were similar to those observed in the energy adjusted analyses when comparing the fourth to the first quartile (HR 0.72; 95% CI 0.36, 1.45, p-trend 0.25), although the association was weaker. Similarly, the penalized spline figure for absolute K2 intake and its association with CHD adjusting for age, sex, total energy intake, physical activity, smoking habits and education showed a tendency toward lower risk of CHD with higher K2 intake.

5. Discussion

5.1 Summary of findings

This project evaluated weight change among older people and nutrients among middle-aged people as predictors of total mortality and CHD, respectively.

In Paper I, we found that in older people, both major weight gain and minor weight loss were associated with increased mortality in comparison with stable weight.

In Paper II, there was an inverse association between dietary SFA and CHD risk among middle-aged people. For carbohydrates, the opposite pattern was observed. When evaluating the association between sources of SFA and carbohydrates with CHD, only SFA from cheese associated with lower CHD risk.

In Paper III, we found no association between dietary vitamin K1 and CHD, while there was a lower risk of CHD associated with higher intakes of vitamin K2.

5.2 Methodological considerations

5.2.1 **Study design**

All three papers are prospective cohort studies, considered to be the strongest observational study design. A cohort study follows a defined group of people over a given period of time, prospectively into the future. A subgroup is identified who is, has been, or in the future may be exposed, or exposed to different degrees, to a factor (exposure) hypothesized to influence the occurrence of an event (endpoint).[219]

Two characteristics of observational studies will be addressed: precision and validity.

5.2.2 **Precision**

Precision is a relative lack of random error and can be evaluated by the standard error, the standard deviation or CIs around the effect estimate. Precision can be improved by increasing the study population or improving the study design.[232] In Paper I, the exposure (weight change) was measured (rather than self-reported) and there was a relatively large number of participants experiencing total mortality,

yielding relatively narrow CIs. The CIs were relatively wider in Papers II and III, due to the relatively small number of participants experiencing CHD (n=112). When stratifying on confounders the precision weakened even more, and stratification became problematic. Further, precision could also have been higher if diet had been measured more than once at baseline in Papers II and III, and also with more than only one measurement method. Most dietary assessment methods will have errors due to unsystematic day-to-day, diurnal, or seasonal variation in a person's diet.[233] However, FFQ used in these papers have lower random within-person variation than other methods since it assesses average usual intake over the past year, that is also the exposure time of etiologic interest for CHD.[234]

5.2.3 **Validity**

Internal validity is the degree to which a study is free from systematic error.[219] In studies with a large study population, almost all errors of concern are systematic errors such as selection bias, information bias, and confounding.[218]
Measures of validity are positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity.[235]

Selection bias

Selection bias results from systematic differences in characteristics between those who participate in the study and those who do not participate and occurs when the association between exposure and disease differs between those who participate and not.[218] It may result from procedures used to select subjects and from factors that influence participation.[235]
In HUSK invitations were sent to individuals born between 1925-27 (Paper I) and 1950-51 (Papers II and III), and who had earlier participated in a population study in Hordaland between 1992-93.[198]

Individuals who do not respond to an invitation to participate in community-based studies are often over-represented by people of lower social classes, single-households, immigrants, receivers of social security benefits, and people with poor self-reported health and an unhealthy lifestyle, and when a considerable number of invitees decline to participate, the study may be distorted by selection bias.[236] Large

prospective cohort studies are generally robust against bias arising from non-participation.[237] In our study, participation rate was 79% for men and 76% for women in Paper I, while in Papers II and III, participation rate was 77% in total, and 87% of the participants completed a semi-quantitative FFQ.[200] However, characteristics of participants and non-participants in HUSK based on data obtained in 1992-93 have been compared in a previous PhD thesis, where non-participants in 1997-99 had a greater proportion of smokers and no regular physical activity in 1992-93 compared to the participants in 1997-99.[238] Further, a report from HUSK 1997-99 found that the educational level was higher among the participants relative to the non-participants, for both men and women.[239]

In all three papers there was a small number of participants who emigrated during the follow-up period (6 participants in Paper I and 15 participants in Papers II and III), and they were evenly distributed between the exposure categories. Also, in Papers II and III, they contributed with follow-up time until they emigrated. Loss to follow-up was therefore not a problem in either of the papers.

In all three papers, missing data on covariates were handled with listwise deletion. This can introduce bias in both estimates of exposure-outcome associations, CIs and p-values if the variables are not missing completely at random.[227] Further, when regression analyses of models with different covariates are carried out, the available cases will differ between the analyses, and differences in results may be both due to the effect of different covariates and also due to different sets of observations.[227]

Information bias

Information bias may occur during data collection if the information collected about or from study participants is erroneous. One type is misclassification, and misclassification of participants can be differential meaning that the misclassification differs according to the value of other study variables or nondifferential, meaning that it is unrelated to other study variables.[218] Non-differential misclassification may reduce the observed effect estimate, while differential misclassification can lead both to increased and decreased effect estimates.[240]

In all three papers, covariates were derived from questionnaires filled out by the participants, which may introduce misclassification since participants may give the answers they think are the most accepted by the community.[241] Especially, in Papers II and III, when participants answered on their dietary habits, but also in all three papers when answering on smoking habits, underreporting bias may occur.[241] Further, in Papers II and III where the FFQ was used, the number of foods recalled tends to be correlated with total intake of both energy and nutrients, thus differential misclassification may occur between those with good and poor memories.[242]

In order to evaluate the precision of anthropometric measurements in Paper I, Bland-Altman plot was used. This is a method of data plotting used to analyze the agreement between two methods of clinical measurement, [243] and in Paper I it was used to analyze the agreement between the height measurements of men participating in 1992-93 and 1997-99. The plot showed that these differences for most of the participants were within ±2SD. Most of the men outside this limit were at the minus part, as expected due to height reduction in older people. This indicates that information on anthropometric values measured with standardized methods[207] in Paper I, seems not to include information bias.

In Papers II and III, regression dilution bias may happen because of fluctuations in the measured values of exposure, caused by longer-term within-person fluctuations. It often results in underestimations of the strength of the real association between the "usual" long-term average level of intake of that nutrient during a particular exposure period and subsequent CHD risk.[244] Processing of nutritional data from observational studies is challenging. Dietary variables are hardly ever dichotomous and rigid, usually every person is "exposed" to some degree, and dietary habits and food composition changes over time. Also, errors in nutrient estimation from food composition tables may occur as they often do not account for the fact that the nutrient content of food varies with season, location of production, growing conditions, storage, processing, and cooking techniques.[233, 234] Inter-individual variation in bioavailability due to genetic predisposition and the influence of other dietary compounds due occur, but is also not considered when estimating nutrient intake from food tables.[230] Systematic sources of variation include omission of foods

consumed due to a lack of the specific food item in food lists used in the studies and over- or under-reporting because of socially perceived norms.[245, 246] Underreporting bias due to underreporting of dietary food intake seems to be largest among women and obese persons.[86] However, underreporting of total energy intake seems not to be a problem when dietary composition is evaluated.[224] In addition, correlates of underreporting such as age, sex and adiposity are often accounted for during statistical adjustments.

In Paper II, assessment of whole grain intake may have been particularly problematic since consumers may have difficulties identifying products containing whole grain.[247]

Nevertheless, FFQs have been shown to have acceptable validity when compared to reference measures,[242] with correlation coefficients for individual nutrients ranging from 0.4 to 0.7. [234] Relevant to Paper II, a validity study of a similar FFQ to that used in HUSK found that the Spearman correlation coefficients between intake of SFA and carbohydrates estimated by the FFQ versus weighed food records were 0.44 and 0.57, respectively.[210] Unfortunately, this validity study did not evaluate the validity of K1 and K2 intake. In previous studies, the validity of FFQs have shown to be better for K2 than for K1,[248] while when Zwakenberg et al validated a Dutch FFQ containing questions on past year average consumption of 79 food items, they found that FFQ is reproducible to rank subjects for both K1 and K2 intake, and further that the relative validity compared to 24-h dietary recalls, to estimate intake of K1 and short-chain K2 was low, but that the relative validity for long-chain K2 was good.[249]

In HUSK, information on exposure came from a 169-item semi-quantitative FFQ providing many food items adapted to Norwegian consumption behaviors, and information was obtained all year round, and also the large number of participants may have offset many of the previously mentioned difficulties when measuring nutrient intake.

Categorization of exposure, performed in all three papers, may introduce non-differential misclassification, while differential misclassification is not a problem as the endpoints are hard, and collected independently of baseline information.[240]

Nutrient biomarkers may be a more objective measures of nutrient status compared to FFQ as they also reflect metabolism.[250] However, none of the dietary exposures in Papers II or III have valid biomarkers that can be assessed. There is an absence of objective biomarkers for assessing carbohydrate intake,[251] and plasma concentrations of SFAs may also reflect carbohydrate intake.[252] Further, circulating levels of K2 are usually nondetectable,[194] and K1 levels correlate with triglycerides and vary according to recent intakes.[253]

Confounding

Confounding occurs when the effect of the exposure is mixed with the effect of another variable, a confounder.[218] A confounder is associated with both the exposure and outcome but is not caused by either, and when not accounted for, it introduces confounding.[233] Recognition of confounders requires knowledge about the causal network where exposure and outcome are part,[219] and selection of confounders that do not integrate knowledge about the topic may introduce bias in the effect estimate.[254, 255] Even though confounders may be accounted for, there will always be unmeasured confounding, and causality can therefore not be established in cohort studies.[256]

In Paper I we adjusted for age, sex, physical activity, smoking, diabetes mellitus, hypertension, and previous MI or stroke. In Paper II we adjusted for age, sex, total energy intake, physical activity and smoking habits, while in Paper III we adjusted for the same variables as in Paper II in addition to education. Several of the covariates were categorical, and a crudely categorized covariate may not fully account for the effect of that variable, resulting in possible residual confounding.[224] Further, people with a "healthy" diet are more likely to have higher education, have higher income, exercise more, have normal BMI and be non-smokers,[257] and the combined effects of such characteristics may not be fully accounted for in adjustments.

Reverse causation refers to the possibility that individuals who are at risk for CHD change their behaviour with respect to the risk factor under study.[219] In Papers II and III, it may be that those at risk for CHD at baseline had changed their dietary

practices. While reverse causation is difficult to address, we did adjust for family history of MI and covariates related to health.

External validity

External validity refers to how well results of a study may be generalized to other populations in other settings, often referred to as generalizability.[235] Internal validity is a prerequisite for external validity. If e.g. non-participation selection bias is present, the study population might not be representative of the target population, further lowering the external validity.[235]

The HUSK study population is relatively homogenous, which in terms of the risk of confounding is a strength, but the results may not be generalizable to populations of a different race or ethnicity, obese or people with specific genetic disorders. Further, all three papers included cohorts with a small age range (46-49 or 70-74 years) and generalizability to other age groups may be low.

In Paper I, participants were community-living at baseline in 1997-99, but we had no information on whether they moved into an institution during follow-up. When comparing results from Paper I to a recently published meta-analysis including 30 studies on weight loss and 27 studies on weight gain, we got very similar estimates,[21] indicating reasonably good external validity of our results.

In 1997-99, the NORKOST2 survey was used to gather knowledge about intake of macronutrients in the general Norwegian population.[258] They used a FFQ, although slightly different from the one used in HUSK. The intake of macronutrients in HUSK used as exposures in Paper II, is overall comparable with intake in NORKOST2 (**Table 4**), which may support external validity of the exposure data. However, there is no external validity without internal validity, so it also suggests that the bias when estimating intake of macronutrient density in HUSK is unproblematic.[241] Further, similarly as in NORKOST2, intake of carbohydrates was highest among women, while intake of total fat was highest among men, although intakes were quite similar. Also, in both studies there were no difference between intake of SFA among men and women. However, in 2004 Drevon et al evaluated intake of vitamin K in NORKOST2.[259] **Table 4** shows that intake of vitamin K is

estimated to be distinctly lower in NORKOST2 then in HUSK, illustrating the difficulties with estimation of vitamin K intake.[248]

Table 4. *Evaluation of nutrient intake in NORKOST2[259] and HUSK*		
Mean intake	**NORKOST2**	**HUSK**
Proteins, E%	15.9	15.8
Carbohydrates, E%	51.6	49.1
Total fat, E%	30.6	32.6
SFA, E%	12.1	12.6
Vitamin K, µg/day, men/women	48.3/39.1	152.2/150.0

5.2.4 **Effect modification**

Effect modification means that the association an independent variable has with the dependent variable varies with the value of a third variable. In this study, this could mean that the associations between weight change and total mortality, or nutrients and CHD, vary in different strata of the third variable, for example sex.[225]

We evaluated possible effect modification in all three papers, but analyses of the effect of the exposure in strata of the different covariates showed few events in several of the categories, especially in Papers II and III. Due to this, the CIs were large, making interpretations difficult. In Paper I, when performing interaction analyses, there were no significant interactions with any of the covariates examined. In Papers II and III we evaluated possible interactions of age, sex, smoking habits, diabetes mellitus, hypertension, physical activity, education, and family history of infarction. We found a borderline significant interaction between SFA and diabetes mellitus in Paper II. Similarly, in Paper III, we found a significant interaction between intake of K2 and diabetes mellitus, but only in model 1. As we had few individuals with diabetes mellitus and since diabetes mellitus may be an intermediate factor between nutrients and CHD, we found it not appropriate to stratify on this variable.

5.3 Discussion of main findings

Paper I: Association between weight change and mortality in community living older people followed for up to 14 years. The Hordaland Health Study (HUSK)

In Paper I we reported that both major weight gain and minor weight loss were associated with increased mortality in comparison with stable weight in older people, in agreement with results of other studies.[21] Whether weight loss is associated with increased mortality also in overweight and obese older people is unclear. Paper I found weight loss to be associated with increased mortality among overweight participants, while among the obese participants the association went towards increased risk. Previous studies have also shown weight loss to be associated with higher mortality independent of baseline BMI in older people.[32, 51] However, it is still unclear whether weight loss in obese older people should be recommended due to few studies and the few participants with BMI >30kg/m^2 in this and previous studies.[32, 51]

We found that the weight gain had to be relatively large to increase the risk of mortality. Previous studies have shown diverse results on weight gain, indicating that a weight gain has to be of at least a certain amount in order to be associated with total mortality in older people.[21, 30, 31, 33, 35, 37-42, 45, 46, 48-50] The trajectory of the weight gain in HUSK was unknown, therefore participants who died may have experienced a continuous weight gain, a large weight gain during a short time, or a combination.

Information on weight cycling may have strengthened the association as it has also been shown to be related to increased mortality.[21, 38, 54] We also did not distinguish between intentional and unintentional weight change as this information was not available. Unintentional weight loss seems to be clearly associated with increased risk of mortality in older people,[260] but it is still unclear whether intentional weight loss is just as hazardous.[33, 36]

Paper II: Intake of carbohydrates and saturated fatty acids and risk of coronary heart disease in middle-age adults. The Hordaland Health Study (HUSK)

In Paper II we report that a higher intake of carbohydrates and a lower intake of SFA was associated with higher risk of CHD.

Praagman et al also reported a decreased risk of CHD with higher intake of SFA,[131] while meta-analyses have concluded on no association between dietary SFA and risk of CHD.[143-145] Overadjustment may have explained the lack of an association, since a number of the included studies adjusted the effect of SFA on CHD for intermediate factors.[143, 261] In Paper II intermediate factors were only adjusted for in the supplementary analysis and did not materially influence the results. This may be explained by the fact that the intermediate factors were measured only once in HUSK, in a relatively young population. Few participants were taking medications for intermediate factors (0.5% for diabetes mellitus and 1.7% for hypercholesterolemia), and the median levels of both HDL cholesterol and triglycerides were within the recommended levels.[262] Further, as in the study by Praagman et al,[131] the intake ranges were small and there was a high mean intake level of SFA, while in the earliest cross-sectional studies that found a positive association between SFA intake and CHD, there were large variations in average SFA intake.[138]

Since the effect estimate of SFA or carbohydrates in the energy-adjusted model has a substitution interpretation,[86] the effect of either nutrient can be assessed only in relation to other nutrients.[4] Therefore, although we provide some evidence that carbohydrates increase risk of CHD more than SFA, we cannot predict whether carbohydrates promote CHD or whether SFA prevent CHD independent of the substituting nutrient.[4] The fact that the replacement nutrient for SFA is of importance in the relation between SFA and CHD, and that the fat-containing foods contain more than only SFA,[263, 264] may explain why we found an inverse association between SFA and CHD.

Replacement of SFAs with refined carbohydrates has shown to exacerbate atherogenic dyslipidemia.[149] A change to carbohydrates may also influence other important biomarkers of CHD risk,[70, 71, 115, 152] and with the current epidemics of

obesity,[265] sugar-rich carbohydrate sources may be a larger threat with regard to CHD than SFA.[70] The national guidelines on dietary habits to reduce risk of CHD emphasize that among people with a high level of blood glucose and triglycerides, a reduction in intake of sugar and refined carbohydrates is of largest importance in order to reduce risk of CHD.[266] In our study, it is a weakness that it was not possible to separate between different kinds of carbohydrates as exposures.

When an association with CHD is found for SFA and carbohydrates, it would lend support to the nutrient findings if the major food sources of these nutrients are also related to risk of CHD.[224] Only SFA from cheese associated with decreased risk of CHD, and we found no clear associations between sources of carbohydrates and risk of CHD. However, the evaluation of each source of carbohydrates separately does not control for intake of other sources of carbohydrates nor intake of total carbohydrates.

Even though no single source of carbohydrates was associated with CHD when evaluated separately, we found that the higher intake quartiles contained more sugar-rich sources than the lower intake quartiles. The g/day per 1,000 kcal provides an indication of dietary habit differences by quartiles. Comparing the lowest to the highest quartile of carbohydrate intake, the intake of bread was 77 vs. 98 g/day/1,000 kcal, respectively, while vegetables and fiber intakes were comparable. Corresponding results for sugar drinks/soft drinks were 18 vs. 34 g/day per 1,000 kcal, and juice 12 vs. 23 g/day per 1,000 kcal, respectively. This and other items suggest that a higher carbohydrate intake reflects greater intake of low fiber carbohydrates and a relatively higher intake of sucrose/fructose carbohydrate sources. The latter finding may further partly explain both the positive association between carbohydrates and CHD, and also the negative association between intake of SFA and CHD. Further, when food sources of carbohydrates in European adults in the 1990s were evaluated, the highest percentage of sugar sweetened beverage consumption was seen among women in the North and West of Norway.[101]

Table 5. *Number of participants in the different carbohydrate and saturated fatty acids intake quartiles*				
Carbohydrate	Saturated fatty acids			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Quartile 1	40	98	208	403
Quartile 2	74	186	252	237
Quartile 3	168	270	216	94
Quartile 4	467	195	72	15

Table 5 illustrates that those with the highest intake of carbohydrates were mainly those with the lowest intake of SFA and vice versa. As expected, based on this assumption, substitution analysis found that substitutions of carbohydrates with both total fat and SFA were associated with decreased risk of CHD, although not significant for SFA. Substitution analyses function best when ranges of intakes between the nutrients evaluated are reasonably comparable,[231] which may explain the weaker association for SFA. Substitution models gives a better insight into the health implication of changing a diet compared with models that assume a change also in energy intake or are unspecific regarding the replacement of the dietary exposure.[230]

In previous studies, [131, 132] residual confounding due to underestimated TFA intakes may be present.[267]Also in our study, we were unable to measure intake of TFA, and margarine was an important contributor to both TFA and unsaturated fat at the time just before HUSK baseline.[268] We therefore could not reliably include unsaturated fat in the analyses, which is a limitation of the study.

Paper II contributes to an already comprehensive research field. However, it contains a comprehensive discussion of the importance of the interplay between SFA and carbohydrates and also of the sources of the macronutrients when evaluating the association between SFA and carbohydrates with CHD.

Paper III: Dietary vitamin K and risk of coronary heart disease in the prospective Hordaland Health Study

In Paper III we found dietary K2 to be associated with reduced risk of CHD, while we found no association between dietary K1 and risk of CHD, in accordance with two previous cohort studies.[187, 190] In contrast, two studies found K1 to be associated

with risk of CHD or CVD mortality.[188, 191] However, K1 intake is an indicator of a healthy diet, and it may be difficult to disentangle the effect of K1 from a generally healthy lifestyle on CHD outcomes.[194] Similarly, K2 correlates with intake of other food products also associated with reduced risk of CHD, as for instance cheese and yoghurt.[165, 269, 270] The relatively weak association for K2 may partly be explained by the narrow difference in K2 intake between the highest and lowest categories of intake, as the potential protective influence of such differences is uncertain.[248]

Unfortunately, intake of vitamin K was not validated in the validation study of a similar FFQ, mentioned earlier. However, vitamin K2 are mainly consumed together with fat and the spearman correlation coefficient for intake of total fat estimated by the FFQ versus weighted food records was 0.46.[210] (For comparison, when evaluating the validity of other vitamins in the same study, the spearman correlation coefficient ranged from 0.46 for vitamin E until 0.62 for vitamin A.[210]) A low validity of K1 assessment with FFQ is found in previous studies,[248] and dietary K2 intake is especially difficult to assess since there are limited food composition data both for total K2 and for certain K2 subtypes.[248] Further, studies have shown diverse content of vitamin K2 among similar food products but from various countries.[271, 272] Also, when it comes to the analyses of vitamin K2, it is a weakness that we did not have data on specific types of vitamin K2.

The study reported in Paper III is one of very few studies that has evaluated the association between dietary K1 and K2 with incident CHD and thus contributes to a growing field of research.

6. Conclusions

In Paper I we report that a weight loss of 5% or above was associated with increased mortality in older individuals. Further, linear models revealed that both major weight gain and minor weight loss were associated with increased mortality in older people.

In Paper II we report that a higher intake of carbohydrates and a lower intake of SFA were associated with higher risk of CHD in middle-aged adults. Also, substituting carbohydrates with total fat was associated with decreased risk of incident CHD. When evaluating sources of SFA and carbohydrates, only SFA from cheese showed a clear association with decreased risk of incident CHD.

In Paper III we report that in middle-aged adults, dietary K2 was associated with reduced risk of incident CHD, while there was no association between dietary K1 and risk of incident CHD.

The thesis adds meaningfully to the literature in several ways and speaks to possible directions for future research and clinical best practice.

7. Future perspectives

Based upon the results reported in Paper I, an early evaluation of weight loss in older individuals would be worthwhile in order to detect possible underlying causes and to identify opportunities for hindering further weight loss and it's health consequences. The paper, however, could not thoroughly evaluate the association between weight loss and mortality in older overweight and obese individuals given the small number of overweight/obese participants and events in the study. Future studies should aim to evaluate study populations with sufficient sample size across a wide spectrum of BMI and weight changes as they relate to total mortality. Furthermore, studies ascertaining whether weight change is voluntary or involuntary are needed.

Results from Paper II demonstrate that the pattern of macronutrient intake and the specific sources of macronutrients are of importance when evaluating associations between single macronutrients and incident CHD. Dietary advice is complex and an overly zealous attempt to limit intake of one nutrient or macronutrient may inadvertently result in risks associated with the substituting source of calories. Our findings support the new direction in nutritional recommendations that focus on foods and dietary patterns rather than single nutrients. Additional studies on the association between whole food groups and hard endpoints such as CHD are needed to further develop dietary recommendations for CHD prevention.

Based on results reported in Paper III we conclude that more research should be performed on the association of vitamin K1 and K2 with incident CHD. Future research on the content of vitamin K in food products and the metabolism of vitamin K would be valuable as it will contribute to improvements in nutritional assessments, cohort study design, and in the interpretation of results. Paper III and the current body of knowledge regarding K2 suggests that vitamin K status may become an important component of nutritional guidance. However, greater research is needed. Carefully constructed dietary advice regarding diet composition and individual food consumption has the potential to be an inexpensive and safe intervention to improve vascular health.

8. Errata

Paper I: Figure 1 should have been labeled Kaplan-Meier failure curves instead of Kaplan-Meier cumulative hazard curves.

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Intake of carbohydrates and SFA and risk of CHD in middle-age adults: the Hordaland Health Study (HUSK)

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Abstract

Objective: Limiting SFA intake may minimise the risk of CHD. However, such reduction often leads to increased intake of carbohydrates. We aimed to evaluate associations and the interplay of carbohydrate and SFA intake on CHD risk.

Design: Prospective cohort study.

Setting: We followed participants in the Hordaland Health Study, Norway from 1997–1999 through 2009. Information on carbohydrate and SFA intake was obtained from a FFQ and analysed as continuous and categorical (quartiles) variables. Multivariable Cox regression estimated hazard ratios (HR) and 95 % CI. Theoretical substitution analyses modelled the substitution of carbohydrates with other nutrients. CHD was defined as fatal or non-fatal CHD (ICD9 codes 410–414 and ICD10 codes I20–I25).

Participants: 2995 men and women, aged 46–49 years.

Results: Adjusting for age, sex, energy intake, physical activity and smoking, SFA was associated with lower risk ($HR_{Q4\ v.\ Q1}$ 0·44, 95 % CI 0·26, 0·76, $P_{trend} = 0·002$). For carbohydrates, the opposite pattern was observed ($HR_{Q4\ v.\ Q1}$ 2·10, 95 % CI 1·22, 3·63, $P_{trend} = 0·003$). SFA from cheese was associated with lower CHD risk ($HR_{Q4\ v.\ Q1}$ 0·44, 95 % CI 0·24, 0·83, $P_{trend} = 0·006$), while there were no associations between SFA from other food items and CHD. A 5 E% substitution of carbohydrates with total fat, but not SFA, was associated with lower CHD risk (HR 0·75, 95 % CI 0·62, 0·90).

Conclusions: Higher intake of predominantly high glycaemic carbohydrates and lower intake of SFA, specifically lower intake from cheese, were associated with higher CHD risk. Substituting carbohydrates with total fat, but not SFA, was associated with significantly lower risk of CHD.

Keywords
Cohort
SFA
Carbohydrates
CHD

According to Ancel Keys 'diet-heart' hypothesis, a habitually high intake of SFA may increase the risk of CHD due to increases in serum total cholesterol (TC)[1,2]. Mensink & Katan[3] published a meta-analysis in 1992, including twenty-seven controlled trials, concluding that the most favourable lipoprotein profile for CHD was achieved if SFA were replaced by unsaturated fatty acids, keeping the intake of total fat unchanged.

The discovery of the additional pathways leading from diet to CHD has made the 'diet-heart' hypothesis more complex[4]. Advice to reduce SFA as a means to prevent CHD may have, indirectly, increased the intake of carbohydrates[5,6]. While carbohydrates have been considered a basis of a healthy diet, with grain products at the base of the Food Guide Pyramid[7], a diet rich in added sugars and refined grains promotes visceral adiposity and reduces

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energy expenditure[8–10], raising concerns of the potential for increased CHD risk. On the other hand, if dietary carbohydrates are replaced by fat, the postprandial rise in blood glucose and insulin decreases while glucagon secretion increases, resulting in lower CHD risk[11–14]. However, among adults with obesity, Hall *et al.*[15] found that restriction of dietary fat was associated with a slightly larger body fat loss than restriction of dietary carbohydrates. Also of twenty-nine diets with different macronutrient compositions tested in mice, only high-fat diets led to overconsumption and weight gain[16]. A review indicated that greater high glycaemic index carbohydrate intake was associated with a higher risk of CVD compared with SFA intake[17]. Further, recent prospective studies and reviews as well as meta-analyses have shown inconclusive associations between self-reported intakes of either SFA or carbohydrates and fatal and non-fatal CHD[18–23].

Given the inconsistencies in the literature, the objective of the current study was to evaluate the associations of carbohydrate and SFA intakes with incident CHD in a sample of middle-age community-dwelling Norwegian adults, where the intake of carbohydrates varied from 21 to 74 energy percentage (E%) with a median intake of 49 E%, and where the intake of SFA varied from 4 to 25 E% with a median intake of 13 E%.

Participants and methods

Study population

The current study is a prospective cohort study of participants in the community-based Hordaland Health Study (HUSK) (https://husk-en.w.uib.no/). The recruitment was based on a cohort from 1992 to 1993 (The Hordaland Homocysteine Study). In 1997–1999, all living cohort members born 1950–1951 and residing in the city of Bergen or the neighbouring suburban municipalities were invited to participate in HUSK. The baseline examinations for the current study were conducted during 1997–1999 as a collaboration between the National Health Screening Service (now The Norwegian Institute of Public Health), The University of Bergen and local health services. The participation rate was 77 %. Participants underwent a brief health examination and provided a non-fasting blood sample. Information on lifestyle was collected via self-administered questionnaires. A semi-quantitative FFQ was completed by 87 % of the participants. A total of 3107 participants aged 46–49 years who answered the FFQ were eligible to be included in the current study.

We excluded twenty-two men and five women who reported prior CHD, and four men and nineteen women due to missing information. Further, we excluded twenty-seven men and thirty-five women who reported extreme energy intakes (below the 1st percentile: <4707·8 kJ for men and 2951·8 kJ for women; or above the 99th percentile: >18907·9 kJ for men and >14944·0 kJ for women). The final study population thus included 2995 participants.

Dietary assessment

Information on food intake was obtained at baseline (1997–1999) using a 169-item past-year semi-quantitative FFQ, a slightly modified version of a previously described FFQ[24]. The validity study of the previous version of the FFQ in a younger population found that the Spearman correlation coefficients between intake of SFA and carbohydrates estimated by the FFQ *v.* weighed food records were 0·44 and 0·57, respectively[24]. The FFQ was handed out on the day of the health examination, filled out at home and returned by mail to the HUSK project centre. It includes frequency alternatives (from once a month to several times/d), the number of units eaten and portion sizes (e.g., slices, glasses and spoons) to capture the habitual diet during the past year. The information is presented as individual food or beverage items, food groups and nutrients. Daily nutrient intakes were computed from a database and software system developed at the Department of Nutrition, University of Oslo (KBS, version 3 . 2). The nutrient database is primarily based on the official Norwegian food composition table[25]. During dietary data collection in 1997–1999, margarine was undergoing rapid compositional changes where large amounts of *trans*-fatty acids, an important contributor to unsaturated fat[5,26], were being reduced due to legislation in Norway[26]. Further, prospectively, there were other changes to unsaturated fat sources[5]; thus, unsaturated fat was not evaluated as a primary dietary exposure in the current study.

Measurements used as independent variables in the current study are the total dietary amount of SFA and carbohydrates, as well as intake of SFA and carbohydrates from different food items. All are expressed as E%.

Health examination and health habits

Baseline examinations included measurements of height, weight, waist circumference, blood pressure and non-fasting blood samples. After at least 2 min seated rest, systolic blood pressure and diastolic blood pressure were measured three times (Dinamap 845 XT equipment (Criticon)). Serum samples of TC, HDL-cholesterol, TAG and glucose were analysed within 7 d at the Department of Clinical Chemistry, Ullevål University Hospital, Oslo, using enzymatic methods with reagents from Boehringer Mannheim (Roche). The Friedewald equation was used for the calculation of LDL-cholesterol. Information on educational level and medication use was self-reported.

Hypertension was considered present if the mean of at least two consecutive measurements of systolic blood pressure was ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg or if the use of medication for hypertension was self-reported.

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Participants taking diabetes medications or reported having been diagnosed with diabetes were defined as having diabetes. Also, participants with a serum glucose level >7 mmol/l who had not eaten a meal during the last 8 h, or with a glucose level >11·1 mmol/l and <8 h since their last meal, were defined as having diabetes. Pre-diabetes was defined as having glucose levels between 5·6 and 7 mmol/l at least 8 h after their last meal or between 7·8 and 11 mmol/l <8 h after their last meal.

Participants answered one question on past-year vigorous physical activity resulting in sweating or shortness of breath (none, <1, 1–2 or ≥3 h/week). This variable was treated as a categorical variable with none as the reference.

Participants were classified as either non-smokers, former smokers or current smokers with non-smokers as the reference.

Outcome

The study endpoints were incident (first time) hospitalisation with CHD (ICD9 codes 410–414 and ICD10 codes I20–I25) as primary or secondary diagnosis or death with CHD as the underlying cause of death. Participants were followed from baseline through 31 December 2009 for CHD events through the Cardiovascular Disease in Norway project (CVDNOR, http://www.cvdnor.no)[27,28] and The Cause of Death Registry. There were 107 non-fatal and five fatal episodes. Follow-up time was calculated as time from participation until CHD, death from other causes, emigration or 31 December ·2009, whichever occurred first.

Statistical analyses

Descriptive characteristics include numbers with percentages and medians (25th, 75th percentiles) for categorical and continuous variables, respectively. Spearman's rank correlation (rho, ρ) was used to evaluate correlations between quartiles of carbohydrate intake and SFA intake with baseline characteristics. In addition, Spearman correlations of intake of carbohydrates with total fat and SFA were evaluated. To evaluate linear trends in baseline characteristics across quartiles of carbohydrate and SFA intakes as percentage of total energy intake, we used ordinal logistic regression for categorical outcome variables, logistic regression for dichotomous outcome variables and linear regression for continuous outcome variables where median intake as E% within each quartile group was used as the independent variable in the analyses. Cox proportional hazard models were used to calculate adjusted hazard ratios (HR) with 95 % CI for CHD associated with continuous and quartile intake of carbohydrates and SFA. The included covariates were potential confounders associated with the intake of carbohydrates and SFA and with CHD, which also modified the association of either SFA or carbohydrate with CHD when included in the multivariable model. Two primary analyses are presented: model 1 adjusted for age (continuous (years)), sex and total energy intake (continuous (kcal/d)); model 2 additionally adjusted for vigorous physical activity (none *v.* <1 h/week, 1–2 h/week or ≥3 h/week) with none as the reference and smoking habits (non-smokers *v.* previous smokers and non-smokers *v.* current smokers). The following additional confounders were also evaluated, but inclusion of the variables did not materially alter the associations of SFA or carbohydrates with CHD: family history of myocardial infarction, educational level and alcohol intake (E%). Further, carbohydrate analyses also evaluated consistency in results after adjustment for energy-adjusted fibre from bread, fruit and vegetables. SFA analyses were further adjusted for energy-adjusted intake of cholesterol, PUFA and protein.

Supplementary analyses evaluated models adjusted for age, sex and energy intake (model 1), with additional adjustments for HDL-cholesterol, LDL-cholesterol, TAG, glucose, systolic blood pressure, diastolic blood pressure and BMI (model 2); with additional adjustments for diabetes/prediabetes, hypertension, family history of myocardial infarction, statins, oral hypoglycaemics (including metformin) and insulin and anti-hypertensive medications (model 3) and with additional adjustments for smoking, physical activity, alcohol consumption in E% and education (model 4) (see online supplementary material, Supplemental Table S1). To test for linear trends across intake quartiles, median intake as E% within each quartile group was used as the independent variable. We also evaluated SFA from cheese and SFA when excluding the contribution from cheese for their associations with incident CHD. In additional supplementary analyses, we stratified intake of SFA on smoking habits (see online supplementary material, Supplemental Table S2) and we also evaluated associations between carbohydrates and SFA from other specific food groups and CHD risk (see online supplementary material, Supplemental Tables S3 and S4). Missing data were handled with listwise deletion.

The proportional hazard assumption was evaluated using Schoenfeld's test.

To evaluate the continuous association between exposure and outcome, and assess potential non-linear associations, smoothed penalised splines were plotted[29].

We used theoretical substitution analyses to model the substitution of carbohydrates with SFA[30]. Variables for the E% (per 5 E% unit increments) of all macronutrients except carbohydrates (SFA, monounsaturated fat, PUFA, protein and alcohol) were included in a Cox model with adjustment for total energy intake, age, sex, physical activity and smoking habits. The HR for SFA is then interpreted as the change in estimated risk for each 5 E% unit increase in SFA while holding all other variables in the model constant but allowing for concomitant decreases in carbohydrate intake as all sources of macronutrients sum to 100 % of energy

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intake. The same approach was used to evaluate the theoretical substitution of carbohydrates with other macronutrients: total fat, protein and PUFA intake per 5 E% unit increase in a model with other macronutrients except carbohydrates[30].

Sensitivity analyses were conducted where we excluded the first 2 years of observation following the baseline assessment in all of the above analyses.

Statistical analyses were performed using Stata version 15 (StataCorp LP) and R version 3.4.0 (https://www.r-project.org/), The R Foundation for Statistical Computing. *P*-values <0·05 were considered statistically significant.

Results

Characteristics of the study population

At baseline, mean age was 48 (SD 0·7) years, median BMI was 24·9 (25th, 75th percentiles 22·8, 27·4) kg/m^2, 33·5 % smoked daily, 45·9 % reported at least 1 h vigorous physical activity per week and 25·3 % had indications of reduced metabolic health defined as having hypertension, prediabetes or diabetes. Intake of total fat ranged from 14 to 53 E% with a median intake of 33 E%. Intake of total carbohydrates ranged from 21 to 74 E% with a median intake of 49 E%. Less than 1 and 6 % had an intake of carbohydrates at or below 30 and 40 E%, respectively, while 3 and <1 % had an intake of carbohydrates at or above 60 and 70 E%, respectively. Intake of protein ranged from 6 to 30 E% with a median intake of 16 E%, while intake of SFA ranged from 4 to 25 E% with a median intake of 13 E%. Less than 1 % had an intake of SFA at or below 6 E%, while 14 % had an intake at or above 15 E%.

During a mean 10·8 (SD 1·3) years of follow-up, representing 32 449 person-years among 2995 participants (1282 men and 1713 women), we documented 112 incident CHD events. Due to missing values (2·1 % for smoking habits and 3·8 % for physical activity), multivariable-adjusted analyses included 2820 participants (1224 men and 1596 women) and 105 CHD events. Sixty participants died due to other causes during follow-up. When evaluating Spearman correlations between carbohydrate quartiles and baseline characteristics, all correlations (ρ) were between −0·2 and <0·1. However, evaluation of baseline characteristics by quartiles of carbohydrate intake identified that the proportion of participants performing at least 1 h vigorous physical activity per week was higher in higher quartiles, while the proportions of men, daily smokers and participants with glucose intolerance were lower in higher quartiles (Table 1). Also, waist circumference, serum levels of TC, LDL-cholesterol and HDL-cholesterol were lower in higher carbohydrate quartile groups. Intakes of total fat, protein and alcohol were lower with higher quartiles of carbohydrate intake. Bread was the major contributor to carbohydrates in this population. While intake (g/d per 1000 kcal) of bread, sweetened beverages, juice, and fruit and berries (both fresh and canned/preserved) was higher with higher quartiles of carbohydrate intake, there were less noticeable differences for other carbohydrate sources across quartiles. Vegetable and fibre intakes (g/d per 1000 kcal), for example, were similar in the various carbohydrate intake quartiles (Table 1).

When evaluating Spearman correlations between SFA quartiles and the baseline characteristics, all rhos (ρ) were between −0·1 and <0·1. However, the percentage daily smokers were higher with higher quartiles of SFA intake, while the percentage of participants who were men, performed at least 1 h vigorous physical activity per week or had hypertension was lower with higher quartiles (Table 2). Also, BMI, waist circumference and TAG levels, as well as the percentage taking medications for hypercholesterolaemia, were lower with higher SFA quartiles. While intake of cheese was higher with higher quartiles of SFA intake, there were less noticeable differences for other SFA sources across quartiles. Family history of myocardial infarction did not differ between quartiles of carbohydrate (P_{trend} 0·95) or SFA (P_{trend} 0·23) intake as percentage of total energy.

Associations between intake of carbohydrates and SFA and incident CHD

Higher intake of carbohydrates was borderline significantly associated with higher risk of CHD in model 1 (adjusted for age, sex and energy intake) ($HR_{Q(quartile)4\ v.\ Q1}$ 1·63, 95 % CI 0·96, 2·76, $P_{trend} = 0·056$) (Table 3). This association became stronger and significant after further adjustment for smoking habits and physical activity (model 2) ($HR_{Q4\ v.\ Q1}$ 2·10, 95 % CI 1·22, 3·63, $P_{trend} = 0·003$). Also, continuous analyses (per 2 E%) showed significantly higher risk of CHD with higher intake of carbohydrates (HR 1·12, 95 % CI 1·05, 1·20), after adjusting for age, sex, energy intake, smoking habits and physical activity. Further adjustments for intermediate factors, relevant medications and potential confounders did not materially influence the association (see online supplementary material, Supplemental Table S1).

Plotting the data adjusting for model 2 covariates indicated a linear relationship (Fig. 1(a)).

When examining the association between carbohydrates from various food items, we found no associations with risk of CHD (see online supplementary material, Supplemental Table S3).

A high intake of SFA was significantly associated with lower risk of CHD in the model adjusted for age, sex and energy intake (model 1) ($HR_{Q4\ v.\ Q1}$ 0·53, 95 % CI 0·32, 0·90, $P_{trend} = 0·013$) (Table 3). This association became stronger after further adjustment for smoking habits and physical activity (model 2) ($HR_{Q4\ v.\ Q1}$ 0·44, 95 % CI 0·26, 0·76, $P_{trend} = 0·002$). Also, continuous analyses (per 2 E%) showed significantly lower risk of CHD with higher intake of SFA (HR 0·78, 95 % CI 0·66, 0·92), after adjusting

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Table 1 Baseline characteristics by quartiles of carbohydrate intake (energy percentage (E%)), The Hordaland Health Study*

	Total		Q1		Q2		Q3		Q4		
	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	P_{trend}†
Carbohydrates (E%)	49	46, 53	43	40, 44	48	47, 48	51	50, 52	56	54, 58	<0·001
Carbohydrates (g/d per 1000 kcal)	123	114, 132	107	101, 110	119	116, 121	127	125, 129	139	135, 145	<0·001
Participants (*n*)	2995		749		749		748		749		
Age (years)	48	47, 48	48	47, 48	48	47, 48	48	47, 48	48	47, 48	0·822
Men	1282	42·8	348	46·5	332	44·3	320	42·8	282	37·7	0·001
College and/or university education	1138	38·3	253	34·0	308	41·3	286	38·4	291	39·5	0·059
Family history of infarction	1186	40·9	301	42·0	283	39·0	297	41·0	305	41·7	0·952
Smoking habits											<0·001
Previous smokers	915	31·2	218	29·5	225	30·4	240	32·9	232	32·1	
Current smokers	982	33·5	337	45·7	268	36·2	203	27·8	174	24·1	
Physical activity											<0·001
None	745	25·9	218	30·0	188	26·0	174	24·1	165	23·3	
<1 h/week	813	28·2	220	30·2	225	31·2	189	26·2	179	25·3	
1–2 h/week	908	31·5	189	26·0	232	32·1	246	34·1	241	34·0	
≥3 h/week	415	14·4	101	13·9	77	10·7	113	15·7	124	17·5	
Hypertension	708	23·7	171	22·9	184	24·6	178	23·8	175	23·4	0·886
Glucose intolerance											0·050
Pre-diabetes	66	2·2	21	2·8	19	2·6	14	1·9	12	1·6	
Diabetes	27	0·9	9	1·2	8	1·1	3	0·4	7	0·9	
Casual glucose (mmol/l)‡	5·01	4·64, 5·49	5·04	4·69, 5·50	5·02	4·65, 5·53	5·01	4·64, 5·45	4·96	4·60, 5·44	0·094
BMI (kg/m^2)	24·9	22·8, 27·4	25·0	23·0, 27·5	24·7	22·7, 27·2	24·9	22·7, 27·4	24·9	22·8, 27·4	0·410
Waist circumference (cm)	85·0	77·0, 94·0	86·0	77·0, 95·0	85·0	76·0, 93·0	85·0	77·0, 93·0	84·0	76·0, 93·0	0·003
Cholesterol (mmol/l)‡	5·65	5·06, 6·30	5·72	5·13, 6·45	5·66	5·04, 6·28	5·64	5·04, 6·27	5·57	5·01, 6·22	0·001
LDL-cholesterol (mmol/l)‡	3·57	3·01, 4·17	3·60	3·03, 4·27	3·58	3·01, 4·15	3·57	3·02, 4·18	3·51	2·96, 4·09	0·010
HDL-cholesterol (mmol/l)‡	1·28	1·06, 1·53	1·29	1·08, 1·54	1·29	1·05, 1·55	1·28	1·06, 1·53	1·26	1·03, 1·51	0·017
TAG (mmol/l)‡	1·40	1·01, 2·04	1·42	1·01, 2·1	1·39	1·00, 1·94	1·37	1·00, 2·01	1·41	1·02, 2·10	0·933
Medications for											
Diabetes	14	0·5	4	0·5	4	0·5	2	0·3	4	0·5	0·842
Hypertension	134	4·5	29	3·9	40	5·3	33	4·4	32	4·3	0·879
Hypercholesterolemia	50	1·7	19	2·5	7	0·9	12	1·6	12	1·6	0·262
Dietary intake											
SFA (E%)	13	11, 14	14	13, 16	13	12, 14	12	11, 13	11	9, 12	<0·001
Total fat (E%)	33	29, 36	38	35, 41	34	32, 36	31	30, 33	27	25, 29	<0·001
Protein (E%)	16	14, 17	17	15, 18	16	15, 17	16	14, 17	15	14, 16	<0·001
Alcohol (E%)	1	0, 3	2	1, 4	1	0, 3	1	0, 2	1	0, 2	<0·001
Cholesterol (mg/d per 1000 kcal)	130	110, 152	152	131, 176	137	119, 156	126	111, 142	107	91, 125	<0·001
Fibre (g/d per 1000 kcal)	11	10, 13	10	9, 11	11	10, 12	12	10, 14	13	11, 16	<0·001
Energy intake (kcal§/d)	2057	1690, 2550	2133	1751, 2654	2128	1750, 2578	2079	1687, 2561	1917	1559, 2399	<0·001

Table 1 *Continued*

	Total		Q1		Q2		Q3		Q4		
	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	Median/ *n*	25th, 75th percentiles/%	P_{trend}†
Intake of food items											
Cakes											
g/d per 1000 kcal	10	5, 17	8	3, 14	11	5, 18	11	6, 18	10	5, 16	0·001
E% carbohydrates	1·5	0·7, 2·6	1·2	0·5, 2·1	1·6	0·7, 2·6	1·6	0·9, 2·8	1·5	0·7, 2·6	<0·001
Snacks											
g/d per 1000 kcal	2	1, 5	3	1, 6	2	1, 5	2	1, 4	1	0, 4	<0·001
E% carbohydrates	0·3	0·1, 0·7	0·4	0·1, 0·8	0·3	0·1, 0·7	0·3	0·1, 0·7	0·2	0, 0·6	<0·001
Soft drinks with sugar											
g/d per 1000 kcal	25	0, 65	18	0, 43	28	2, 68	27	2, 63	34	1, 86	<0·001
E% carbohydrates	1·0	0, 2·6	0·7	0, 1·7	1·1	0·1, 2·8	1·1	0·1, 2·6	1·4	0·0, 3·6	<0·001
Fresh fruit and berries											
g/d per 1000 kcal	62	35, 98	43	24, 71	59	35, 91	66	42, 104	85	48, 139	<0·001
E% carbohydrates	3·3	1·9, 5·3	2·3	1·3, 3·7	3·2	1·9, 4·8	3·6	2·2, 5·6	4·5	2·6, 7·5	<0·001
Juice											
g/d per 1000 kcal	20	2, 49	12	0, 32	21	4, 48	26	6, 58	23	2, 63	<0·001
E% carbohydrates	0·8	0·1, 2·0	0·5	0, 1·3	0·8	0·2, 1·9	1·0	0·2, 2·3	0·9	0·1, 2·5	<0·001
Conserved fruit and berries											
g/d per 1000 kcal	13	3, 25	7	1, 18	13	4, 24	16	6, 28	17	5, 32	<0·001
E% carbohydrates	2·3	0·4, 4·8	1·0	0, 3·4	2·3	0·5, 4·4	2·9	0·9, 5·3	3·1	0·7, 6·1	<0·001
Bread											
g/d per 1000 kcal	85	69, 105	77	60, 93	83	67, 99	88	72, 108	98	78, 120	<0·001
E% carbohydrates	16·4	13·2, 20·1	14·7	11·7, 17·8	15·8	13·0, 18·9	16·8	13·8, 20·7	18·7	14·8, 22·9	<0·001
Rice, pasta, flour, cereals											
g/d per 1000 kcal	19	12, 28	16	10, 23	19	12, 26	20	13, 29	21	13, 33	<0·001
E% carbohydrates	3·7	2·3, 5·9	3·0	2·0, 4·6	3·6	2·3, 5·5	4·1	2·6, 6·4	4·5	2·6, 7·3	<0·001
Potatoes											
g/d per 1000 kcal	48	32, 67	47	30, 63	47	33, 64	48	31, 67	52	33, 71	<0·001
E% carbohydrates	4·1	2·7, 5·6	4·0	2·6, 5·4	4·1	2·9, 5·5	4·1	2·7, 5·6	4·3	2·8, 5·8	<0·001
Vegetables											
g/d per 1000 kcal	85	54, 131	82	53, 122	85	55, 129	88	57, 132	87	52, 136	0·136
E% carbohydrates	2·2	1·5, 3·2	2·2	1·4, 3·1	2·2	1·5, 3·2	2·3	1·5, 3·2	2·3	1·4, 3·3	0·038

Q, quartile.
*Values are presented as *n* and % and median (25th, 75th percentiles) for categorical and continuous variables, respectively.
†Logistic regression for categorical variables with two categories, ordered logistic regression when more than two categories and linear regression for continuous variables where median intake as E% within each quartile group was used as the independent variable in the analyses.
‡In serum.
§To convert kcal to kJ, multiply by 4·184.

for age, sex, energy intake, smoking habits and physical activity. Further adjustments for intermediate factors, relevant medications and potential confounders did not materially influence the association (see online supplementary material, Supplemental Table S1).

Figure 1(b) illustrates lower risk of CHD with a higher intake of SFA until an intake of about 13 E%, after which the curve levelled off, after adjustment for model 2 variables.

When stratifying on smoking habits, there was a tendency of lower risk of CHD with higher intake of SFA in all groups, but less so among current smokers (see online supplementary material, Supplemental Table S2).

When examining the association between SFA from various food items, we found that only SFA from cheese was significantly associated with a lower risk of CHD (Table 3). The median intake of SFA from cheese ranged from 0·5 E% (Q1) to 4·1 E% (Q4). After adjustments for age, sex, energy intake, physical activity and smoking habits (model 2), SFA from cheese was significantly associated with lower risk of CHD in the quartile analyses ($HR_{Q4\ v.\ Q1}$ 0·44, 95 % CI 0·24, 0·83, $P_{trend} = 0·006$). Results from the evaluation of SFA from cheese as a continuous variable (per 1 E%) were similar.

We further evaluated the association between SFA and CHD after excluding the SFA contribution from cheese, and in the quartile analyses, we found that intake of SFA after exclusion of cheese was associated with lower risk of CHD ($HR_{Q4\ v.\ Q1}$ 0·58, 95 % CI 0·34, 0·98, $P_{trend} = 0·030$), after adjustment for age, sex, energy intake, physical activity and smoking habits (model 2, Table 3). Results from the continuous analyses were in the same direction as the quartile analyses. Upon further evaluation (Fig. 1(c)), we observed deviations from linearity in the association between SFA intake and CHD risk after excluding SFA from cheese.

Higher intake of total carbohydrates correlated significantly with lower intake of SFA ($\rho = -0·6$, $P < 0·001$) and lower intake of total fat ($\rho = -0·8$, $P < 0·001$). Results from the theoretical substitution analyses are shown in Fig. 2. Substitution of 5 % of total energy intake from carbohydrates with SFA was associated with a 26 % lower risk of CHD (model 2 HR 0·74, 95 % CI 0·40, 1·36), although not statistically significant. A substitution of carbohydrates with total fat was also associated with lower risk of CHD (model 2 HR 0·75, 95 % CI 0·62, 0·90). To further evaluate whether substitution analyses of carbohydrates with SFA or with total fat could be attributed to an underlying beneficial effect of PUFA, we evaluated results of analyses substituting carbohydrates with PUFA in which we found a non-significant association with incident CHD (model 2 HR 1·42, 95 % CI 0·82, 2·47). Further, the substitution of carbohydrates with protein was not associated with the risk of CHD (model 2 HR 1·09, 95 % CI 0·71, 1·68). When adjusting for age, sex and energy intake only, results of all substitution models were in the same direction as in the fully adjusted model, but were non-significant.

Exclusion of events occurring during the first 2 years of follow-up yielded no material differences in results.

Discussion

In this community-based study population, high intake of carbohydrates and low intake of SFA were associated with higher risk of incident CHD. Intake of SFA from cheese was significantly associated with lower CHD risk. When evaluating SFA intake after excluding the contribution of SFA from cheese, the association became weaker, but remained significant. Substituting 5 % of total energy intake from carbohydrates with SFA and total fat was associated with lower CHD risk (HR of 0·74 and 0·75, respectively), but was statistically significant only for total fat. The lack of a statistically significant finding for SFA may reflect, in part, the narrower range of SFA intake compared with total fat and carbohydrate intake.

Carbohydrates reflect a variety of sources including sucrose, fructose and refined cereals, as well as fibre-rich whole grains, vegetables and legumes. Refined carbohydrates and added sugar accounted for a large part of carbohydrate intake in the Norwegian diet at the time of HUSK baseline in 1997–1999[5]. Even today, few Norwegians comply with the Nordic nutrition recommendations for fibre intake[31,32]. Per capita sales data indicate that intake of sugar-containing foods and beverages peaked at the end of the 1990s[5]. In addition, a nationwide diet survey among men and women 16–79 years of age (1997–1999) found that their diet contained inadequate amounts of food products rich in fibre and that the intake of added sugar was 10 and 9 E% among men and women, respectively[33]. When evaluating baseline characteristics in this cohort, the intake of fruit and berries, sugar-sweetened beverages and juice doubled from the lowest to the highest quartile of carbohydrate intake. In contrast, intake of rice, pasta, flour and cereals was only modestly higher and vegetable intake did not differ across quartiles of total carbohydrate intake. Also, while recommended intake of fibre is ≥25 g/d in women and ≥35 g/d in men[31], the median intake of fibre in the total study population was 24 g/d and the median fibre intake in the highest quartile of carbohydrate intake was 26 g/d. However, FFQ are affected by systematic errors and do not precisely estimate dietary intake; therefore, these data should be interpreted with caution.

Previous cohort studies and meta-analyses have shown diverse results regarding the association between intake of carbohydrates and CHD when evaluating total carbohydrates. A study of men and women 30–59 years of age found that carbohydrate intake was associated with a lower CHD mortality risk (RR 0·96, 95 % CI 0·94, 0·99)[34]. However, a large cohort study of individuals aged 35–70 years found that higher carbohydrate intake was not associated with the risk of CVD (HR 1·01, 95 % CI 0·88, 1·15) or myocardial infarction (HR 0·90, 95 % CI 0·73, 1·10)[23]. Carbohydrate intake was not consistently associated with CHD when

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Table 2 Baseline characteristics by quartiles of saturated fat intake (energy percentage (E%)), The Hordaland Health Study*

	Total		Q1		Q2		Q3		Q4		
	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	P_{trend}†
SFA (E%)	13	11, 14	10	9, 11	12	11, 12	13	13, 14	15	15, 16	<0·001
SFA (g/d per 1000 kcal)	14	12, 16	11	10, 12	13	13, 14	15	14, 15	17	16, 18	<0·001
Participants (*n*)	2995		749		749		748		749		
Age (years)	48	47, 48	48	48, 49	48	47, 48	48	47, 48	48	47, 48	0·151
Men	1282	42·8	327	43·7	349	46·6	318	42·5	288	38·5	0·016
College and/or university education	1138	38·3	291	39·4	281	37·6	290	39·2	276	37·0	0·121
Family history of infarction	1186	40·9	316	43·4	295	40·7	284	39·2	291	40·5	0·227
Smoking habits											<0·001
Previous smoker	915	31·2	248	34·2	241	32·9	230	31·2	196	26·7	
Current smoker	982	33·5	197	27·2	233	31·8	259	35·1	293	39·9	
Physical activity											<0·001
None	745	25·9	150	21·0	196	27·3	199	27·4	200	27·7	
<1 h/week	813	28·2	192	26·9	168	23·4	221	30·4	232	32·2	
1–2 h/week	908	31·5	241	33·7	243	33·8	221	30·4	203	28·2	
≥3 h/week	415	14·4	132	18·5	112	15·6	85	11·7	86	11·9	
Hypertension	708	23·7	196	26·2	183	24·4	179	24·0	150	20·0	0·006
Glucose intolerance											0·296
Pre-diabetes	66	2·2	15	2·0	17	2·3	11	1·5	23	3·1	
Diabetes	27	0·9	6	0·8	6	0·8	9	1·2	6	0·8	
Casual glucose (mmol/l)‡	5·01	4·64, 5·49	5·04	4·66, 5·51	5·01	4·66, 5·47	4·99	4·65, 5·49	4·98	4·60, 5·43	0·400
BMI (kg/m^2)	24·9	22·8, 27·4	25·2	23·0, 27·6	25·2	23·0, 27·5	24·8	23·0, 27·4	24·6	22·2, 27·1	0·002
Waist circumference (cm)	85·0	77·0, 94·0	85·0	77·0, 94·0	86·0	78·0, 94·0	85·0	77·0, 93·0	84·0	75·0, 93·0	0·021
Cholesterol (mmol/l)‡	5·65	5·06, 6·30	5·64	5·06, 6·35	5·61	5·01, 6·26	5·69	5·10, 6·28	5·65	5·08, 6·35	0·729
LDL-cholesterol (mmol/l)‡	3·57	3·01, 4·17	3·55	2·96, 4·17	3·53	2·99, 4·11	3·58	3·07, 4·17	3·61	3·02, 4·23	0·250
HDL-cholesterol (mmol/l ‡	1·28	1·06, 1·53	1·29	1·06, 1·53	1·25	1·04, 1·50	1·29	1·07, 1·54	1·32	1·08, 1·57	0·064
TAG (mmol/l)‡	1·40	1·01, 2·04	1·41	1·04, 2·15	1·47	1·03, 2·08	1·40	1·01, 1·99	1·33	0·95, 1·93	0·005
Medications for											
Diabetes	14	0·5	3	0·4	2	0·3	6	0·8	3	0·4	0·704
Hypertension	134	4·5	36	4·8	37	4·9	33	4·4	28	3·7	0·270
Hypercholesterolaemia	50	1·7	20	2·7	11	1·5	14	1·9	5	0·7	0·007
Dietary intake											
Carbohydrates (E%)	49	46, 53	54	51, 58	51	48, 53	48	45, 51	45	42, 48	<0·001
Total fat (E%)	33	29, 36	27	25, 29	31	30, 33	34	32, 36	37	35, 40	<0·001
Protein (E%)	16	14, 17	16	14, 17	16	14, 17	16	15, 17	16	14, 17	0·876
Alcohol (E%)	1	0, 3	1	0, 3	1	0, 3	1	0, 3	1	0, 2	<0·001
Cholesterol (mg/d per 1000 kcal)	130	110, 152	115	95, 137	128	110, 149	133	116, 156	143	122, 164	<0·001
Fibre (g/d per 1000 kcal)	11	10, 13	13	11, 16	12	10, 13	11	10, 13	10	8, 11	<0·001
Energy intake (kcal§/d)	2057	1690, 2550	1900	1537, 2335	2093	1731, 2584	2112	1712, 2623	2182	1773, 2584	<0·001
Intake of food items											

Table 2 *Continued*

	Total		Q1		Q2		Q3		Q4		
	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	Median/*n*	25th, 75th percentiles/%	P_{trend}†
Butter‖											
g/d per 1000 kcal	0	1	0	0	0	1	0	1	0	3	<0·001
E% SFA	0	1	0	0	0	0	0	0	0	1	<0·001
Cheese											
g/d per 1000 kcal	13	7, 21	9	4, 14	11	7, 18	15	9, 24	19	11, 32	<0·001
E% SFA	2	1, 3	1	1, 2	2	1, 2	2	1, 3	3	2, 4	<0·001
Margarine											
g/d per 1000 kcal	3	2, 8	2	1, 4	3	2, 7	3	2, 9	3	2, 11	<0·001
E% SFA	1	1, 2	1	0, 1	1	1, 2	1	1, 2	1	1, 3	<0·001
Milk and milk products											
g/d per 1000 kcal	129	65, 205	131	61, 214	140	71, 213	128	69, 196	119	61, 196	0·031
E% SFA	1	1, 2	1	1, 2	1	1, 2	1	1, 2	2	1, 3	<0·001
Meat and meat products											
g/d per 1000 kcal	55	41, 70	49	36, 63	56	43, 70	57	43, 74	57	42, 73	<0·001
E% SFA	2	2, 3	2	2, 3	2	2, 3	2	2, 3	3	2, 3	<0·001
Minced meat products											
g/d per 1000 kcal	24	15, 34	20	12, 29	25	16, 33	26	17, 36	26	17, 35	<0·001
E% SFA	1	1, 2	1	1, 1	1	1, 2	1	1, 2	1	1, 2	<0·001

Q, quartile.
*Values are presented as *n* and % and median and 25th, 75th percentiles for categorical and continuous variables, respectively.
†Logistic regression for categorical variables with two categories, ordered logistic regression when more than two categories and linear regression for continuous variables where median intake as E% within each quartile group was used as the independent variable in the analyses.
‡In serum.
§To convert kcal to kJ, multiply by 4·184.
‖Intake is reported as median and mean because of a large number of zero intake reporting.

Table 3 Associations between macronutrients and risk of incident CHD, The Hordaland Health Study. Mean follow-up time 10·8 years

		CHD		Model 1†		Model 2‡	
Intake of macronutrients (range in E%)*	*n*	*n*	%	HR	95 % CI	HR	95 % CI
Carbohydrates	2995	112					
Q1 (21, 45)	749	23	3·1	1 (ref)		1 (ref)	
Q2 (45, 49)	749	25	3·3	1·11	0·63, 1·96	1·09	0·60, 1·98
Q3 (49, 53)	748	29	3·9	1·30	0·75, 2·24	1·67	0·96, 2·89
Q4 (53, 74)	749	35	4·7	1·63	0·96, 2·76	2·10	1·22, 3·63
P_{trend}§				0·056		0·003	
Continuous (per 2 E%)	2995	112		1·08	1·01, 1·15	1·12	1·05, 1·20
Saturated fat	2995	112					
Q1 (4, 11)	749	44	5·9	1 (ref)		1 (ref)	
Q2 (11, 13)	749	24	3·2	0·55	0·34, 0·91	0·46	0·27, 0·78
Q3 (13, 14)	748	23	3·1	0·55	0·33, 0·92	0·47	0·28, 0·79
Q4 (14, 25)	749	21	2·8	0·53	0·32, 0·90	0·44	0·26, 0·76
P_{trend}§				0·013		0·002	
Continuous (per 2 E%)	2995	112		0·82	0·70, 0·97	0·78	0·66, 0·92
Saturated fat from cheese	2995	112					
Q1 (0, 1)	749	45	6·0	1 (ref)		1 (ref)	
Q2 (1, 2)	748	28	3·7	0·68	0·43, 1·10	0·78	0·49, 1·27
Q3 (2, 3)	749	25	3·3	0·64	0·39, 1·04	0·60	0·35, 1·03
Q4 (3, 18)	749	14	1·9	0·38	0·21, 0·70	0·44	0·24, 0·83
P_{trend}§				0·002		0·006	
Continuous (per 1 E%)	2995	112		0·84	0·74, 0·97	0·87	0·75, 0·99
Saturated fat after excluding saturated fat from cheese	2995	112					
Q1 (3, 9)	748	34	4·6	1 (ref)		1 (ref)	
Q2 (9, 10)	750	29	3·9	0·85	0·51, 1·39	0·71	0·42, 1·20
Q3 (10, 12)	748	20	2·7	0·56	0·32, 0·98	0·46	0·26, 0·81
Q4 (12, 21)	749	29	3·9	0·81	0·49, 1·34	0·58	0·34, 0·98
P_{trend}§				0·277		0·030	
Continuous (per 2 E%)	2995	112		0·94	0·79, 1·12	0·85	0·71, 1·02

E%, energy percentage; CHD, incident CHD; *n*, number of participants; HR, hazard ratio; Q, quartile.
*Minimum and maximum intake of the macronutrient.
†Cox proportional hazard regression analysis adjusted for age, sex and energy intake.
‡Adjusted in addition for physical activity and smoking habits.
§P_{trend}, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.

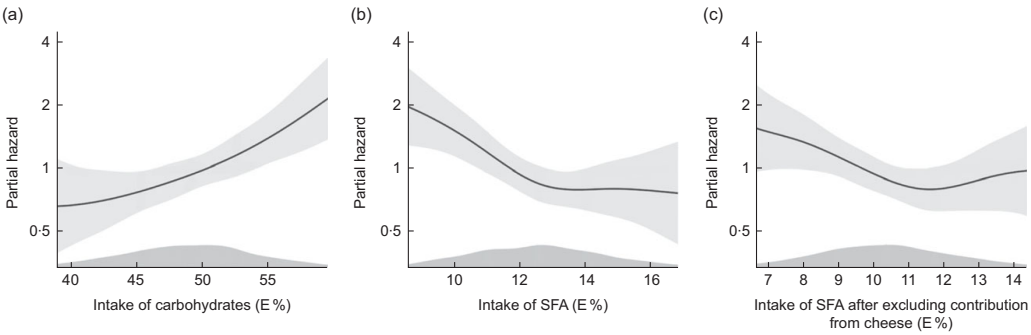

Fig. 1 Cox proportional hazards regression with penalized splines, The Hordaland Health Study. Distribution of partial hazard (black line) with 95% CI (shadow) for CHD across the distribution of a) intake of carbohydrates in E%, b) intake of saturated fatty acids (SFA) in E% and c) intake of SFA after excluding contribution from cheese in E%. The model includes age, sex, energy intake, physical activity and smoking habits. Intake above the 5thth percentile and below the 95th percentile is included in the figure

different sources of carbohydrates were considered separately. Li *et al.*[35] found in a cohort study that higher intake of carbohydrates from whole grains was associated with lower risk of incident CHD (HR 0·90, 95 % CI 0·83, 0·98), while carbohydrates from refined starches/added sugars were positively associated with higher risk of CHD (HR 1·10, 95 % CI 1·00, 1·21).

Fung *et al.*[36] studied the association between consumption of sugar-sweetened beverages and the risk of CHD in the Nurses' Health Study and found that regular consumption of sugar-sweetened beverages was associated with a higher CHD risk. In addition, a meta-analysis of cohort studies reported that intake of sugar-sweetened beverages was associated with increased risk of myocardial

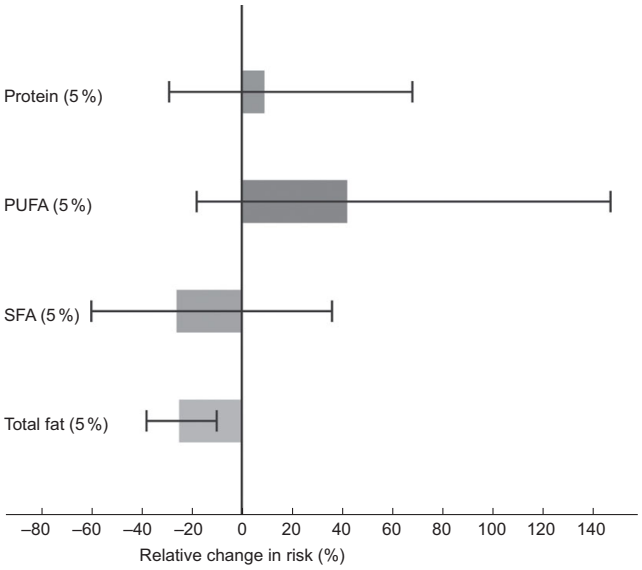

Fig. 2 Theoretical substitution analyses, illustrating an isocaloric substitution of 5E% from carbohydrates with total fat, saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) or protein and its association with CHD. Adjusted for age, sex, energy intake, physical activity and smoking habits. Mean 10·8 years follow-up of the Hordaland Health Study participants

infarction[37]. In randomised controlled trials, dietary sugar intake has been found to increase blood pressure and serum TAG, TC and LDL-cholesterol[38]. While we did not identify any one particular source of carbohydrates to contribute to the overall carbohydrate association with CHD, we did note differences in the quality of carbohydrate sources between low to high carbohydrate intake quartiles where intake of fibre, vegetables and many carbohydrate sources remained essentially stable, while bread, sugar-sweetened beverages, juice, and preserved and fresh fruit and berries increased across the quartiles of carbohydrate intake. Thereby indicating that increased carbohydrate intake in the current study population represented increases in low-fibre and higher sucrose/fructose carbohydrates.

SFA intake in our study population came primarily from dairy products, especially cheese. The intake of cheese more than doubled from the lowest to the highest quartile of SFA intake, and cheese was also the main contributor to SFA intake in the highest quartile. As dairy products are important contributors of SFA, the general recommendation in Norway has been to reduce the intake of high-fat dairy products[39]. However, studies do not consistently support that this recommendation would reduce risk of CHD[40–42]. A systematic review and meta-analysis did not report a statistically significant association between total dairy intake and CHD (Summary RR 0·91, 95 % CI 0·80, 1·04)[41]. Further, the only dairy product significantly associated with lower CHD risk was cheese (Summary RR 0·82, 95 % CI 0·72, 0·93)[41]. In addition, Qin *et al.*[42] reported no association between dairy intake and CHD (RR 0·94, 95 % CI 0·82, 1·07), and CHD risk was lowered by cheese consumption also in this study (RR 0·84, 95 % CI 0·71, 1·00).

We found that intake of SFA from cheese was the only food source associated with a lower risk of CHD. Underlying mechanisms for a potential CHD protective effect of cheese may relate to (i) fermentation which may influence dairy fat's contribution to LDL-cholesterol[43] and (ii) menaquinones (vitamin K_2) which comes primarily from cheese in European diets[44]. Geleijnse *et al.*[45] found that menaquinone intake was inversely associated with serum TC and aortic calcification and positively associated with serum HDL-cholesterol. Menaquinones transported together with SFA may, therefore, be associated with lower CHD risk. Also, as most cheeses are not homogenised, they still contain milk fat globule membranes. Rosqvist *et al.*[46] reported that intake of milk fat enclosed by milk fat globule membranes did not impair the lipoprotein profile when compared with butter oil. When evaluating the association between SFA and CHD after excluding the contribution from cheese, intake of SFA was still associated with lower risk of CHD. The penalised spline illustrates almost the same pattern as for total SFA, but with a tendency of higher risk at higher intakes.

A systematic review and meta-analysis found that when comparing the highest *v.* lowest intake of SFA, there was no association observed between SFA intake and CHD

(RR 1·03, 95 % CI 0·98, 1·07)[18]. Another meta-analysis of cohort studies found that the highest *v.* lowest quintile intake of SFA had a weak association with the risk of CHD (RR 1·06, 95 % CI 0·95, 1·17)[19]. However, the quality of the documentation was regarded as very low, and in an analysis not adjusted for cardiovascular risk factors such as serum cholesterol, there was a significantly higher risk of CHD mortality comparing the highest *v.* lowest intake of SFA (RR 1·20, 95 % CI 1·02, 1·41)[19].

Our results differ from these meta-analyses and likely reflect that, in the current study population, cheese was the predominant contributor to SFA, there was a narrow range of median SFA intake in the four quartiles, and there was an inverse association between SFA and carbohydrate intake.

Theoretical substitution analyses

Analysing the effect of one nutrient when considering the nutrients it substitutes provides another means of understanding the observed associations[30]. Another study suggested that reducing the intake of carbohydrates from refined grains and added sugars may produce beneficial metabolic effects that may decrease the risk of CHD[22]. Jakobsen *et al.*[21] showed that when substituting 5 E% from SFA by carbohydrates, there was no association with fatal CHD (RR 0·96, 95 % CI 0·82, 1·13), but a statistically significant increase in the overall CHD risk (RR 1·07, 95 % CI 1·01, 1·14). When separately evaluating carbohydrates with high and low glycaemic index, only a substitution of SFA with high glycaemic index carbohydrates was associated with a higher risk of myocardial infarction (HR 1·33, 95 % CI 1·08, 1·64)[22]. Chen *et al.*[47] evaluated the association between dairy fat and CHD in US adults and found no significant benefit of replacing dairy fat with the same energy intake from refined starch and added sugar. However, the substitution of 5 % of energy from dairy fat by carbohydrates from whole grains was associated with a significantly lower risk of CHD (RR 0·66, 95 % CI 0·62, 0·70).

The tendency for a lower risk of CHD when replacing carbohydrates with total fat and SFA may reflect a combination of the beneficial association observed between cheese consumption and CHD as well as the deleterious association between low-fibre carbohydrate intake and CHD. Total fat and SFA intake in the context of high-cheese consumption may not be generalisable to total fat and SFA intake in a low-cheese consumption context.

Strengths and limitations

Strengths of our study include a community-based sample of men and women with a relatively long follow-up time. Only sixty participants died due to other reasons until 2009; therefore, there was minimal competing risk from other causes of death. Linkage to the CVDNOR project database assured as good as complete follow-up. Also, we had information on health status, medication use, health habits and history of CHD at baseline, enabling us to evaluate incident CHD. Further, the FFQ captured the major sources of carbohydrates and SFA expected in the current study population, and energy adjustment of the statistical models is a well-established approach for reducing the bias related to self-reported dietary data.

Theoretical substitution analyses were performed, modelling the substitution of carbohydrates with PUFA, SFA, protein and total fat. Another strength is the robustness of the results which were similar from model to model after various adjustments.

Limitations include the relatively small number of participants and events limiting stratified analyses and multivariable adjustments.

Another limitation is the lack of information on possible changes over time in diet, medications and other risk factors. Both dietary habits and food products have changed during the study period, due to the recommendations on reducing intake of SFA as the source of fat and increasing intake of whole grains as the source of carbohydrates[31,48]. Intake of cooking oil has tripled from the late 1990s to about 2013, and the consumption of vegetables also increased, while intake of margarine and sugar-containing food decreased according to per capita sales data[5].

Blood samples were non-fasting. Since postprandial TAG remain elevated for several hours, and the Friedewald equation, used for the calculation of LDL-cholesterol, assumes fasting TAG values, LDL-cholesterol may be underestimated[49]. Also, most reference values for serum lipids and glucose are established on fasting blood specimen.

Further, a common problem with FFQ is systematic under- or overreporting of nutrient and energy intake, limiting the estimation of absolute intake. However, the FFQ is well suited to rank participants by dietary intake for evaluation of associations with health endpoints[50]. Given that FFQ are not optimal for determining absolute nutrient intake, caution is required in the interpretation of the theoretical substitution models[51].

There may also be other limitations. A large proportion (75 %) of the participants reported zero intake of butter, likely reflecting underreporting. Also, we did not have extensive information on carbohydrate quality particularly for bread due to lack of historical food recipes, lack of food label details and type of carbohydrate content for the recipes from the dietary database at the end of the 1990s.

Nevertheless, when we adjusted for estimated fibre from bread, vegetables and fruit intake, total carbohydrate intake remained a statistically significant predictor of higher CHD risk. Another limitation of the current study is that the results cannot be generalisable to populations with a greater range in carbohydrate or SFA intake. In the current study, the intake of SFA varied from 4 to 25 E% and the intake of carbohydrates varied from 21 to 74 E% resulting

in a narrower range of intake when we evaluated the median intake between the lowest and highest quartiles (i.e., 10–15 E% for SFA and 43–56 E% for carbohydrates), precluding our ability to generalise to lower and higher intake values. The current study can therefore not be compared with previous studies that have shown higher all-cause and cause-specific mortality associated with much lower carbohydrate intakes than our study population[52,53]. Finally, the available data were not appropriate for studying unsaturated fat, given the changing *trans*-fatty acid composition of unsaturated fat during the study period.

While reverse causation is a general concern in observational studies of dietary habits and disease outcomes, we noted a similar percentage of participants with a family history of CHD and similar baseline BMI values across quartiles of carbohydrate and SFA intake. Further, adjusting for family history of CHD and BMI did not alter our findings. Although we performed multivariable analyses, residual confounding may still be present.

Lastly, it is of note that at the end of follow-up, participants' age was generally lower than the mean age of acute myocardial infarction in Norway which is 73·8 years for men and 79·1 years for women[54]. Thus, our findings may reflect mechanisms involved in early-onset CHD and may not necessarily be generalisable to older populations.

Conclusion

The focus of the current study was to evaluate the importance of the interplay between SFA and total carbohydrates, including SFA sources, when evaluating the association between SFA and CHD. A high intake of carbohydrates, reflecting low-fibre and relatively higher sucrose/fructose dietary sources, and a low intake of SFA were associated with higher CHD risk in the current study population. Substituting carbohydrates with total fat was associated with lower risk. Also, SFA from cheese was associated with lower risk of CHD.

Further research evaluating potential benefits of dairy products and their nutritional constituents is warranted. Also, there is a need to clarify the relative health trade-offs between replacing carbohydrate intake with fat intake in study populations with diverse dietary habits and a wider range in carbohydrate and SFA intakes. In addition, results of our study suggest that dietary guidelines development and their communication to the public, especially regarding reductions in certain foods and nutrients, need to consider the potential health impact of alternative sources of energy.

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Disclaimer

The current study used data from the Norwegian Cause of Death Registry. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the registry is intended nor should be inferred.

Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S1368980020003043

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Intake of carbohydrates and saturated fatty acids and risk of coronary heart disease in middle-age adults. The Hordaland Health Study (HUSK)

Supplementary table 1 Associations between macronutrients and risk of incident coronary heart disease. The Hordaland Health Study (HUSK)

Intake of macronutrients, E%	Model 1 HR (95% CI)*	Model 2 HR (95% CI)†	Model 3 HR (95% CI)‡	Model 4 HR (95% CI)§
	N = 2995	N = 2986	N = 2883	N = 2697
	CHD, N = 112	CHD, N = 112	CHD, N = 104	CHD, N = 93
Carbohydrates				
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	1·11 (0·63, 1·96)	1·13 (0·64, 1·99)	1·26 (0·69, 2·29)	1·16 (0·63, 2·17)
Q3	1·30 (0·75, 2·24)	1·32 (0·76, 2·29)	1·45 (0·81, 2·60)	1·49 (0·82, 2·73)
Q4	1·63 (0·96, 2·76)	1·54 (0·91, 2·63)	1·62 (0·92, 2·84)	1·50 (0·81, 2·80)
p – trend‖	0·056	0·088	0·082	0·150
Continuous, per 2E%	1·08 (1·01, 1·15)	1·07 (1·00, 1·14)	1·09 (1·02, 1·17)	1·09 (1·01, 1·18)
Saturated fatty acids				
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0·55 (0·34, 0·91)	0·55 (0·33, 0·91)	0·54 (0·32, 0·90)	0·47 (0·27, 0·84)
Q3	0·55 (0·33, 0·92)	0·57 (0·34, 0·94)	0·55 (0·32, 0·94)	0·50 (0·28, 0·88)
Q4	0·53 (0·32, 0·90)	0·56 (0·33, 0·94)	0·51 (0·29, 0·90)	0·47 (0·26, 0·84)
p – trend‖	0·013	0·021	0·013	0·010
Continuous, per 2E%	0·82 (0·70, 0·97)	0·84 (0·71, 0·99)	0·80 (0·67, 0·95)	0·79 (0·66, 0·94)

E%, energy percent; HR, hazard ratio; CI, confidence interval; N, number of participants; CHD, incident coronary heart disease; Q, quartile

*Model 1: Cox proportional hazards regression analysis adjusted for age, sex, and energy intake

†Model 2: Additionally adjusted for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose (continuous), systolic blood pressure, diastolic blood pressure, and body mass index

‡Model 3: Additionally adjusted for hypertension, glucose intolerance, family history of infarction, statins, oral hypoglycemics (including metformin) and insulin, and anti-hypertensive medications

§Model 4: Additionally adjusted for smoking habits, physical activity, alcohol consumption in E%, and education

‖P – trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.

Supplementary table 2 Associations between saturated fatty acids and risk of incident coronary heart disease, stratified by smoking habits. The Hordaland Health Study (HUSK)

Intake of saturated fatty acids, E%	N (CHD)	Non-smokers HR (95% CI)*	N (CHD)	Previous smokers HR (95% CI)*	N (CHD)	Smokers HR (95% CI)*
Q1	270 (8)	1 (ref)	235 (17)	1 (ref)	189 (17)	1 (ref)
Q2	251 (3)	0·50 (0·13, 1·96)	229 (5)	0·32 (0·12, 0·88)	223 (13)	0·60 (0·29, 1·24)
Q3	241 (3)	0·46 (0·12, 1·76)	224 (7)	0·45 (0·18, 1·10)	251 (12)	0·53 (0·25, 1·13)
Q4	239 (1)	0·15 (0·02, 1·17)	187 (2)	0·17 (0·04, 0·74)	281 (17)	0·74 (0·37, 1·46)
p – trend†		0·037		0·005		0·431
Continuous, per 2E%	1001 (15)	0·71 (0·44, 1·13)	875 (31)	0·60 (0·44, 0·82)	944 (59)	0·90 (0·73, 1·12)

E%, energy percent; N, number of participants; CHD, incident coronary heart disease; HR, hazard ratio; CI, confidence interval; Q, quartile

*Adjusted for age, sex, energy intake and physical activity.

†P – trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.

Supplementary table 3 Associations between carbohydrates from different food items and incident coronary heart disease. The Hordaland Health Study (HUSK)

Carbohydrates from food items, E%		HR (95%CI) Q1 (ref)	Q2	Q3	Q4	P – trend*	Continuous, per 1E%
Rice, pasta, flour, cereals							
	Model 1†	1 (ref)	0·84 (0·51, 1·39)	0·65 (0·37, 1·11)	0·88 (0·54, 1·44)	0·631	1·00 (0·94, 1·06)
	Model 2‡	1 (ref)	1·00 (0·59, 1·68)	0·80 (0·46, 1·41)	1·13 (0·67, 1·91)	0·683	1·03 (0·97, 1·09)
Bread							
	Model 1†	1 (ref)	1·06 (0·60, 1·85)	1·36 (0·80, 2·32)	1·09 (0·63, 1·89)	0·649	1·01 (0·97, 1·04)
	Model 2‡	1 (ref)	1·16 (0·65, 2·09)	1·64 (0·95, 2·84)	1·23 (0·69, 2·18)	0·378	1·01 (0·98, 1·05)
Soft drinks with sugar							
	Model 1†	1 (ref)	0·94 (0·54, 1·63)	0·94 (0·54, 1·62)	1·13 (0·67, 1·90)	0·507	1·04 (1·00, 1·09)
	Model 2‡	1 (ref)	0·89 (0·50, 1·58)	0·89 (0·51, 1·55)	1·00 (0·58, 1·71)	0·860	1·03 (0·99, 1·08)
Juice							
	Model 1†	1 (ref)	1.04 (0·63, 1·71)	1·00 (0·60, 1·67)	0·79 (0·45, 1·37)	0·328	0·98 (0·88, 1·10)
	Model 2‡	1 (ref)	1·30 (0·78, 2·17)	1·24 (0·73, 2·13)	0·86 (0·47, 1·55)	0·406	0·97 (0·87, 1·09)
Fruit and berries							
	Model 1†	1 (ref)	0·80 (0·47, 1·34)	1·01 (0·62, 1·66)	0·98 (0·58, 1·67)	0·882	1·00 (0·96, 1·05)
	Model 2‡	1 (ref)	1·06 (0·62, 1·82)	1·40 (0·83, 2·35)	1·38 (0·78, 2·45)	0·186	1·04 (0·99, 1·09)

E%, energy percent; Q, quartile; HR, hazard ratio; CI, confidence interval
*P – trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.
†Age, sex and energy intake adjusted Cox proportional hazards regression analysis
‡Adjusted in addition for physical activity and smoking habits

Supplementary table 4 Associations between saturated fatty acids from different food items and incident coronary heart disease. The Hordaland Health Study (HUSK)

	HR (95%CI)					
Saturated fat from food items, E%	Q1 (ref)	Q2	Q3	Q4	P – trend*	Continuous, per 1E%
Margarine						
Model 1†	1 (ref)	0·90 (0·55, 1·49)	0·80 (0·47, 1·35)	0·81 (0·48, 1·35)	0·478	1·00 (0·86, 1·17)
Model 2‡	1 (ref)	0·85 (0·51, 1·43)	0·72 (0·42, 1·25)	0·68 (0·40, 1·16)	0·202	0·95 (0·81, 1·12)
Butter§						
Model 1†	1 (ref)	-	-	0·69 (0·43, 1·10)	0·120	0·91 (0·76, 1·08)
Model 2‡	1 (ref)	-	-	0·70 (0·43, 1·14)	0·154	0·90 (0·75, 1·07)
Milk and milk products						
Model 1†	1 (ref)	1·22 (0·73, 2·04)	0·76 (0·43, 1·34)	1·16 (0·69, 1·93)	0·861	1·06 (0·93, 1·21)
Model 2‡	1 (ref)	1·60 (0·94, 2·74)	0·95 (0·52, 1·73)	1·25 (0·73, 2·15)	0·838	1·02 (0·89, 1·17)
Meat						
Model 1†	1 (ref)	2·32 (1·32, 4·10)	1·69 (0·93, 3·07)	1·27 (0·68, 2·35)	0·927	0·98 (0·81, 1·18)
Model 2‡	1 (ref)	1·94 (1·08, 3·47)	1·51 (0·83, 2·74)	0·93 (0·49, 1·76)	0·332	0·89 (0·74, 1·08)
Minced meat products						
Model 1†	1 (ref)	1·24 (0·72, 2·14)	1·23 (0·72, 2·10)	1·02 (0·59, 1·77)	0·942	1·01 (0·77, 1·31)
Model 2‡	1 (ref)	1·27 (0·73, 2·23)	1·13 (0·64, 1·98)	0·95 (0·54, 1·67)	0·646	0·94 (0·71, 1·24)

E%; energy percent; Q, quartile; HR, hazard ratio; CI, confidence interval

*P – trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.

† Cox proportional hazards regression analysis adjusted for age, sex and energy intake.

‡Adjusted in addition for physical activity and smoking habits

§Because of a large number of zero intake reporting, Cox regression compares >0 intake versus <=0 intake.

III

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Association of dietary vitamin K and risk of coronary heart disease in middle-age adults: the Hordaland Health Study Cohort

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ABSTRACT

Objective The role of vitamin K in the regulation of vascular calcification is established. However, the association of dietary vitamins K1 and K2 with risk of coronary heart disease (CHD) is inconclusive.

Design Prospective cohort study.

Setting We followed participants in the community-based Hordaland Health Study from 1997 - 1999 through 2009 to evaluate associations between intake of vitamin K and incident (new onset) CHD. Baseline diet was assessed by a past-year food frequency questionnaire. Energy-adjusted residuals of vitamin K1 and vitamin K2 intakes were categorised into quartiles.

Participants 2987 Norwegian men and women, age 46–49 years.

Methods Information on incident CHD events was obtained from the nationwide Cardiovascular Disease in Norway (CVDNOR) Project. Multivariable Cox regression estimated HRs and 95% CIs with test for linear trends across quartiles. Analyses were adjusted for age, sex, total energy intake, physical activity, smoking and education. A third model further adjusted K1 intake for energy-adjusted fibre and folate, while K2 intake was adjusted for energy-adjusted saturated fatty acids and calcium.

Results During a median follow-up time of 11 years, we documented 112 incident CHD cases. In the adjusted analyses, there was no association between intake of vitamin K1 and CHD (HR_{Q4vsQ1} = 0.92 (95% CI 0.54 to 1.57), p for trend 0.64), while there was a lower risk of CHD associated with higher intake of energy-adjusted vitamin K2 (HR_{Q4vsQ1} = 0.52 (0.29 to 0.94), p for trend 0.03). Further adjustment for potential dietary confounders did not materially change the association for K1, while the association for K2 was slightly attenuated (HR_{Q4vsQ1} = 0.58 (0.28 to 1.19)).

Conclusions A higher intake of vitamin K2 was associated with lower risk of CHD, while there was no association between intake of vitamin K1 and CHD.

Trial registration number NCT03013725

Strengths and limitations of this study

- ► The study had a long follow-up time with minimal competing risk from other causes of death.
- ► Linkage to a nationwide database assured complete cohort follow-up.
- ► We had information on history of coronary heart disease (CHD) at baseline which enabled us to evaluate incident (new onset) CHD.
- ► The Food Frequency Questionnaire was not validated for intake of vitamin K.
- ► It was not possible to differentiate the various subtypes of vitamin K2.

INTRODUCTION

Vitamin K is a fat-soluble vitamin including vitamin K1 (K1; phylloquinone) from green leafy vegetables and vegetable oils as the main dietary sources, and vitamin K2 (K2; menaquinones) from dairy products, meat and egg yolk as the main dietary sources in Europe.[1–3] K2 has a longer half-life in the circulation than K1.[4] Both are absorbed from the small ileum and jejunum. K1 and K2 are incorporated into chylomicrons and delivered to the liver. K2 is also transported via low-density lipoprotein and high-density lipoprotein (HDL) particles to extrahepatic tissue.[4 5]

Vitamin K functions as a cofactor for the enzyme gamma-glutamyl carboxylase which converts protein-bound glutamate residues into gammacarboxyglutamate (Gla).[6 7] Gla-containing proteins are involved in, for example, the coagulation of blood,[8] inhibition of arterial calcification (Matrix Gla Protein) and vascular smooth muscle cell apoptosis and movement that is considered protective against vascular injury (Gas-6).[9] Matrix Gla Protein is involved in both medial and intimal calcification, and low vitamin K status has been associated with both types of calcification.[10–14] In addition, a study that examined the effect of warfarin (a vitamin K antagonist) on medial and intimal plaque

calcification in apoE$^{-/-}$ mice concluded that warfarin accelerates both medial and intimal calcification of atherosclerotic plaque.[15] Patients with both medial and intimal calcification have a higher cardiovascular risk when compared with similar patients without calcification.[16 17] Therefore, an inverse association between vitamin K intake and coronary heart disease (CHD) could be expected. Results from observational studies on the association between intake of vitamin K and CHD are inconsistent.[18–24] Among the identified studies, three found reduced risk of CHD in multivariable adjusted analyses at higher dietary K2[19 20] or K1.[24]

Nordic Nutrition Recommendations include a provisional recommended intake of vitamin K of 1 µg/kg body weight per day,[3] while adequate intake is 90 µg/day for women and 120 µg/day for men.[25] However, these recommendations may not be sufficient to attain complete carboxylation of extrahepatic vitamin K-dependent proteins.[26 27]

Given the limited number of epidemiological studies,[18–24] and the fact that dietary vitamin K sources and content differ between countries,[28–31] further research is warranted. The purpose of the current study was to evaluate the association between intake of both K1 and K2 and subsequent CHD events among community-living middle-age adults in Norway.

SUBJECTS AND METHODS

Study population

The current study is a prospective, community-based cohort study of participants living in Hordaland County, Norway (known as The Hordaland Health Study (HUSK); https://husk.w.uib.no/). The recruitment was based on a cohort from 1992 - 1993 (The Hordaland Homocysteine Study), where eligible subjects (Hordaland County residents born 1950–1951) were identified from the National Population Register on 31 December 1992.[32 33] In 1997–1999, all living Homocysteine Study cohort members born 1950–1951 and residing in the city of Bergen or the neighbouring suburban municipalities were invited to participate in HUSK. The baseline examinations were conducted during 1997–1999 as a collaboration between the National Health Screening Service (now The Norwegian Institute of Public Health), The University of Bergen and local health services. Participation rate was 77%. Participants underwent a brief health examination and provided a non-fasting blood sample. Information on lifestyle was collected via self-administered questionnaires. A semiquantitative Food Frequency Questionnaire (FFQ) was completed by 87% of the participants yielding 3107 men and women age 47–49 years eligible for the current study.

We excluded from the analyses 27 men and 35 women who reported extreme energy intakes (below the first percentile: <1125 kcal for men and <705 kcal for women; or above the 99th percentile: >4519 kcal for men and >3571 kcal for women). Further, we excluded 27 participants (22 men and 5 women) who had prior CHD based on self-reported information and/or prior CHD hospitalisations during 1994–1999. Additionally, those with missing information on self-reported myocardial infarction from the Homocysteine Study (1992–1993; 4 men and 19 women) were excluded. Further, we excluded two participants (one man and one woman) who reported use of warfarin and six participants (two men and four women) with missing measurement on dietary vitamin K intake. The final study population thus included 1279 men and 1708 women.

Patient and public involvement

Participants were not involved in designing the research question, conducting the study, or in the interpretation, or writing of the results. There are no plans to involve participants or relevant patient communities in dissemination of results. Results are disseminated to study participants via website (https://husk.w.uib.no).

Dietary assessment

Information on food intake was obtained at baseline (1997–1999) using a slightly modified version of a previously described[34] past-year 169-item semiquantitative FFQ. The FFQ was handed out on the health examination day, filled out at home and returned by mail to the HUSK project centre. The questionnaire included frequency alternatives (from once a month to several times per day), the number of units consumed and portion sizes (eg, slices, glasses, spoons) to capture the habitual diet during the past year. The dietary information presented includes individual food or beverage items, food groups and nutrient intakes. Daily nutrient intakes were computed from a database and software system developed at the Department of Nutrition, University of Oslo (KBS, V.3.2). The nutrient database is primarily based on the official Norwegian food composition table[35] and available literature.[28] Data for K1 are mostly developed by public authorities in Finland,[36] Sweden[37] and USA.[38] For some Norwegian food products, analyses were performed using high performance liquid chromatography of fermented foods.[39] K2 was evaluated as one entity with no distinction between the different menaquinones. At time of study, the most commonly used dietary supplements in Norway did not contain vitamin K. Thus, vitamin K intake reflects only dietary sources. Measurements used as independent variables in this study are the total dietary amount of K1 and K2, expressed as energy-adjusted residuals.[40]

Health examination and health habits

Baseline examinations included measurements of height, weight, waist circumference, resting blood pressure (Dinamap 845 XT equipment (Criticon)) and non-fasting venous blood samples for evaluation of serum lipids and glucose. Serum samples of total cholesterol, HDL cholesterol, triglycerides and glucose were analysed within 7 days at the department of Clinical Chemistry, Ullevål University Hospital, Oslo, using enzymatic methods with

reagents from Boehringer Mannheim (Roche, Basel, Switzerland).

Information on educational level and medication use was collected through self-administered questionnaires.

Hypertension was considered present if the mean of at least two consecutive measurements of systolic blood pressure was ≥140 mm Hg or of diastolic blood pressure ≥90 mm Hg or if use of medication for hypertension was reported.

Diabetes was diagnosed according to diagnostic criteria at the time of the screening/survey. Participants taking diabetic medications or who reported a diagnosis of diabetes were defined as having diabetes mellitus. Also, participants with a serum glucose level >7 mmol/L who had not eaten a meal during the last 8 hours, or with glucose level >11.1 mmol/L and less than 8 hours since their last meal, were defined as having diabetes. Prediabetes was defined as having glucose levels between 5.6 and 7 mmol/L at least 8 hours after their last meal or between 7.8 and 11 mmol/L less than 8 hours after their last meal.

Participants answered one categorical question on past-year vigorous physical activity resulting in sweating or breathlessness (none, <1 h/week, 1–2 h/week, or ≥3 h/week). This variable was treated as a categorical variable with none as the reference.

Participants were classified as non-smokers, former smokers or current smokers and this variable was treated as a categorical variable with non-smokers as reference.

Outcome

The study endpoints were incident (first time) hospitalisation with CHD (International classification of diseases (ICD)9 codes 410–414, ICD10 codes I20–I25) as primary or secondary diagnosis or death with CHD as the underlying cause of death. Participants were followed from baseline through 31 December 2009 for CHD events through the Cardiovascular Disease in Norway project database (CVDNOR, www.cvdnor.no)[41 42] and The Cause of Death Registry. Follow-up time represented time from baseline (1997–1999) until CHD, death from other causes, emigration or 31 December 2009, whichever came first. During follow-up, there were 107 non-fatal and 5 fatal events of interest while 60 participants died due to other causes and were censored at date of death.

Statistical analyses

Energy-adjusted residuals were obtained from linear regression models with total energy intake as independent variable and K1 or K2 as dependent variables. The residuals measure the difference between actual intake and expected intake predicted by total energy intake[40] and thereby provides an assessment of K1 and K2 intake relative to energy consumed. Residuals were then categorised into sex-specific quartiles.

Descriptive characteristics included counts with percents and medians (interquartile range) for categorical and continuous variables, respectively. Trends in dichotomous, categorical and continuous baseline characteristics across energy-adjusted quartiles of K1 and K2 were evaluated using logistic, ordinal logistic and linear regression analyses, respectively. The median residuals for each quartile group was specified as a continuous independent variable in the regression models.

Cox proportional hazards models were used to calculate adjusted HR and 95% CIs for CHD associated with sex-specific energy-adjusted quartiles and per 10 µg increments of K1 or K2 intake. The covariates included were either those associated with intake of K1 or K2 and with CHD, or those that modified the association of either K1 or K2 with CHD when included in the multivariable model. Analyses included adjustments for sex, age (years) and total energy intake (kcal/day) (model 1), with additional adjustment for categories of vigorous physical activity (none vs <1 hour/week, 1–2 hours/week and ≥3 hours/week), smoking habits (previous smokers and current smokers, respectively vs non-smokers) and education (high school or vocational school, and any college or university, respectively vs primary school(≤10 years)) (model 2). In a third model, K1 was adjusted additionally for energy-adjusted intake of fibre (g/day) and folate (mg/day); K2 was additionally adjusted for energy-adjusted intake of saturated fatty acids (SFA) (g/day) and calcium (mg/day) (model 3). The following additional potential confounders were also evaluated but not included in the tables as they did not noticeably alter the vitamin K1 or K2 coefficients for CHD: family history of myocardial infarction and energy-adjusted alcohol intake (g/day). Further, adjusting for the following intermediate factors: body mass index (BMI, kg/m^2), diabetes mellitus (pre-diabetes and diabetes, respectively, vs no diabetes), hypertension, serum total cholesterol (mmol/L) and statin use, only attenuated the association to a small degree.

To test for linear trends across energy-adjusted quartiles of K1 and K2 intakes, the median value of the residuals within each quartile group was entered as a continuous independent variable. Supplementary analyses re-evaluated K1 and K2 intake as sex-specific quartiles of absolute intake rather than energy-adjusted residuals.

Missing data on physical activity (3.8%), education (0.8%) and smoking habits (2.1%) were handled with listwise deletion in all analyses included in the main manuscript. In supplementary analyses, missing values for physical activity, smoking and education were imputed using ordinal logistic regression as the imputation model in MICE (multiple imputation using chained equation) with 20 imputations. All variables in the Cox regression models were included as imputation variables together with total cholesterol, HDL cholesterol, triglycerides and BMI as auxiliary variables due to their correlation with physical activity, smoking and education.

The proportional hazards assumption was evaluated using Schoenfeld's test and log–log test.

In Cox regression with penalised splines, the functional form of the association between absolute K2 intake (not

residuals) and risk of CHD was estimated by smoothing splines, in which the estimated smooth functions were used to plot the relative hazards of CHD.[43] Intakes above the 95th percentile and below the 5th percentile are excluded in the figure.

To test for sex interactions between K1 and K2, we compared models with and without an interaction term using likelihood-ratio test.

Statistical analyses were performed using Stata V.15 (Stata Corp LP) and R V.3.4.0 (https://www.r-project.org/, The R Foundation for Statistical Computing, Vienna, Austria). P<0.05 were considered statistically significant.

Consent to participate

All subjects gave their written consent to participate in the study.

RESULTS

Reported intake of energy-adjusted K1 ranged from 8 to 1063 µg/day/1000 kcal (median 48 µg/day/1000 kcal) and were higher for women compared with men. Intake of energy-adjusted K2 ranged from 1 to 31 µg/day/1000 kcal (median 7 µg/day/1000 kcal) and were slightly higher for women compared with men.

The major dietary sources of K1 were vegetables (64%), fruits and berries (6%) and milk and milk products (6%), while sources of K2 were cheese (40%), other dairy products (14%), meat (24%) and eggs (13%).

In the evaluation of baseline characteristics associated with K1 intake, the concentration of HDL cholesterol and the proportion of participants who were highly educated and reported at least 1 hour of vigorous physical activity per week were higher with higher quartiles of K1 intake (table 1). Further, intakes of energy-adjusted total vitamin K, folate and fibre were higher with higher K1 intake quartiles. In contrast, a lower proportion with a family history of CHD and lower energy-adjusted K2, SFA and carbohydrate intakes were noted with higher K1 intake. In addition, intake of fruit and berries and vegetables were higher with higher K1 intake quartiles, while intake of cheese, milk and milk products and soft drinks with sugar were lower with higher intake quartiles of energy-adjusted K1 intake.

Evaluation of baseline characteristics by quartiles of energy-adjusted K2 intake identified that the proportion of participants highly educated, and the concentration of HDL cholesterol were higher with higher quartiles of K2 intake, while the concentration of triglycerides was lower (table 2). Further, intake of energy-adjusted total fat, SFA and calcium was higher with higher K2 intake quartiles. In contrast, lower intake of energy-adjusted K1 and carbohydrates was noted with higher K2 intake. In addition, intake of butter, eggs, cheese, meat and minced meat were higher with higher quartiles, while intake of soft drinks with sugar and fruit and berries were lower with higher quartiles of energy-adjusted K2 intake.

Association between dietary vitamin K1 and CHD

During a mean 10.8 (SD 1.3) years follow-up, representing 32 362 person years among 2987 participants, we documented 112 incident CHD events. Due to listwise deletion of missing values (2.1% for smoking habits, 0.8% for education and 3.8% for physical activity), multivariable-adjusted analyses included 6.5% fewer participants compared with model 1 analyses (ie, 2792 (1213 men and 1579 women) participants and 100 CHD events).

When adjusting for age, sex and total energy intake, there was no association between intake of energy-adjusted K1 and CHD comparing the fourth to the first quartile and there was no trend (table 3, model 1). The results were similar when further adjusting for physical activity, smoking habits and education ($HR_{Q4vs.Q1}$=0.92 (0.54 to 1.57), p for trend 0.64; table 3, model 2). In analyses of energy-adjusted K1 intake as a continuous variable (per 10 µg increase), there was no association between K1 and CHD in the adjusted analysis (table 3, model 2). Additional adjustments for energy-adjusted fibre and folate did not materially change the results (table 3, model 3). In supplementary analyses, where missing data were handled with multiple imputation, results were similar to those presented in table 3 (online supplementary table 1, models 2 and 3).

Results were consistent with the above analyses in the supplemental analyses evaluating sex-specific quartiles of absolute K1 intake rather than energy-adjusted residuals (online supplementary table 2).

Association between dietary vitamin K2 and CHD

When adjusting for age, sex and total energy intake, there was a lower risk of CHD with energy-adjusted K2 in the fourth compared with the first quartile ($HR_{Q4vs.Q1}$=0.50 (0.28 to 0.88), p for trend 0.02; table 3, model 1). Results were consistent when further adjusting for physical activity, smoking habits and education ($HR_{Q4vs.Q1}$=0.52 (0.29 to 0.94), p for trend 0.03; table 3, model 2). Consistency in results was observed in analyses of K2 intake as a continuous variable (per 10 µg increase; HR=0.74 (0.52 to 1.05), p=0.09). Additional adjustments for energy-adjusted SFA and calcium slightly attenuated the risk estimates for the association between K2 intake and CHD ($HR_{Q4vs.Q1}$=0.58 (0.28 to 1.19), p for trend 0.16; table 3, model 3). Similar results were found in supplementary analyses where missing data were handled with multiple imputation (model 2: $HR_{\text{per 10µg increase}}$=0.70 (0.50 to 0.98), p=0.04) (online supplementary table 1, models 2 and 3).

When evaluating sex-specific absolute K2 intake rather than energy-adjusted residuals, HRs were similar to those observed in the primary analyses ($HR_{Q4vs.Q1}$=0.72 (0.36 to 1.45), p for trend 0.25; online supplementary table 2, model 2). Similarly, the penalised spline figure for absolute K2 intake and its association with CHD adjusting for model 2 covariates showed a tendency towards lower risk of CHD with higher K2 intake (figure 1).

Table 1 Baseline characteristics by sex-specific quartiles of energy-adjusted residuals of vitamin K1 intake: the Hordaland Health Study

	Total	Q1	Q2	Q3	Q4	P trend*
Subjects, n	2987	746	747	748	746	
Age, years	48 (47 to 48)	48 (47 to 48)	48 (47 to 48)	48 (48 to 49)	48 (47 to 49)	0.135
Men	1279 (42.8)	319 (42.8)	320 (42.8)	321 (42.9)	319 (42.8)	0.993
Any college and/or university education	1136 (38.3)	265 (36.0)	288 (38.9)	289 (38.8)	294 (39.6)	0.018
Family history of CHD	1183 (40.9)	314 (43.3)	309 (42.6)	286 (39.3)	274 (38.4)	0.034
Smoking habits						0.104
Previous smokers	914 (31.3)	214 (29.4)	227 (30.8)	237 (32.4)	236 (32.5)	
Current smokers	978 (33.5)	239 (32.8)	231 (31.4)	261 (35.7)	247 (34.0)	
Physical activity						<0.001
None	741 (25.8)	198 (27.8)	201 (28.0)	188 (26.0)	154 (21.4)	
<1 hour/week	810 (28.2)	226 (31.7)	192 (26.7)	201 (27.8)	191 (26.5)	
1–2 hours/week	907 (31.6)	207 (29.0)	239 (33.3)	226 (31.3)	235 (32.6)	
≥3 hours/week	415 (14.4)	82 (11.5)	86 (12.0)	107 (14.8)	140 (19.4)	
Hypertension	707 (23.7)	172 (23.1)	176 (23.6)	185 (24.7)	174 (23.3)	0.945
Glucose intolerance						0.875
Pre-diabetes	66 (2.2)	24 (3.2)	12 (1.6)	14 (1.9)	16 (2.2)	
Diabetes	27 (0.9)	8 (1.1)	4 (0.5)	5 (0.7)	10 (1.4)	
Body mass index, kg/m^2	24.9 (22.8 to 27.4)	25.0 (22.8 to 27.4)	25.0 (22.8 to 27.6)	24.9 (22.9 to 27.5)	24.7 (22.6 to 27.2)	0.148
Waist circumference, cm	85.0 (77.0 to 94.0)	85.0 (77.0 to 94.0)	85.0 (77.0 to 94.0)	85.0 (77.0 to 93.0)	85.0 (76.0 to 93.0)	0.266
Serum cholesterol, mmol/L	5.65 (5.06 to 6.30)	5.58 (5.05 to 6.25)	5.70 (5.11 to 6.44)	5.66 (5.05 to 6.27)	5.65 (5.03 to 6.25)	0.331
Serum LDL-C, mmol/L	3.56 (3.01 to 4.17)	3.53 (2.98 to 4.14)	3.65 (3.06 to 4.29)	3.56 (3.02 to 4.11)	3.54 (2.94 to 4.10)	0.072
Serum HDL-C, mmol/L	1.28 (1.06 to 1.53)	1.27 (1.04 to 1.52)	1.28 (1.07 to 1.51)	1.27 (1.05 to 1.53)	1.31 (1.07 to 1.58)	0.004
Serum triglycerides, mmol/L	1.40 (1.01 to 2.03)	1.43 (1.01 to 2.02)	1.39 (1.00 to 1.99)	1.39 (1.04 to 2.11)	1.38 (0.98 to 2.05)	0.462
Energy intake, kcal/day	2057 (1690 to 2550)	2152 (1712 to 2671)	1944 (1608 to 2353)	2032 (1627 to 2485)	2171 (1775 to 2687)	<0.001
Dietary intake						
Total vitamin K, µg/day	120 (85 to 175)	78 (58 to 99)	95 (76 to 118)	137 (111 to 161)	234 (189 to 301)	<0.001
Total vitamin K, µg/day/1000 kcal	56 (43 to 79)	36 (31 to 42)	49 (44 to 55)	65 (57 to 76)	105 (84 to 144)	<0.001
Vitamin K2, µg/day	15 (11 to 21)	16 (12 to 22)	14 (11 to 20)	15 (11 to 20)	15 (12 to 20)	0.336
Vitamin K2, µg/day/1000 kcal	7 (6 to 9)	8 (6 to 9)	7 (6 to 9)	7 (6 to 9)	7 (6 to 9)	<0.001
Vitamin K1, µg/day	103 (69 to 157)	61 (44 to 77)	81 (63 to 101)	121 (99 to 143)	218 (172 to 282)	<0.001
Vitamin K1 µg/day/1000 kcal	48 (35 to 71)	29 (23 to 33)	41 (37 to 47)	58 (50 to 67)	98 (77 to 136)	<0.001
Total fat, E%	32 (29 to 36)	32 (28 to 35)	33 (29 to 36)	33 (30 to 37)	33 (29 to 36)	<0.001
SFA, E%	13 (11 to 14)	13 (11 to 14)	13 (11 to 14)	13 (11 to 14)	12 (11 to 14)	0.004
PUFA, E%	7 (6 to 8)	6 (5 to 7)	7 (6 to 8)	7 (6 to 9)	7 (6 to 9)	<0.001
MUFA, E%	10 (9 to 12)	10 (9 to 11)	10 (9 to 12)	11 (9 to 12)	10 (9 to 12)	0.357
Protein, E%	16 (14 to 17)	16 (14 to 17)	16 (14 to 17)	16 (14 to 17)	16 (15 to 18)	<0.001
Carbohydrates, E%	49 (46 to 53)	50 (47 to 54)	50 (46 to 53)	49 (45 to 52)	48 (45 to 52)	<0.001
Alcohol, E%	1 (0 to 3)	1 (0 to 3)	1 (0 to 3)	2 (0 to 3)	2 (1 to 3)	0.001
Folate, µg/day/1000 kcal	110 (95 to 133)	99 (88 to 113)	105 (93 to 121)	112 (98 to 131)	135 (113 to 164)	<0.001
Fibre, g/day/1000 kcal	11 (10 to 13)	10 (9 to 12)	11 (10 to 13)	11 (10 to 13)	13 (11 to 16)	<0.001
Intake of food items, g/day/1000 kcal						
Butter†	0 (1.2)	0 (1.3)	0 (1.1)	0 (1.1)	0 (1.2)	0.749
Margarine	3 (2 to 8)	2 (1 to 3)	3 (2 to 8)	3 (2 to 11)	3 (2 to 9)	<0.001
Cheese	13 (7 to 21)	15 (8 to 24)	13 (7 to 22)	12 (7 to 19)	12 (6 to 20)	<0.001
Yoghurt	5 (0 to 18)	6 (0 to 21)	5 (0 to 16)	6 (0 to 18)	5 (0 to 17)	0.740
Milk and milk products	129 (65 to 205)	157 (86 to 230)	134 (71 to 220)	127 (57 to 193)	105 (51 to 174)	<0.001
Sausages	20 (2 to 49)	17 (1 to 47)	18 (1 to 47)	21 (4 to 53)	21 (5 to 53)	0.067
Meat	55 (41 to 70)	54 (39 to 68)	55 (42 to 73)	56 (43 to 70)	53 (40 to 67)	0.651

Continued

Table 1 Continued

	Total	Q1	Q2	Q3	Q4	P trend*
Minced meat	24 (16 to 34)	25 (15 to 35)	25 (16 to 35)	25 (16 to 34)	22 (14 to 31)	<0.001
Soft drinks with sugar	25 (0 to 65)	31 (3 to 76)	28 (2 to 69)	24 (0 to 61)	18 (0 to 51)	<0.001
Fruit and berries	104 (65 to 154)	91 (56 to 132)	103 (67 to 150)	105 (68 to 167)	114 (71 to 164)	<0.001
Vegetables	85 (54 to 131)	49 (35 to 72)	74 (53 to 101)	98 (67 to 134)	154 (104 to 212)	<0.001

Values are presented as N (%) and median (interquartile range) for continuous and categorical data, respectively.
*Logistic regression for dichotomous categories, ordered logistic regression when more than two categories and linear regression for continuous variables where median residuals within each quartile group was used as the independent variable in the analyses.
†Mean (median) are reported due to a large proportion with zero intake.
CHD, coronary heart disease; E%, energy per cent; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; Q, quartile; SFA, saturated fatty acids.

DISCUSSION

Among community-dwelling middle-age adults in Western Norway, a higher energy-adjusted reported intake of K2 was associated with a lower risk of subsequent CHD events, whereas intake of K1 was not associated with incident CHD. Similar direction of associations was observed when further adjusting for potential dietary confounders.

Strengths and weaknesses

Strengths of our study include a long follow-up time with minimal competing risk from other causes of death in this relatively young study population. Linkage to the CVDNOR project database assured complete follow-up. In addition, we had information on several possible confounders including baseline health status, medication use, health habits and history of CHD which enabled us to evaluate incident CHD.

Weaknesses include self-reported information on dietary intake, health habits and medication use which may lead to misclassification in covariates used in the analyses. Furthermore, we lack information on changes in diet including intake of vitamin K, medications and risk factors over time. Inherent problems with FFQs are systematic under-reporting and over-reporting. However, the FFQ is well suited to rank individuals when adjusting for total energy intake.[44] This FFQ is not validated specifically for intake of vitamin K. Vitamin K content of foods differs according to production conditions, and the bioavailability is dependent on preparation, fat content of meals, the food matrix and subtypes of vitamin K. Therefore, although the rank ordering of participants may be valid, the absolute vitamin K intake based on FFQ is likely inaccurate.[5 29 30 45 46] In addition, K2 can be produced by intestinal gut microbiota, but little is known about its contribution to vitamin K status since the majority is located in bacterial membranes in the colon and is probably not available for absorption.[26]

Further, vitamin K2 intake may be underestimated in this study population since much of the information on vitamin K content of food used in this study comes from a Dutch study,[28] and recent research have shown that Norwegian cheeses are especially rich in vitamin K2.[29 47] In addition, we could not differentiate the subtypes of vitamin K2[19] in our study.

Although we performed multivariable analyses, residual confounding may still be present.

Results in relation to other studies

This study did not find an association between intake of K1 and CHD, in line with results from most previous studies.[19 20 22 23] However, Erkkilä *et al* concluded that high K1 intake may be a marker of low CHD risk, but that dietary patterns associated with K1 intakes, rather than intake of K1 itself might account for this association.[21] Similarly, Juanola-Falgarona *et al* studied the association between dietary K1 and K2 with mortality in a cohort with high cardiovascular disease (CVD) risk, and found that an increase in dietary intakes of both K1 and K2 were associated with a reduced risk of all-cause mortality, while only K1 was associated with a reduced risk of CVD mortality.[24] However, since participants came from a Mediterranean country in which the consumption of fruit, vegetables and vegetable oils was quite high, K1 could be regarded as a marker of adherence to a healthy diet.[24]

Regarding vitamin K2, Geleijnse *et al* found a 41% lower risk of CHD comparing the highest with the lowest tertile of K2 intake in the Rotterdam study,[20] similar to our results. Gast *et al* found a dose–response relationship with a 9% lower CHD risk with each 10 µg higher K2 intake, with the strongest association shown for long-chain K2.[19] Opposite from this study where the association attenuated when further adjusting for SFA and calcium, the association became stronger in both these studies in their multivariable models.[19 20] Adjusting for SFA and calcium, however, may be an overadjustment as dairy products rich in SFA and calcium are also major sources of K2.[24] Zwakenberg *et al* found that only intake of long-chain K2 (per10µg) was borderline significantly inversely associated with CHD mortality (p for trend 0.06).[23] This discrepancy compared with our study may be because lifestyle factors such as diet may have a larger impact on total CHD events (fatal and non-fatal) given the underlying mechanisms of reducing calcification. Treatment, however, is probably of larger importance for CHD mortality.[48]

In the western diet, cheese is the most important source of long-chain K2, and hard cheese is, in general, richer in K2 than soft cheese.[28 29] Fu *et al* showed that vitamin K concentrations in cheese ranged from 40 µg to 850 µg per

Table 2 Baseline characteristics by sex-specific quartiles of energy-adjusted residuals of vitamin K2 intake: the Hordaland Health Study

	Total	Q1	Q2	Q3	Q4	P trend*
Subjects, n	2987	746	747	747	747	
Age, years	48 (47 to 48)	48 (47 to 49)	48 (47 to 48)	48 (47 to 49)	48 (47 to 48)	0.600
Men	1279 (42.8)	319 (42.8)	320 (42.8)	320 (42.8)	320 (42.8)	0.977
Any college and/or university education	1136 (38.3)	261 (35.3)	272 (36.8)	284 (38.3)	319 (42.9)	0.001
Family history of CHD	1183 (40.9)	292 (40.7)	308 (42.1)	284 (39.3)	299 (41.6)	0.904
Smoking habits						0.267
Previous smokers	914 (31.3)	217 (29.7)	241 (33.1)	229 (31.2)	227 (31.1)	
Current smokers	978 (33.5)	239 (32.7)	244 (33.5)	240 (32.7)	255 (34.9)	
Physical activity						0.114
None	741 (25.8)	185 (25.8)	181 (25.5)	194 (26.9)	181 (25.0)	
<1 hour/week	810 (28.2)	189 (26.3)	179 (25.2)	224 (31.0)	218 (30.2)	
1–2 hours/week	907 (31.6)	214 (29.8)	244 (34.4)	224 (31.0)	225 (31.1)	
≥3 hours/week	415 (14.4)	130 (18.1)	106 (14.9)	80 (11.1)	99 (13.7)	
Hypertension	707 (23.7)	185 (24.8)	180 (24.1)	184 (24.6)	158 (21.2)	0.100
Glucose intolerance						0.543
Pre-diabetes	66 (2.2)	18 (2.4)	15 (2.0)	17 (2.3)	16 (2.2)	
Diabetes	27 (0.9)	6 (0.8)	7 (0.9)	2 (0.3)	12 (1.6)	
Body mass index, kg/m^2	24.9 (22.8 to 27.4)	24.8 (22.7 to 27.4)	25.1 (23.0 to 27.5)	25.0 (22.9 to 27.3)	24.8 (22.6 to 27.4)	0.830
Waist circumference, cm	85 (77 to 94)	84 (77 to 93)	85 (77 to 94)	85 (77 to 94)	85 (76 to 93)	0.724
Serum cholesterol, mmol/L	5.65 (5.06 to 6.30)	5.66 (5.02 to 6.30)	5.64 (5.07 to 6.36)	5.7 (5.1 to 6.32)	5.57 (5.05 to 6.20)	0.124
Serum LDL-C, mmol/L	3.56 (3.01 to 4.17)	3.57 (3.00 to 4.14)	3.58 (2.99 to 4.19)	3.60 (3.07 to 4.24)	3.52 (2.97 to 4.09)	0.227
Serum HDL-C, mmol/L	1.28 (1.06 to 1.53)	1.27 (1.03 to 1.52)	1.27 (1.07 to 1.54)	1.30 (1.06 to 1.55)	1.30 (1.06 to 1.54)	0.043
Serum triglycerides, mmol/L	1.40 (1.01 to 2.03)	1.44 (1.04 to 2.16)	1.40 (1.00 to 2.05)	1.39 (1.01 to 1.99)	1.36 (0.97 to 1.96)	0.022
Energy intake, kcal/day	2057 (1690 to 2550)	2098 (1682 to 2645)	1976 (1603 to 2398)	2014 (1653 to 2469)	2215 (1795 to 2637)	0.002
Dietary intake						
Total vitamin K, µg/day	120 (85 to 175)	119 (82 to 179)	116 (78 to 169)	114 (83 to 165)	133 (94 to 186)	0.728
Total vitamin K, µg/day/1000 kcal	56 (43 to 79)	56 (40 to 80)	55 (42 to 81)	55 (43 to 76)	59 (46 to 80)	0.011
Vitamin K2, µg/day	15 (11 to 21)	10 (8 to 13)	13 (11 to 16)	16 (14 to 19)	24 (21 to 29)	<0.001
Vitamin K2, µg/day/1000 kcal	7 (6 to 9)	5 (4 to 5)	7 (6 to 7)	8 (8 to 9)	11 (10 to 13)	<0.001
Vitamin K1, µg/day	103 (69 to 157)	109 (72 to 167)	101 (67 to 155)	97 (67 to 149)	104 (71 to 156)	0.329
Vitamin K1, µg/day/1000 kcal	48 (35 to 71)	51 (36 to 78)	49 (35 to 74)	46 (35 to 67)	47 (34 to 68)	0.038
Total fat, E%	32 (29 to 36)	30 (27 to 34)	31 (29 to 35)	33 (30 to 36)	35 (32 to 38)	<0.001
SFA, E%	13 (11 to 14)	11 (19 to 12)	12 (11 to 13)	13 (12 to 14)	14 (13 to 16)	<0.001
PUFA, E%	7 (6 to 8)	7 (6 to 9)	7 (6 to 8)	7 (6 to 8)	6 (6 to 8)	<0.001
MUFA, E%	10 (9 to 12)	10 (8 to 11)	10 (9 to 11)	11 (10 to 12)	11 (10 to 12)	<0.001
Protein, E%	16 (14 to 17)	15 (13 to 16)	16 (14 to 17)	16 (15 to 17)	16 (15 to 18)	<0.001
Carbohydrates, E%	49 (46 to 53)	53 (49 to 57)	50 (47 to 53)	48 (45 to 51)	46 (43 to 49)	<0.001
Alcohol, E%	1 (0 to 3)	1 (0 to 3)	1 (0 to 3)	1 (0 to 3)	1 (0 to 3)	0.387
Calcium, mg/day/1000 kcal	385 (313 to 468)	332 (264 to 410)	373 (302 to 448)	389 (329 to 464)	443 (374 to 538)	<0.001
Fibre, g/day/1000 kcal	11 (10 to 13)	12 (11 to 15)	12 (10 to 13)	11 (9 to 13)	11 (9 to 12)	<0.001
Intake of food items, g/day/1000 kcal						
Butter†	0 (1.2)	0 (0.5)	0 (1.0)	0 (1.3)	0 (1.9)	<0.001
Margarine	3 (2 to 8)	3 (2 to 10)	3 (2 to 7)	3 (2 to 8)	3 (2 to 5)	<0.001
Egg	8 (4 to 11)	5 (3 to 8)	8 (5 to 11)	8 (5 to 12)	8 (4 to 11)	<0.001
Cheese	13 (7 to 21)	7 (3 to 12)	10 (6 to 15)	14 (9 to 20)	25 (17 to 34)	<0.001
Yoghurt	5 (0 to 18)	4 (0 to 15)	5 (0 to 17)	6 (0 to 19)	5 (0 to 19)	0.456
Milk and milk products	129 (65 to 205)	127 (51 to 209)	144 (82 to 213)	135 (69 to 209)	112 (55 to 181)	<0.001

Continued

Table 2 Continued

	Total	Q1	Q2	Q3	Q4	P trend*
Sausage	20 (2 to 49)	21 (2 to 53)	22 (3 to 53)	21 (3 to 50)	17 (2 to 42)	<0.001
Meat	55 (41 to 70)	47 (33 to 58)	56 (43 to 71)	61 (46 to 77)	58 (42 to 76)	<0.001
Minced meat	24 (16 to 34)	19 (12 to 28)	24 (16 to 33)	27 (18 to 37)	27 (17 to 36)	<0.001
Soft drinks with sugar	25 (0 to 65)	29 (1 to 72)	26 (0 to 66)	26 (2 to 64)	23 (0 to 54)	<0.001
Fruit and berries	104 (65 to 154)	116 (74 to 174)	105 (67 to 162)	100 (64 to 149)	93 (57 to 135)	<0.001
Vegetables	85 (54 to 131)	85 (50 to 133)	90 (58 to 139)	82 (55 to 125)	84 (53 to 122)	0.006

Values are presented as N(%) and median (interquartile range) for categorical and continuous variables, respectively.
*Logistic regression for dichotomous categories, ordered logistic regression when more than two categories and linear regression for continuous variables where median residuals within each quartile group was used as the independent variable in the analyses.
†Mean (median) are reported due to a large proportion with zero intake.
CHD, coronary heart disease; E%, energy per cent; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; Q, quartile; SFA, saturated fatty acids.

100 g, and that reduced-fat products contained 5%–22% of the vitamin K found in full-fat equivalents.[30] K2 in cheese originates from bacterial processes present at the start of the cheese-making process.[26] As different lactic acid bacteria are used in cheese making, a large variability in K2 content is found. Cheeses from Norway are among those with the highest long-chain K2 content.[29 47]

A meta-analysis including only two published studies of sufficient quality did not conclude that there is a lower risk of cardiovascular events with higher intake of K2.[49] However, a systematic review and meta-analysis found that supplementation with vitamin K (K1 and K2) significantly reduced vascular calcification, but not vascular stiffness, compared with controls.[50] However, Shea *et al* studied

Table 3 Associations between intake of energy-adjusted vitamin K1 and vitamin K2 and incident coronary heart disease (CHD)*

Exposure	Intake, µg/day mean (SD)	N	CHD, N(%)	Model 1 HR (95% CI)† n=2987	Model 2 HR (95% CI)‡ n=2792§	Model 3 HR (95% CI)¶ n=2792§
Vitamin K1						
		2987	112			
Q1	63 (25)	746	33 (4.4)	1 (ref)	1 (ref)	1 (ref)
Q2	83 (27)	747	18 (2.4)	0.47 (0.27 to 0.85)	0.50 (0.27 to 0.93)	0.48 (0.26 to 0.89)
Q3	122 (32)	748	31 (4.1)	0.84 (0.51 to 1.39)	0.89 (0.53 to 1.51)	0.83 (0.49 to 1.41)
Q4	269 (191)	746	30 (4.0)	0.91 (0.55 to 1.49)	0.92 (0.54 to 1.57)	0.69 (0.38 to 1.27)
P for trend**				0.64	0.64	0.59
Continuous, per 10 µg				1.00 (0.99 to 1.02), p=0.57	1.00 (0.99 to 1.02), p=0.62	0.99 (0.97 to 1.01), p=0.27
Vitamin K2						
		2987	112			
Q1	10 (4)	746	35 (4.7)	1 (ref)	1 (ref)	1 (ref)
Q2	13 (4)	747	30 (4.0)	0.79 (0.48 to 1.29)	0.79 (0.47 to 1.34)	0.83 (0.49 to 1.43)
Q3	17 (4)	747	29 (3.9)	0.77 (0.47 to 1.26)	0.77 (0.45 to 1.31)	0.84 (0.47 to 1.48)
Q4	26 (8)	747	18 (2.4)	0.50 (0.28 to 0.88)	0.52 (0.29 to 0.94)	0.58 (0.28 to 1.19)
P for trend**				0.02	0.03	0.16
Continuous, per 10 µg				0.71 (0.50 to 0.99), p=0.04	0.74 (0.52 to 1.05), p=0.09	0.82 (0.51 to 1.30), p=0.39

Sex-specific quartiles with 1279 men and 1708 women. The Hordaland Health Study.
*HR are presented as Q2 versus Q1, Q3 versus Q1, Q4 versus Q1.
†Cox proportional hazards regression analysis adjusted for age, sex and total energy intake.
‡Adjusted in addition for physical activity, smoking habits and education.
§Analyses were based on a reduced number of participants (n=2792) and CHD events (n=100) due to listwise deletion when covariates were missing.
¶Vitamin K1 is adjusted in addition for energy-adjusted fibre and folate, while vitamin K2 is adjusted in addition for energy-adjusted calcium and saturated fatty acids.
**P trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.
N, number of participants; Q, quartile.

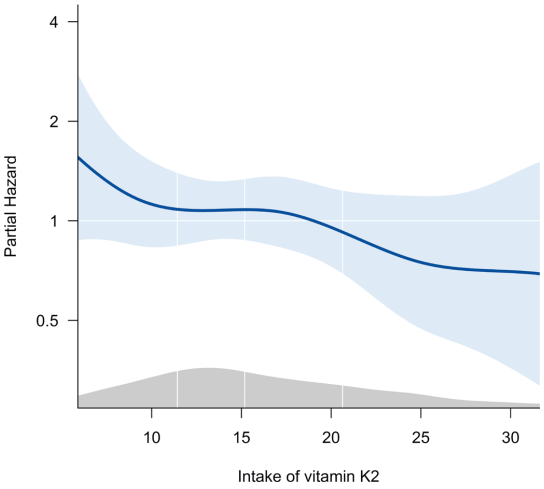

Figure 1 Cox proportional hazards regression with penalised splines, The Hordaland Health Study. Distribution of partial HR (solid line) with 95% CI (shadow) for coronary heart disease across the distribution of dietary vitamin K2 in µg per day (not energy-adjusted residuals). The model includes adjustment for age, sex, total energy intake, physical activity, smoking habits and education. Intakes above the 95th percentile and below the 5th percentile are excluded in the figure.

supplementation with K1 on coronary artery calcification progression in older men and women and found no difference between the control and treatment groups in the main analyses. Less progression of coronary artery calcification was found in participants who were ≥85% adherent to supplementation and in those with pre-existing coronary artery calcification.[51]

Potential mechanisms

The lower risk of CHD with a high intake of K2 may have different explanations. Jakobsen *et al* showed that intake of SFA seems to be preferable compared with intake of carbohydrates with high glycaemic index in order to reduce risk of myocardial infarction.[52] Further, intake of K2 correlates positively with intake of SFA, especially dairy sources as cheese, and negatively with intake of carbohydrates, especially sugar-rich sources as soft drinks with sugar and fruit and berries (both fresh and canned). Further, cheese has been associated with lower risk of CHD,[53] and the median intake of cheese more than triples between the first and fourth quartile of K2 intake. This may also partly explain why adjusting for SFA and calcium attenuated the association between intake of K2 and CHD (table 3, model 3).

The lower risk of CHD with a high intake of K2 may further be explained by carboxylation of vascular Matrix Gla Protein and consequently less arterial calcification.[54] Intimal calcification starts in the inner layer of large arteries, is associated with dyslipidaemia and may cause ischemia and arterial infarction, while calcification of the medial layer occurs even in small arteries and may lead to arterial stiffness, hypertension and left ventricular hypertrophy that further increases risk of CHD.[55]

The observed association for K2 only may be due to the fact that in addition to being cleared by the liver, it is also transported to extrahepatic tissues.[5] However, extrahepatic vitamin K-dependent proteins seem to be of lower priority compared with those in the liver.[26 27] Thus, one hypothesis is that intake of vitamin K has to be of a certain magnitude in order to have an effect on CHD. The different results on K1 and K2 may also be due to biological differences between K1 and K2 or to lower ability of the FFQ to estimate K1.[4 26 56] Due to different bioavailability, the contribution of K2 to vitamin K status is at least equal to that of K1 even though dietary K1 contributes to the majority of the total vitamin K intake.[26 46 57]

Alternatively, our findings may reflect that K2 may be a marker of another nutrient or food constituent that has heart-healthy properties.

Implications and future research

Our findings contribute to the sparse literature relating dietary vitamin K to future CHD risk. Current dietary guidelines are based on insufficient knowledge with regard to vitamin K metabolism and the different characteristics of K1 and K2. Therefore, our results indicate a need for more studies on the association between K2 and CHD. In addition, more knowledge about the absorption, transport and bioactivity of K2 is warranted.

Conclusion

In this Norwegian community-based study population, we observed that intake of K2 was associated with lower risk of CHD, while there was no association between intake of K1 and CHD. These results are considered generalisable to other middle-aged Western populations in which dairy products are the primary source of K2.

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Supplementary table 1 Associations between intake of energy-adjusted vitamin K1 and K2 and incident coronary heart disease (CHD)[a]. Sex-specific quartiles with 1279 men and 1708 women. Missing data are imputed with multiple imputation.[b]
The Hordaland Health Study (HUSK).

Exposure	Intake, µg/day mean (SD)	N	CHD, N(%)	Model 1 HR (95% CI)[c] N = 2987	Model 2 HR (95% CI)[d] N = 2987	Model 3 HR (95% CI)[e] N = 2987
Vitamin K1						
		2987	112			
Q1	63 (25)	746	33 (4.4)	1 (ref)	1 (ref)	1 (ref)
Q2	83 (27)	747	18 (2.4)	0.47 (0.27 to 0.85)	0.49 (0.27 to 0.87)	0.47 (0.26 to 0.84)
Q3	122 (32)	748	31 (4.1)	0.84 (0.51 to 1.39)	0.83 (0.50 to 1.36)	0.77 (0.47 to 1.27)
Q4	269 (191)	746	30 (4.0)	0.91 (0.55 to 1.49)	0.93 (0.56 to 1.53)	0.71 (0.40 to 1.25)
P for trend[f]				0.64	0.60	0.60
Continuous, Per 10 µg				1.00 (0.99 to 1.02), p = 0.57	1.00 (0.99 to 1.02), p = 0.61	0.99 (0.97 to 1.01), p = 0.26
Vitamin K2						
		2987	112			
Q1	10 (4)	746	35 (4.7)	1 (ref)	1 (ref)	1 (ref)
Q2	13 (4)	747	30 (4.0)	0.79 (0.48 to 1.29)	0.80 (0.49 to 1.31)	0.86 (0.52 to 1.42)
Q3	17 (4)	747	29 (3.9)	0.77 (0.47 to 1.26)	0.79 (0.48 to 1.30)	0.90 (0.52 to 1.53)
Q4	26 (8)	747	18 (2.4)	0.50 (0.28 to 0.88)	0.50 (0.28 to 0.88)	0.60 (0.30 to 1.19)
P for trend[f]				0.02	0.02	0.17
Continuous, Per 10 µg				0.71 (0.50 to 0.99), p = 0.04	0.70 (0.50 to 0.98), p = 0.04	0.80 (0.52 to 1.25), p = 0.33

[a]HR are presented as Q2 vs. Q1, Q3 vs. Q1, Q4 vs. Q1.
[b]Missing values for physical activity, smoking and education were imputed using ordinal logistic regression as the imputation model in MICE (multiple imputation using chained equation) with 20 imputations.
[c] Cox proportional hazards regression analysis adjusted for age, sex and total energy intake.

[d]Adjusted in addition for physical activity, smoking and education.
[e] Vitamin K1 is adjusted in addition for energy-adjusted fiber and folate, while vitamin K2 is adjusted in addition for energy-adjusted calcium and saturated fatty acids.
[f] P – trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.
SD, standard deviation; N, number of participants; CHD, incident coronary heart disease; HR, hazard ratio; CI, confidence interval; Q, quartile

Supplementary table 2 Associations between intake of absolute (not energy adjusted) vitamin K1 and K2 and incident coronary heart disease (CHD)[a]. Sex-specific quartiles with 1279 men and 1708 women. The Hordaland Health Study (HUSK).

Dietary intake	Intake, µg/day mean (SD)	N	CHD, N(%)	Model 1 HR (95% CI)[b] N = 2987	Model 2 HR (95% CI)[c] N = 2792[e]	Model 3 HR (95% CI)[d] N = 2792[e]
Vitamin K1						
		2987	112			
Q1	51 (13)	747	34 (4.6)	1 (ref)	1 (ref)	1 (ref)
Q2	86 (10)	747	26 (3.5)	0.89 (0.52 to1.50)	0.97 (0.55 to 1.71)	0.92 (0.52 to 1.62)
Q3	127 (16)	747	26 (3.5)	0.94 (0.54 to 1.62)	0.97 (0.54 to 1.74)	0.86 (0.47 to 1.55)
Q4	274 (188)	746	26 (3.5)	1.03 (0.58 to 1.84)	1.04 (0.55 to 1.96)	0.72 (0.35 to 1.48)
P for trend[f]				0.79	0.87	0.37
Continuous, Per 10 µg				1.00 (0.99 to 1.02), p = 0.57	1.00 (0.99 to 1.02), p = 0.62	0.99 (0.97 to 1.01), p = 0.27
Vitamin K2						
		2987	112			
Q1	9 (2)	749	33 (4.4)	1 (ref)	1 (ref)	1 (ref)
Q2	13 (2)	745	35 (4.7)	1.15 (0.70 to 1.87)	1.27 (0.75 to 2.17)	1.38 (0.80 to 2.40)
Q3	18 (2)	748	27 (3.6)	0.94 (0.54 to 1.62)	1.00 (0.56 to 1.78)	1.21 (0.64 to 2.29)
Q4	27 (7)	745	17 (2.3)	0.62 (0.32 to 1.22)	0.72 (0.36 to 1.45)	0.97 (0.41 to 2.28)
P for trend[f]				0.12	0.25	0.83
Continuous, Per 10 µg				0.71 (0.50 to 0.99), p = 0.04	0.74 (0.52 to 1.05), p = 0.09	0.82 (0.51 to 1.30), p = 0.39

[a]HRs are presented as Q2 vs. Q1, Q3 vs. Q1, Q4 vs. Q1.

[b]Cox proportional hazards regression analysis adjusted for age, sex and total energy intake.

[c]Adjusted in addition for physical activity, education and smoking habits.

[d] Vitamin K1 is adjusted in addition for energy-adjusted fiber and folate, while vitamin K2 is adjusted in addition for energy-adjusted calcium and saturated fatty acids.
[e] Analyses were based on a reduced number of participants (n=2792) and CHD events (n=100) due to listwise deletion when covariates were missing.
[f] P – trend, to test for linear trends across quartiles, we modelled the median intake of each quartile as a continuous variable.
SD, standard deviation; N, number of participants; CHD, incident coronary heart disease; HR, hazard ratio; CI, confidence interval; Q, quartile

Appendix A

The Hordaland Homocystein Study questionnaire

A FAMILIE

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 12

B EGEN SYKDOM

Har De, eller har De hatt:

- Hjerteinfarkt? 13
- Angina pectoris(hjertekrampe)? 14
- Hjerneslag? 15
- Sukkersyke? 16

Hvis De har sukkersyke, i hvilket år ble diagnosen stillet? 17

19____

Er De under medikamentell behandling for høyt blodtrykk? 19

C SYMPTOMER

Får De smerter eller ubehag i brystet når De:

- Går i bakker, trapper eller fort på flat mark? 20
- Går i vanlig takt på flat mark? 21

Dersom De får smerter eller vondt i brystet ved gange, pleier De da å:

- Stoppe? 22
- Saktne farten? .....
- Fortsette i samme takt? .....

Dersom De stopper eller saktner farten, forsvinner smertene da:

- Etter mindre enn 10 minutter? 23
- Etter mer enn 10 minutter? .....

Har De vanligvis:

- Hoste om morgenen? 24
- Oppspytt fra brystet om morgenen? 25

D MOSJON

Bevegelse og kroppslig anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.
Sett kryss i den ruta hvor «JA» passer best

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 26

Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uka? .....
(Her skal De også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m.)

Driver mosjonsidrett, tyngre hagearbeid e.l.? .
(Merk at aktiviteten skal være minst 4 timer i uka.)

Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka? .....

E SALT/FETT

Hvor ofte bruker De salt kjøtt eller salt fisk til middag?
Sett kryss i den ruta hvor «JA» passer best

- Aldri eller sjeldnere enn en gang i måneden 27
- Opptil en gang i uka .....
- Opptil to ganger i uka .....
- Mer enn to ganger i uka .....

Hvor ofte pleier De strø ekstra salt på middagsmaten?
Sett kryss i den ruta hvor «JA» passer best

- Sjelden eller aldri 28
- Av og til eller ofte .....
- Alltid eller nesten alltid .....

Hva slags margarin eller smør bruker De til vanlig på brød?
Sett kryss i den ruta hvor «JA» passer best

- Bruker ikke smør eller margarin på brød 29
- Smør .....
- Hard margarin .....
- Myk (Soft) margarin .....
- Smør/margarin blanding .....

Hva slags fett blir til vanlig brukt til matlaging i Deres husholdning?
Sett kryss i den ruta hvor «JA» passer best

- Smør eller hard margarin 30
- Myk (Soft) margarin eller olje .....
- Smør/margarin blanding .....

F RØYKING

Røyker De

- Sigaretter daglig? 31
  (håndrullet eller fabrikkframstilte)
- Sigarer eller scrutter/sigarillos daglig? 32
- Pipe daglig? 33

Hvis De ikke røyker daglig nå, besvar da:

- Har De røykt daglig tidligere? 34

Hvis De svarte «JA», hvor lenge er det siden De sluttet?

- Mindre enn 1 år? 35
- Mer enn 1 år? .....

Besvares av dem som røyker nå eller som har røykt tidligere:

- Hvor mange år tilsammen har De røykt daglig? 36

Hvor mange sigaretter røyker eller røykte De daglig?

- Oppgi tallet på sigaretter daglig 38
  (håndrullet + fabrikkframstilte)

G KAFFE

Hvor mange kopper kaffe drikker De vanligvis daglig?
Sett kryss i den ruta hvor «JA» passer best

- Drikker ikke kaffe, eller mindre enn en kopp 42
- 1 – 4 kopper .....
- 5 – 8 kopper .....
- 9 eller flere kopper .....

Hva slags kaffe drikker De vanligvis daglig?

- Kokekaffe 43
- Filterkaffe 44
- Pulverkaffe 45
- Koffeinfri kaffe 46
- Drikker ikke kaffe 47

H ARBEID

Har De i det siste året hatt:
Sett kryss i den ruta hvor «JA» passer best

- For det meste stillesittende arbeid? 48
  (f.eks. skrivebordsarbeid, urmakerarbeid, montering)
- Arbeid som krever at De går mye? .....
  (f.eks. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor De går og løfter mye? .....
  (f.eks. postbud, tyngre industriarb., bygningsarbeid)
- Tungt kroppsarbeid? .....
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Har De i Deres arbeid noen gang vært i kontakt med:

- Asbeststøv? 49
- Kvartsstøv? 50

Har De vanligvis skiftarbeid eller nattarbeid? 51

Er husarbeid i hjemmet hovedyrket Deres? 52
(Svar: «NEI» hvis lønnet arbeid utenom husarbeid er 18 timer eller mer pr. uke)

Har De daglig omsorg for syke eller funksjonshemmede i familien? 53

Har De i løpet av de siste 12 måneder fått arbeidsledighetstrygd? 54

Er De for tiden sykmeldt, eller får De attføringspenger? 55

Har De full eller delvis uførepensjon? 56

I ETTERUNDERSØKELSE

Er to eller flere av dine besteforeldre av finsk ætt? 57

Er to eller flere av dine besteforeldre av samisk ætt? 58

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere:
Hvilken almenpraktiserende lege/kommunelege ønsker du da å bli henvist til?

Skriv navnet på legen her →

..... 59

Ingen spesiell lege 62

Ikke skriv her

Ikke skriv her

Appendix B

The Hordaland Health Study (HUSK) questionnaire

Hvor ofte i løpet av de siste 4 ukene har du hatt mye overskudd? Sett bare ett kryss.

	JA
Hele tiden	☐ 1
Nesten hele tiden	☐ 2
Mye av tiden	☐ 3
En del av tiden	☐ 4
Litt av tiden	☐ 5
Ikke i det hele tatt	☐ 6

Hvor ofte i løpet av de siste 4 ukene har du følt deg nedtor og trist? Sett bare ett kryss.

	JA
Hele tiden	☐ 1
Nesten hele tiden	☐ 2
Mye av tiden	☐ 3
En del av tiden	☐ 4
Litt av tiden	☐ 5
Ikke i det hele tatt	☐ 6

I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang(som det å besøke venner, slekt)? Sett bare ett kryss.

	JA
Hele tiden	☐ 1
Nesten hele tiden	☐ 2
Mye av tiden	☐ 3
En del av tiden	☐ 4
Litt av tiden	☐ 5
Ikke i det hele tatt	☐ 6

Stort sett, vil du si at din helse er:

Utmerket	Meget god	God	Nokså god	Dårlig
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. BRUK AV MEDISINER

Med medisiner mener vi her alle slags medisiner, både:
- *med og uten resept, naturmedisin, vitaminer og mineraler*
- *medisin som svelges, inhaleres eller injiseres, stikkpiller, salver, kremer eller dråper.*

	JA	NEI
Tok du noen slags medisiner I GÅR?	☐	☐

Hvis NEI, kan du gå til avsnitt 12.
Hvis JA, besvar følgende:
Hvilke medisiner tok du I GÅR, og hva var grunnen til at du tok medisinen (diagnose, sykdom, symtom, helseeffekt)?
Sett svarene inn i skjemaet nedenfor, en linje for hver medisin. Kryss av for ja om du bruker medisinen daglig eller nesten daglig.

Navn på medisinen *(ett navn pr. linje):*	Grunn til bruk av medisinen I GÅR var:	Daglig JA	Daglig NEI

Dersom det ikke er nok plass her, kan du fortsette på eget ark som legges ved.

12. ARBEID

Besvares av dem som har hatt inntektsgivende arbeid i minst 100 timer det siste året:
Beskriv virksomheten på det arbeidsstedet der du utførte inntektsgivende arbeid i lengst tid de siste 12 mnd. *(Skriv f.eks. jordbruk, barneavd. på sykehus, snekkeravd. på skipsverft e.l.).*

Virksomhet:

Hvilket yrke/tittel har eller hadde du på dette arbeidsstedet? *(Skriv f.eks. kornbonde, anestesisykepleier, snekker e.l.)*

Yrke:

Hvor lenge har du praktisert i dette yrket i ditt liv? ..... *Antall år i yrket* ☐☐

Har du noen av de følgende yrker (*heltid eller deltid*)? *Sett kryss for hvert spørsmål.*

	JA	NEI
Sjåfør	☐	☐
Bonde/gårdbruker	☐	☐
Fisker	☐	☐

Har du tidligere i ditt liv (*ikke i dag*) hatt inntektsgivende arbeid som:

	JA	NEI
Bilmekaniker/biloppretter	☐	☐
Frisør	☐	☐

13. SAMLIV

Oppgi antall egne barn (eventuelt 0) av hvert kjønn:

Antall gutter ☐☐ *Antall jenter* ☐☐

	JA	NEI
Har du noen gang hatt regelmessig samliv uten prevensjon i ett år eller mer uten at det har ført til graviditet?	☐	☐

Med prevensjon menes også mer usikre metoder som avbrutt samleie, «sikre perioder» etc.

De følgende spørsmål besvares bare av kvinner

Har du noen gang spontanabortert (ufrivillig mistet fosteret) etter at graviditet var sikkert påvist?

NEI	USIKKER	JA	Hvis JA:
☐	☐	☐	*Antall ganger* ☐☐

Følgende spørsmål besvares bare hvis du har vært gravid:
Oppgi antall måneder det tok med regelmessig samliv uten prevensjon (eller evt. amming), til du ble gravid:

Siste svangerskap ..... ☐☐ *mnd. uten prevensjon*

Nest siste svangerskap..... ☐☐ *mnd. uten prevensjon*

Tredje siste svangerskap ..... ☐☐ *mnd. uten prevensjon*

14. ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker

Ikke skriv i disse rutene ☐☐☐☐ ☐☐☐

Takk for utfyllingen!
Nok en gang: ***Velkommen til undersøkelsen***

IE 3215801 (ID.NR. 1.97)- 30.000- Beyer-Hecce 9.97

HELSEUNDERSØKELSEN I HORDALAND 1997-99

☐ Adresse endring

HUSK

Personlig innbydelse

SP02B

Spørreskjemaet er en viktig del av helseundersøkelsen. Vennligst fyll ut skjemaet på forhånd og ta det med til helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem stå ubesvart til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen.
Alle svar vil bli behandlet strengt fortrolig.

Det utfylte skjemaet vil bli lest av en maskin. Bruk blå eller sort farge ved utfylling. Det er viktig at du går fram slik:
- i de små boksene setter du kryss for det svaret som passer best for deg
- i de store boksene skriver du tall eller blokkbokstaver – NB! innenfor rammen for boksen.

Eksempler:
Avkryssing: ☒ Tall: 1 2 3 4 5 6 7 8 9 0 Bokstaver: A B C

Med vennlig hilsen

Statens helseundersøkelser ♥ Kommunehelsetjenesten ♥ Helseundersøkelsen i Hordaland

1. EGEN HELSE

Hvordan er helsen din nå? *(Sett bare ett kryss)*

Dårlig	Ikke helt god	God	Svært god
☐ 1	☐ 2	☐ 3	☐ 4

Har du, eller har du hatt:	JA	NEI	Alder første gang
Hjerteinfarkt	☐	☐	år
Angina pectoris (hjertekrampe)	☐	☐	år
Hjerneslag/hjerneblødning	☐	☐	år
Astma	☐	☐	år
Diabetes (sukkersyke)	☐	☐	år
Multippel sklerose	☐	☐	år

Bruker du medisin mot høyt blodtrykk?

Nå	Før, men ikke nå	Aldri brukt
☐ 1	☐ 2	☐ 3

Har du noen gang det siste året hatt eksem (rød, kløende, sår og sprukken hud):	JA	NEI
På hendene?	☐	☐
I ansiktet?	☐	☐
Andre steder på kroppen?	☐	☐

Med «hvite fingre» mener vi plager i form av at en eller flere fingre blir hvite og at man samtidig mister følelsen i dem når det er kaldt. Har du slike plager?	JA	NEI
	☐	☐

2. HVORDAN FØLER DU DEG?

Har du de siste to ukene følt deg:	Nei	Litt	En god del	Svært mye
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst?	☐	☐	☐	☐
Trygg og rolig?	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom?	☐ 1	☐ 2	☐ 3	☐ 4

3. SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?	JA	NEI	VET IKKE
	☐	☐	☐

Har en eller flere foreldre/søsken hatt:			
Hjerteinfarkt *før* de fylte 60 år?	☐	☐	☐
Hjerneslag/hjerneblødning *før* de fylte 70 år?	☐	☐	☐

4. MUSKEL- OG SKJELETTPLAGER

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?	JA	NEI
	☐	☐

Hvis NEI, gå til avsnitt 5.
Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke	☐	☐
Skuldre (aksler)	☐	☐
Albuer	☐	☐
Håndledd/hender	☐	☐
Bryst, mage	☐	☐
Øvre del av ryggen	☐	☐
Korsryggen	☐	☐
Hofter	☐	☐
Knær	☐	☐
Ankler, føtter	☐	☐

Hvor lenge har plagene vart sammenhengende?
Svar for det området hvor plagene har vart lengst.

Hvis under 1 år, oppgi antall måneder ..... *Antall mnd.*

Hvis 1 år eller mer, oppgi antall år ..... *Antall år*

Har plagene redusert din arbeidsevne det siste året?
Gjelder også hjemmearbeidende. Sett bare ett kryss.

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐ 1	☐ 2	☐ 3	☐ 4

Har du vært sykmeldt p.g.a. disse plagene det siste året?	JA	NEI	Ikke i arbeid
	☐	☐	☐

Har plagene ført til redusert aktivitet i fritiden?	JA	NEI
	☐	☐

5. MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året?
Tenk deg et ukentlig gjennomsnitt for året.
Arbeidsvei regnes som fritid. Besvar begge spørsmålene.

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐ 1	☐ 2	☐ 3	☐ 4

6. KAFFE / TE / ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig.

Antall kopper daglig	Kokekaffe	Annen kaffe	Te

	JA	NEI
Er du total avholdsmann/-kvinne?	☐	☐

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. ..... *Antall ganger*

Hvor mange glass øl, vin eller brennevin drikker du VANLIGVIS i løpet av to uker?
Regn ikke med lettøl. Sett 0 hvis du ikke drikker alkohol.

Glass øl	Glass vin	Glass brennevin

7. RØYKING

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? ..... *Antall hele timer*
Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:	JA	NEI
Sigaretter daglig?	☐	☐
Sigarer/sigarillos daglig?	☐	☐
Pipe daglig?	☐	☐

Aldri røykt daglig ..... (Sett kryss) ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? ..... *Antall år*

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ..... *Antall sigaretter*

Hvor gammel var du da du begynte å røyke daglig? ..... *Alder i år*

Hvor mange år til sammen har du røykt daglig? ..... *Antall år*

8. ENDRING AV HELSEVANER

Dette gjelder din interesse for å endre helsevaner. Røykespørsmålet besvares bare av dem som røyker.

	Spise sunnere JA	Spise sunnere NEI	Trimme mer JA	Trimme mer NEI	Slutte å røyke JA	Slutte å røyke NEI
Har du de siste 12 mnd. forsøkt å:	☐	☐	☐	☐	☐	☐
Om 5 år, tror du at du har endret vaner på noen av disse områdene?	☐	☐	☐	☐	☐	☐

Anslå din høyeste og laveste vekt i løpet av de siste 5 år. *(Hele kg)* *(Se bort fra vekt under svangerskap)*	Høyeste vekt	Laveste vekt

9. UTDANNING

Hvilken utdanning er den høyeste du har fullført?
Sett bare ett kryss.

Mindre enn 7 år grunnskole	☐
Grunnskole 7-10 år, framhaldsskole, folkehøgskole	☐ 1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole	☐ 2
Artium, ek.gymnas, allmennfaglig retning i videregående skole	☐ 3
Høgskole/universitet, mindre enn 4 år	☐ 4
Høgskole/universitet, 4 år eller mer	☐ 5

10. HELSE OG TRIVSEL

De neste spørsmålene handler om hvordan du ser på din egen helse. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene NÅ?

Moderate aktiviteter som å flytte bord, støvsuge, gå en tur eller drive med hagearbeid:

Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
☐	☐	☐

Gå opp trappen flere etasjer:

Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
☐	☐	☐

I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?	JA	NEI
Du har utrettet mindre enn du hadde ønsket	☐	☐
Du har vært hindret i å utføre visse typer arbeid eller gjøremål	☐	☐

I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål p.g.a. følelsesmessige problemer? *(Som f.eks. å være deprimert eller engstelig)*	JA	NEI
Du har utrettet mindre enn du hadde ønsket	☐	☐
Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig	☐	☐

I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid?
(Gjelder både i og utenfor hjemmet) Sett bare ett kryss.

	JA
Ikke i det hele tatt	☐ 1
Litt	☐ 2
En del	☐ 3
Mye	☐ 4
Svært mye	☐ 5

Hvor ofte i løpet av de siste 4 ukene har du følt deg rolig og harmonisk? Sett bare ett kryss.

	JA
Hele tiden	☐ 1
Nesten hele tiden	☐ 2
Mye av tiden	☐ 3
En del av tiden	☐ 4
Litt av tiden	☐ 5
Ikke i det hele tatt	☐ 6

Appendix C

Food Frequency questionnaire in

The Hordaland Health Study

HVA SPISER DU?

I dette skjemaet spør vi om dine spisevaner slik de **vanligvis** er. Vi er klar over at kostholdet varierer fra dag til dag. Prøv derfor så godt du kan å gi et **"gjennomsnitt"** av dine spisevaner. Ha det siste året i tankene når du fyller ut skjemaet. Der du er usikker, anslå svaret.

Skjemaet skal leses av en maskin, og derfor er det viktig at du setter et tydelig kryss i avmerket rute.

Riktig markering er slik: ☒

Bruk helst bløt blyant. Feil kan da rettes med viskelær.
Kulepenn og svart tusjpenn kan også brukes.

Av hensyn til den maskinelle lesingen pass på at arkene ikke blir brettet.

Alle svar vil bli behandlet strengt fortrolig.

EKSEMPEL PÅ UTFYLLING AV SPØRSMÅL 1.

Kari Nordmann spiser daglig 5 skiver brød og ett knekkebrød. Hun spiser vanligvis kneippbrød, men i helgene blir det en del loff. I tillegg spiser hun ett knekkebrød hver dag. Hun fyller ut første spørsmål slik:

1. HVOR MYE BRØD PLEIER DU Å SPISE?

Legg sammen det du bruker til alle måltider i løpet av en dag.

(1/2 rundstykke = 1 skive, 1 baguett = 5 skiver, 1 ciabatta = 4 skiver)

	Antall skiver pr. dag												
	0	1/2	1	2	3	4	5	6	7	8	9	10	11	12+
Fint brød (loff, baguetter, fine rundstykker o.l.)	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mellomgrovt brød (lys helkorn, lys kneipp, lyst hj.bakt o.l.)	☐	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
Grovt brød (fiberkneipp, mørk kneipp, mørkt hj.bakt o.l.)	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knekkebrød (kavring, grov skonrok o.l.)	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr. dag = 6

Antall skiver pr. uke: 6 x 7 = 42 Tallet brukes i spørsmål 5.

1. HVOR MYE BRØD PLEIER DU Å SPISE?

Legg sammen det du bruker til alle måltider i løpet av en dag.

(1/2 rundstykke = 1 skive, 1 baguett = 5 skiver, 1 ciabatta = 4 skiver)

	Antall skiver pr. dag													
	0	1/2	1	2	3	4	5	6	7	8	9	10	11	12+
Fint brød (loff, baguetter, fine rundstykker o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mellomgrovt brød (lys helkorn, lys kneipp, lyst hj.bakt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grovt brød (fiberkneipp, mørk kneipp, mørkt hj.bakt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knekkebrød (kavring, grov skonrok o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr. dag = ____

Antall skiver pr. uke: ____ x 7 = ____. Tallet brukes i spørsmål 5.

2. HVA PLEIER DU Å SMØRE PÅ BRØDET?

Merk av både for hverdag og helg, selv om du bruker det samme.

Hverdager		Lørdager, søndager
☐	Bruker ikke	☐
☐	Smør (meierismør)	☐
☐	Bremykt, Smøregod	☐
☐	Brelett	☐
☐	Soft, soyamargarin (pakke, beger)	☐
☐	Solsikke	☐
☐	Oliven	☐
☐	Vita	☐
☐	Olivero	☐
☐	Omega	☐
☐	Soft light	☐
☐	Vita lett	☐
☐	Annen margarin	☐

3. OM DU BRUKER FETT PÅ BRØD, HVOR MYE BRUKER DU?

En porsjonspakning på 12 g rekker til antall skiver

1 ☐

2 ☐

3 ☐

4 ☐

5 ☐

4. MELK SOM DRIKK

(1 glass = 1,5 dl)

	Drikker sjelden/ ikke	Antall glass pr. dag								
		1/2	1	2	3	4	5	6	7	8+
Helmelk, søt, sur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettmelk, søt, sur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettmelk, ekstra lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Skummet melk, søt, sur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

5. PÅLEGGSSORTER

Bruk sum skiver pr. uke fra spørsmål 1.

Til antall skiver pr. uke

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Brun ost, prim	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hvit ost, helfet, 27% fett (Jarlsberg, Norvegia o.l., smøreost; eske, tube)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hvit ost, halvfet, 16% fett (Jarlsberg, Norvegia o.l., smøreost; eske, tube)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ost med mer enn 27% fett (kremoster, Normanna, Ridderost)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Leverpostei, vanlig	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Leverpostei, mager	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Servelat, vanlig	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lett servelat, kalverull, kokt skinke, okserull o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Salt pølse, spekepølse (fårepølse, salami o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Kaviar	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Makrell i tomat, røkt makrell	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sardiner, sursild, ansjos o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Laks, ørret	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Reker, krabbe	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Syltetøy, marmelade, frysetøy	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Honning, sirup, sjokolade-, nøttepålegg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	0	1/2	1	2-3	4-5	6-7	8-14	15-21	22-28	29-35	36+
Grønnsaker som pålegg (agurk, tomat o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Frukt som pålegg (banan, eple o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Salater med majones	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Majones på smørbrød	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

6. EGG

Antall pr. uke

	0	Mindre enn 1	1	2	3-4	5-6	7	8+
(kokt, stekt, eggerøre, omelett)	☐	☐	☐	☐	☐	☐	☐	☐

7. FROKOSTGRYN, GRØT OG YOGHURT

Svar enten pr. måned **eller** pr. uke. <1 betyr sjeldnere enn 1 gang.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang			
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1	1 1/2	2	3+
Havregryn, kornblandinger (4-korn, usøtet müsli o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Cornflakes, puffet ris, havrenøtter o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Havregrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Sukker til frokostgryn, grøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ts)	1 ☐	2 ☐	3-4 ☐	5+ ☐
Yoghurt, naturell, frukt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(beger)	1/2 ☐	1 ☐	1 1/2 ☐	2+ ☐
Lettyoghurt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(beger)	1/2 ☐	1 ☐	1 1/2 ☐	2+ ☐
Go´morgen yoghurt inkl. müsli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(beger)	1/2 ☐	1 ☐	1 1/2 ☐	2+ ☐
Melk søt, sur på gryn, grøt og dessert	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	3/4 ☐	1 ☐	2 ☐	3+ ☐

8. KAFFE OG TE

(1 kopp kaffe = 1,2 dl 1 kopp te = 2 dl)

	Drikker ikke/ikke daglig	Antall kopper pr. dag: 1/2	1	2	3-4	5-6	7-8	9-10	11+
Kaffe, kokt	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe, traktet, filter	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe, pulver (instant)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe, koffeinfri	☐	☐	☐	☐	☐	☐	☐	☐	☐
Te	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nypete, urtete	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Antall teskjeer eller biter pr. kopp: 0	1/2	1	2	3	4+
Sukker til kaffe	☐	☐	☐	☐	☐	☐
Sukker til te	☐	☐	☐	☐	☐	☐
Kunstig søtstoff til kaffe eller te	☐	☐	☐	☐	☐	☐
Fløte til kaffe	☐	☐	☐	☐	☐	☐

9. ANDRE DRIKKER?

Svar enten pr. måned **eller** pr. uke. < 1 betyr sjeldnere enn 1 gang.
Merk at porsjonsenhetene er forskjellige. 1/3 liter tilsvarer en halvflaske øl og 2/3 liter tilsvarer en helflaske.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang						
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1/2	1	2	3	4	5+	
Vann	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐	
Appelsinjuice	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Annen juice, most, nektar	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Saft, solbærsirup m. sukker	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Saft, kunstig søtet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Brus, Cola, Solo o.l., med sukker	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐	
Brus, Cola, Solo o.l., kunstig søtet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐	
Farris, Selters, Soda o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐	
Alkoholfritt øl, vørterøl, lettøl	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐	
Pilsnerøl	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/4 ☐	1/3 ☐	1/2 ☐	2/3 ☐	1 ☐	11/2+ ☐	
Vin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐	
Brennevin, likør	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(1 dram = 4 cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐	

10. MIDDAGSRETTER

Vi spør både om middagsmåltidene og det du spiser til andre måltider. Tell til slutt sammen antall retter du har merket for og se om summen virker sannsynlig.
En "dl" tilsvarer omtrent mengden i en suppeøse. Med "ss" menes en spiseskje.

	Gang pr. måned										Mengde pr. gang					
	0	<1	1	2	3	4	5-6	7-8	9+		1/2	2/3	1	11/2	2+	
Kjøttpølse, medisterpølse	☐	☐	☐	☐	☐	☐	☐	☐	☐	(kjøttpølse)	☐	☐	☐	☐	☐	
Hamburger, karbonader o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Grill- og wienerpølse	☐	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Hamburger-, pølsebrød, lomper	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Kjøttkaker, medisterkaker, kjøttpudding	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Kjøttdeigretter (saus eller gryte med kjøttdeig, lasagne o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Taco (med kjøtt og salat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
Pastaretter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	

	Gang pr. måned										Mengde pr. gang				
	0	<1	1	2	3	4	5-6	7-8	9+		1/8	1/4	1/2	3/4	1+
Pizza (500-600 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(pizza)	☐	☐	☐	☐	☐
											1/2	1	1 1/2	2	2 1/2+
Biff (alle typer kjøtt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1/2	1	1 1/2	2	2 1/2+
Koteletter (lam, okse, svin)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1-2	3-4	5-6	7-8	9+
Stek (lam, okse, svin)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐
											1-2	3-4	5-6	7-8	9+
Stek (elg, hjort, reinsdyr o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐
Gryterett med helt kjøtt, frikassé, fårikål o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Lapskaus, suppelapskaus, betasuppe	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
											1-2	3-4	5-6	7-8	9+
Bacon, stekt flesk	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐
											1/4	1/3	1/2	3/4	1+
Kylling, høne	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1-2	3-4	5-6	7-8	9+
Leverretter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐
	0	<1	1	2	3	4	5-6	7-8	9+						
Fiskekaker, fiskepudding, fiskeboller	☐	☐	☐	☐	☐	☐	☐	☐	☐	(kake)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
											1-2	3-4	5-6	7-9	10+
Fiskepinner	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Torsk, sei, hyse (kokt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Torsk, sei, hyse (stekt, panert)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Sild (fersk, speket, røkt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(filet)	☐	☐	☐	☐	☐
											1/2	1	1 1/2	2	3+
Makrell (fersk, røkt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(filet)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Laks, ørret (sjø, oppdrett)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐
Fiskegryte, -grateng, suppe med fisk	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
											1	2	3	4	5+
Reker, krabbe	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl, renset)	☐	☐	☐	☐	☐
	0	<1	1	2	3	4	5-6	7-8	9+						
Risgrøt, annen melkegrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
											1-2	3-4	5-6	7-8	9+
Pannekaker	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
Suppe (tomat, blomkål, ertesuppe o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Vegetarrett, vegetarpizza grønnsakgrateng, -pai	☐	☐	☐	☐	☐	☐	☐	☐	☐	(bit/dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
	0	<1	1	2	3	4	5-6	7-8	9+		1/2	1	1 1/2	2	2 1/2+
Brun/hvit saus	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐
Smeltet margarin, smør til fisk	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
											1	2	3	4	5+
Bearnaisesaus o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Majones, remulade	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
											1	2	3	4	5+
Ketchup	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐

11. POTETER, RIS, SPAGHETTI, GRØNNSAKER

Svar enten pr. måned **eller** pr. uke. <1 betyr sjeldnere enn 1 gang.
Disse spørsmålene dreier seg først og fremst om tilbehør til middagsretter, men spiser du for eksempel en rå gulrot eller salat til lunsj, skal det tas med her.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang				
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1	2	3	4	5+
Poteter, kokte	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐
Pommes frites, stekte poteter	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Potetmos, -stuing, gratinerte poteter	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Ris	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Spaghetti, makaroni, pasta	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Gulrot	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	1 1/2 ☐	2 ☐	3+ ☐
Hodekål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skalk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kålrot	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Blomkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(bukett)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Brokkoli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(bukett)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Rosenkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Grønnkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Løk	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Spinat, andre bladgrønns.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Sopp	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Avocado	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/4 ☐	1/2 ☐	3/4 ☐	1 ☐	1 1/4 + ☐
Paprika	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(strimmel)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Tomat	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	1 1/2 ☐	2 ☐	3+ ☐
Tomatbønner, bønner/linser	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Mais	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Erter, frosne grønnsak-blandinger	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Salatblandinger	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Dressing	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Rømme	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐

Hvor mange ganger om dagen spiser du vanligvis grønnsaker utenom grønnsakene du spiser til middag?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+ ☐

12. TYPE FETT TIL MATLAGING

Smør/margarin	Oljer
☐ Smør (meierismør)	☐ Olivenolje
☐ Bremykt	☐ Soyaolje
☐ Melange, Per	☐ Maisolje
☐ Soft-, soyamargarin (pakke, beger)	☐ Solsikkeolje
☐ Solsikke	☐ Valnøttolje
☐ Oliven	☐ Andre oljer
☐ Annen margarin	

13. FRUKT

Svar enten pr. måned **eller** pr. uke. < 1 betyr sjeldnere enn 1 gang.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang			
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1/2	1	2	3+
Eple	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Appelsin, mandarin, grapefrukt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Banan	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Druer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(klase)	☐	☐	☐	☐
Eksotisk frukt (kiwi, mango)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Annen frukt (fersken, pære m.v.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Jordbær, bringebær (friske, frosne)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Blåbær	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Multer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐

Hvor mange frukter spiser du vanligvis pr. dag?

0	1	2	3	4	5	6	7	8	9+
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

14. DESSERT, KAKER, GODTERI

Svar enten pr. måned **eller** pr. uke. < 1 betyr sjeldnere enn 1 gang.

	Gang pr. måned					Gang pr. uke						Mengde pr. gang			
	0	<1	1	2	3	1	2-3	4-5	6-7	8+		1/2	1	2	3+
Hermetisk frukt, fruktgrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Puddinger (sjokolade, karamell o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Is (1 dl = 1 pinne = 1 kremmerhus)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Boller, julekake, kringle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Skolebrød, skillingsbolle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Wienerbrød, -kringle o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Smultring, formkake	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Vafler	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(plate)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Sjokoladekake, bløtkake, annen fylt kake	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Søt kjeks, kakekjeks (Cookies, Bixit, Hob Nobs)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Sjokolade (60 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(plate)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Drops, lakris, seigmenn o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Smågodt (1 hg = 100g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(hg)	1/2 ☐	3/4 ☐	1 ☐	1 1/2+ ☐
Potetgull (1 pose 100g = 7 dl)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Annen snacks (skruer, crisp, saltstenger, lettsnacks o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Peanøtter, andre nøtter (1 pose 100g = 4 never)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	(neve)	1 ☐	2 ☐	3 ☐	4+ ☐

15. KOSTTILSKUDD (bs = barneskje, ts = teskje)

	Hele året	Bare vinter-halvåret	Gang pr. uke: 0	<1	1	2-3	4-5	6-7		Mengde pr. gang: 1 ts	1 bs	1 ss	
Tran	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	
Trankapsler	☐	☐	☐	☐	☐	☐	☐	☐	kapsler	1 ☐	2+ ☐		
Fiskeoljekapsler	☐	☐	☐	☐	☐	☐	☐	☐	kapsler	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Multipreparater													
			0	<1	1	2-3	4-5	6-7		1	2	3	4+
Sanasol	☐	☐	☐	☐	☐	☐	☐	☐	bs	☐	☐	☐	☐
Biovit	☐	☐	☐	☐	☐	☐	☐	☐	bs	☐	☐	☐	☐
Vitaplex	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Kostpluss	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Vitamineral	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Hvis annet, hvilket?													
Jernpreparater													
			0	<1	1	2-3	4-5	6-7		1	2	3	4+
Ferro C	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Hemofer	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Duroferon Duretter	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Hvis annet, hvilket?													
			0	<1	1	2-3	4-5	6-7		1	2	3	4+
B-vitaminer	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
C-vitamin	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
D-vitamin	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
E-vitamin	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Folat (folsyre)	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
			0	<1	1	2-3	4-5	6-7		1	2	3	4+
Kalktabletter	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Fluortabletter	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Annet	☐	☐	☐	☐	☐	☐	☐	☐	tablett	☐	☐	☐	☐
Hvis annet, hvilket?													

16. NÅR SPISER DU PÅ HVERDAGER?

HOVEDMÅLTIDER som frokost, formiddagsmat, middag, kvelds.

Omtrent klokken

6	8	10	12	14	16	18	20	22	24	2	4
☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐

MELLOMMÅLTIDER som kaffe, frukt, godteri, snacks m.v.

Omtrent klokken

6	8	10	12	14	16	18	20	22	24	2	4
☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐

17. MENER DU SVARENE I SPØRRESKJEMAET GIR ET BRUKBART BILDE AV KOSTHOLDET DITT?

Ja ☐ Nei ☐

Er det matvarer/produkter du regelmessig bruker, og som ikke er nevnt i skjemaet?

.....

.....

18. ER DU FORNØYD MED KROPPSVEKTEN DIN SLIK DEN ER NÅ?

- ☐ Ja
- ☐ Nei, jeg ønsker å slanke meg
- ☐ Nei, jeg ønsker å legge på meg

19. KJØNN

Mann ☐ Kvinne ☐

Vennligst se etter at du har svart på alle spørsmål.

Takk for innsatsen!

Appendix D

Protocol for baseline health examination

and statement of consent

RUTINER

FOR HJERTE-KARUNDERSØKELSER i HUSK 1997--99

TILHØRER

spl. kode nr:

A :huskruti.rev
26.03.98 MH
08.07.98 mh

RUTINER HJERTE-KARLAG

Stasjon 1 - Registrering (Se også protokoll tilhørende området registrering)

*****08.07.98_ I Bergen kommune blir det invitert fra hele kommunen fortløpende, ikke bydelsvis**

INN-KALTE: Kun personer med innkalling skal undersøkes. Unntak er personer med fast bopel i fylket, tilhørende aldersgruppene, og som ikke har mottatt inviterte. Andre som ønsker undersøkelse henvises til kommunehelsetjenesten.

RENE HK-LAG: Lagene får tilsendt alfabetisk innkallingsliste for orientering. Mottatt melding om fravær registreres ikke på listen.

FREMMØTTE: Dersom den fremmøtte ikke har med originae spørreskjema, leveres det ut nytt spørreskjema på stedet. Skjemaet får påført etikett med navn, 11 siffret personnummer, adresse, og undersøkelses kommune i lesbar tekst og strekkode.

Målekortet får påføres etikett med navn og persondata (11 siffer), i strekkoder og lesbar tekst.
Undersøkelses-kommunens nummer / navn.

FOR EKS: NY-INNFLYTTET TIL FYLKET: Er personen nylig flyttet til fylket og derfor ikke kommet med på innkallingslisten, skal spørreskjemaet merkes over feltet for kommune: «NYINNFLYTTET FRA .....» (fylkets navn).

ETIKETT: Etiketter skrives ut maskinelt ved registreringen. De skrives ut i klartekst og med strekkoder og ligger på en samenhengende papirstrimmel.
Etikettene blir automatisk merket for de områder de skal brukes til, og etikettene limes på det materiellet som tilhører de deler av undersøkelsen som respondenten skal delta i.
Det har forekommer at etiketter har blitt forvekslet. Hver stasjon skal derfor kontrollere navn og fødselsdata på fremmøtte for å sjekke at det er brukt riktig etikett.

BASISMATERIELL Som leveres ut ved registreringen:
Før klientene forlater registreringen får alle med seg plastlomme med: spørreskjema 1, ett målekort, en SST- vacutainer, ett EDTA plastrør 5ml.

DE ulike grupper får i tillegg til basismaterialet:

-Homosysteingruppen får med EDTA 7 ml. plastrør,
-Ett Pony vials plastrør m/skrukork til plasma,
-Spørreskjema tilhørende homosystein,
-Kostholdskjema med plass til etikett på siste arkets bakside.

-40 års gruppen får i tillegg utlevert Spørreskjema 2 i den aktuelle utgave som bestemmes av fødselsdato (se protokoll side. 3)

-Kvinnekohorte-gruppen får i tillegg med seg det informasjon/samtykke arket som får påført riktig etikett.

-Osteoporose-gruppen får med seg eget informasjon/samtykke arket med plass til opplysninger om høyde og vekt

*** 08.07.98-**Ungdoms**-gruppen undersøkelsen går ut på grunn av økonomien

-Kognitiv-gruppen får i sin mappe lagt et farget info ark m/samtykkeerklæring

-Spirometri-gruppen får i sin mappe farget info.ark med plass til etikett, høyde, vekt og alder i år.

Samme person kan tilhøre en eller flere av disse gruppene.

Stasjon 2 - Høyde/vekt-måling- Hofte/midje måling

HØYDE/ VEKT: Høyde/vekt måles uten sko og yttertøy, høyden centimeter, vekten med én desimal. Det rundes av til nærmeste hele eller halve kilo (husk alltid nuller til venstre dersom pasienten er under 100 kilo). Ved avvik i målingen kodes posisjon 25 («ANM») på målekortet etter følgende kodeliste:

ANM:
Blank = normal måling.
0 = fritatt pga invaliditet
1 = nekter både høyde- og vektmåling.
2 = nekter, gravid.
3 = nekter høydemåling.
4 = nekter veiing.
5 = målt med sko, også halte med sko.
6 = målt uten sko, halt.
7 = målt, bøyd nakke, ryggkrumning eller bøyde knær.
8 = målt, men annen invaliditet.
9 = målt, gravid.

Resultatet av målingene føres på målekortet i felter for høyde og

vekt.

«OK»

Skriv «OK» når følgende verdier er registrert:

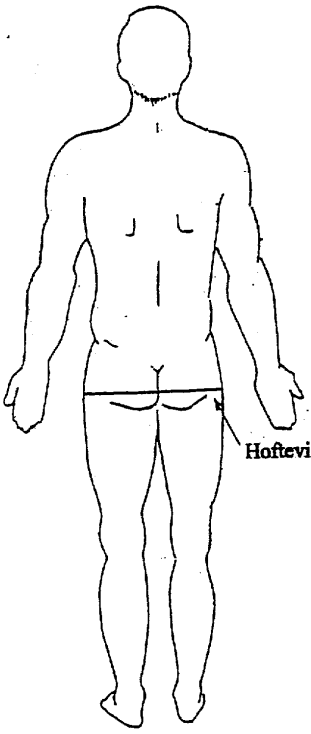
HØYDE under 130 - over 205
VEKT under 045 - over 120

HOFTE / MIDJEMÅL

- Det benyttes stålband.
- Måles mens deltakeren står med armene hengendes løst langs siden, vekten likt fordelt på begge ben og med hodet horisontalt.
- **Hofteomkretsen** måles rundt tykkeste delen av hoften (se figur 1)
- **Midjeomkretsen.**. Be deltageren om å puste normalt. Det måles over navlen (se figur 2).
- Påse ved begge målinger at målbandet er horisontalt ved å sjekke målbandet både foran og bak.(**dette er vanligvis største årsaken til feilaktig måling)**
- Målbandet skal ligge tett, men ikke for stramt over hoften/ midjen.
-
- Måleverdiene noteres i hele cm.på analysekortet som har eget, avmerket felt for begge måleverdiene.

FIGUR 1

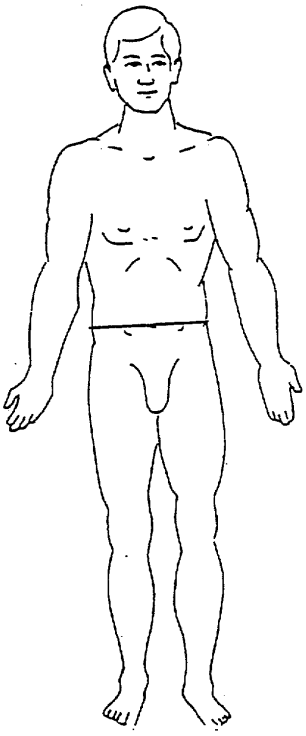
HOFTEOMKRETS



Hoftevidden tas over det tykkeste på setemuskulaturen

FIGUR 2

MIDJEOMKRETS



Livvidden tas over navl

Stasjon 3 - Blodtrykksmåling - Kontroll av spørreskjema

Sykepleierkoden til den sykepleier som **måler BT** føres på målekortet i høyre **øvre hjørne**.
Sykepleierkoden til den sykepleier som tar **blodprøven** fører på målekortet høyre **nedre hjørne**.
Kontroller at det er brukt etikett som stemmer med person.
Kontroller at høyde og vekt er riktig påført, og at verdiene harmoniserer med personens kroppsbygning.
Den innkalte plasseres avslappet i stolen med høyre overarm i tilnærmet hjertehøyde, ikke strammende tøy på armen.

SITTE-/ARM-STILLING: Armen skal ha en posisjon som fører til at:
fossa cubiti har samme høyde som krysspunktet av medio clav.linjen og 4de intercostalrommet (I.C.R.) (det skal ikke brukes mm-mål).

ARM: Overarmens omkrets måles i hele centimeter 10 cm ovenfor albuebøyen. Resultatet noteres på målekortet i felt merket «ARM».

Velg riktig mansjett etter følgende reglement:

Armmål 24 cm eller mindre:	Liten mansjett	= kode 1
Armmål 25 - 34 cm:	Vanlig mansjett	= kode 2
Armmål 35 cm eller mer:	Stor mansjett	= kode 3
	Lårmansjett	= kode 4

*** **P.L-L 10.03.98**.(Ved siste innkjøp av mansjetter er cm tallene som er skrevet på mansjettene ikke helt samsvarende med de armmål som her står oppført. Vi forholder oss til hva vi måler.)

Dersom stor mansjett blir for liten, brukes lårmansjett.
Dersom riktig mansjett ikke vil sitte pga uvanlig form på armen, brukes (og kodes) større mansjett. **Noter i klartekst på målekortet om det må benyttes avvikende mansjett. Dette for at prosjektkontoret ved rettting av avvik skal kunne vite om det er feilkodet eller om det ble benyttet annen mansjett.**

MAN: Kode for mansjett-størrelse skrives i felt merket «MAN».

Mansjetten legges fast, men ikke stramt, med nedre kant ca 2 cm ovenfor albuebøyen. Midten av ballongen legges over arteria brachealis, slangene skal komme ut av mansjetten distalt. Pass på at det ikke er knekk på slangene.

APP.NR.: Feltet på målekortet for ap.nr. skal fylles ut med de 2 siste siffer av Dinamaps apparatnummer.
Disse numrene står skrevet på apparatet.

Start stoppeklokken

Respondenten skal hvile i 2 min før BT-målingen starter.

I hvileperioden orienteres klienten om at det skal foretas 3 automatiske blodtrykksmålinger, og at det ikke skal snakkes under målingene.

Sittestillingen mest mulig avslappet, og begge bena parallelt i gulvet (ikke krysset).

TSM: Deretter kontrolleres spørreskjemaet, og det spørres om tid siden siste måltid ble avsluttet. Tiden kodes i felt TSM etter følgende regler:

0 - 59 min	= kode 0
1 time - 1 time og 59 min	= kode 1
2 timer - 2 timer og 59 min	= kode 2 osv
8 timer - 8 timer og 59 min	= kode 8
9 timer +	= kode 9,

dvs vi runder av ned til nærmeste hele time.

Vi har tidligere diskutert hva som er et måltid. Om dette har vi skrevet at det først og fremst må brukes sunn fornuft. Man har regnet en hel liten brødskive eller en halv brødskive med pålegg som et måltid. Også te eller kaffe med sukker, et glass melk eller et stykke frukt er regnet med som et måltid. Kaffe eller te uten sukker er ikke å regne som måltid.

Demonstrasjonsservering på undersøkelsesstedet styres til etter at personen har gjennomgått undersøkelsen. Dette på grunn av glucoseverdiene.

MÅLING: Etter minst 2 minutter ro starter 3 kontinuerlige 1-minutts målinger.

Resultatet skrives i målekortet i felt Måling 1, 2 og 3.
Skriv alltid null (0) til venstre dersom resultatet ikke er 3-sifret.

Avvikende blodtrykksmåling
Dinamap kan få problemer ved arytmier, pulsus alternans eller dersom det systoliske blodtrykket er over ca 230. Dersom man fortsatt ikke får registrert måling 1 på 3 forsøk, avbrytes Dianmap-målingen, og blodtrykket måles 2 ganger med 1 minutts intervall med vanlig Erca-meter.

Pulsen telles etter siste måling i 30 sekunder, puls pr. minutt angis. Første Erca-måling noteres på målekortet under «Måling 2», annen Erca-måling og pulsen noteres på målekortet under «Måling 3».

I dette tilfellet skrives kode 1 i felt for avvikende blodtrykksmåling.

Dersom måling 1 har latt seg registrere, men Dinamap ikke greier måling 2 på 2 forsøk, avbrytes Dinamap-målingen, og det foretas 2 Erca-målinger med 1 minutts intervall med pulstelling etter siste måling. Erca-målingene noteres i felt for måling 2 og måling 3.

I dette tilfellet skrives kode 2 for avvikende blodtrykksmåling.

Dersom måling 1 og 2 har latt seg registrere med Dinamap, men måling 3 ikke har latt seg registrere på 2. forsøk, måles blodtrykket 1 gang med Erca-meter, etterfulgt av pulstelling. Resultatet noteres i målekortet i felt for måling 3.
I dette tilfellet skrives kode 3 for avvikende blodtrykksmåling.
Ved ufullstendige BT-måling eller avvikende resultater må klienten få melding om dette av sykepl. Klienten må også få melding om at svarbrevet kan få denne meldingen:
«Ufullstendige måleresultater».
Klienten må selv ta kontakt med sin lege for å avtale time dersom etterundersøkelse blir anbefalt.

AVVIK:

Kodeliste for avvikende blodtrykksmåling

Kode 1: Måling 1 mangler,
- måling 2 og 3 foretatt med Erca. (MAP regnes ikke ut)

Kode 2: Måling 1 foretatt med Dinamap,
- måling 2 og 3 foretatt med Erca. (MAP regnes ikke ut)

Kode 3 Måling 1 og 2 foretatt med Dinmap,
- måling 3 foretatt med Erca.

Kode 4: Måling 1 foretatt, - 2 og 3 mangler,
f.eks. besvimelse.

Kode 5: Måling 1 og 2 foretatt, - 3 mangler,
f.eks. besvimelse.

Kode 6: Måling 1, 2 og 3 foretatt, men uvel, besvimelse.

Kode 7: Ingen måling er utført.

STRAKS-MELDING:

Dersom det laveste diastoliske trykk under måling 2 eller 3 er 125 mm Hg eller mer, skal klienten informeres om at lege bør kontaktes. Avdelingssykepleier er ansvarlig for at klientens lege blir meddelt resultatet samme dag eller neste morgen i kontortiden. Bruk eget skjema som klienten tar med til legen. Kopien er en sykepleier-dokumentasjon som viser at sykepleier har fulgt instruksen.
OBS Vi har i det siste oppdaget at rutinene for innsending av straksmeldinger må forandres.pga kontroll opp mot EDB avd. og utskrift av meldekort.
For ettertiden ber vi om at ett eksemplar av straksmeldingen sendes *** ***fortløpende med dagrapporten*** til prosjektkontoret for oppbevaring.
*** **Samlet antall straksmeldinger noteres på dagrapporten.**
Vi får da kopin med navn og fødselsdata så personopplysningene føres ikke på dagrapporten.

INFO: Når klienten spør om resultatet av blodtrykksmålingen (BT), gis opplysning om laveste målte tall for systolisk og diastolisk BT registrert under måling 2 eller 3. Dersom alle BT under måling 2 og 3 er under de aldersspesifikke grenser som laget har fått utdelt, dvs i grønn sone i NSAM´s handlingsprogram versjon 1994, opplyses

det at trykket var normalt.

Dersom BT er så høyt at laget har varslingsplikt direkte til lege, informeres klienten om dette. Man regner ellers med at sykepleierne bruker sitt sunne skjønn og stimulerer til legekontakt i tilfeller der de får fornemmelse av at 4- 6 ukers ventetid blir for lenge.

Ved spørsmål om hva tallene betyr, svares det at alle undersøkte personer får eget svarbrev til privat adresse. Svarbrevet gir opplysninger om resultatene fra undersøkelsen og kommentarer til disse verdiene. Viser analyseresultatene behov for etterundersøkelse, vil det bli gitt melding om det i brev.

Klientens lege vil få tilsendt de samlede resultater og har dermed mulighet til å gi det beste svaret på hva tallene står for.

SAMTYKKEERKLÆRINGEN

I brosjyren "HUSK" er jeg orientert om Hordalands-undersøkelsens formål. Jeg har også sett informasjonsskrivet "HUSK INFO" som bl.a. omtaler delprosjekter, og er kjent med at undersøkelsen består av spørreskjema, blodprøver og måling av blodtrykk, høyde, vekt, liv-og hoftevidde.

Jeg er kjent med at opplysninger om meg blir behandlet strengt fortrolig og at undersøkelsen er vurdert og tilrådd av Den regionale komite for medisinsk forskningsetikk og godkjent av Datatilsynet. Det er ikke satt noen spesiell tidsbegrensning for hvor lenge opplysningene kan lagres, men jeg er klar over at jeg på hvilket som helst tidspunkt kan trekke meg fra undersøkelsen og kan reservere meg mot bruk av opplysninger om meg.

1. Jeg samtykker i at resultater fra blodprøven og andre deler av undersøkelsen, samt resultater fra eventuelle spesialundersøkelser, blir sendt til den legen jeg har oppgitt på spørreskjemaet.

2. Dersom jeg ikke har oppgitt navn på lege, eller legen min ikke deltar i undersøkelsen, samtykker jeg i at mine resultater sendes til kommunelege 1.

3. Jeg samtykker i at jeg kan få tilbud om spesialundersøkelser, og at jeg kan bli kontaktet av en lege med tanke på tilbud om behandling eller for å forebygge sykdom.

4. jeg samtykker i at mine resultater kan brukes til medisinsk forskning, eventuelt ved å sammenholde opplysninger om meg med opplysninger fra andre helse-, trygd- og sykdomsregistre, eller med mine resultater fra tidligere helseundersøkelser i Hordaland. Når disse opplysningene sammenholdes, vil mitt navn og personnummer ikke bli tatt med.

5. Jeg samtykker i at blodprøve oppbevares. All bruk av denne vil bare skje etter godkjenning fra Datatilsynet og Den regionale komite for medisinsk forskningsetikk.

Vennligst stryk det/de avsnitt du reserverer deg mot.

....

Sted og dato Underskrift

SAMTYKKEERKLÆRING

SAMTYKKE: **Retningslinjer for koding.**

Målekortet inneholder samtykkeerklæringen. Dette gir muligheter til å reservere seg for ulike deler av undersøkelsen.

Kodingen dekker to hovedområder: underskrift og samtykke.

Alle skal underskrive, også de som reserverer seg for hele eller deler av undersøkelsen.

Handikappede/psykisk utviklingshemmede

Den som ledsager personer til undersøkelsen utfører om nødvendig underskriften av samtykkeerklæringen.
Sykepleieren fører på sine initialer i tillegg.

Kopi av samtykkeerklæringen
Alle som har skrevet under samtykkeerklæringen får av sykepleieren utlevert en kopi av erklæringen. Dette for at de for ettertiden skal ha et dokument som viser hva de har skrevet under på, om de på et senere tidspunkt skulle ønske å reservere seg for hele eller deler av samtykkeerklæringen.
Kopiene er trykt opp i blokker. Det rives av ett og ett eksemplar som levers til respondentene.

Dersom en person reserverer seg mot 1. + 2. +3. punktene i samtykkeerklæringen skal det skrives **«Reservert»** i rubrikken for ønsket lege **på spørreskjema.**

SVARBREV Svarbrev med analyseresultater blir sendt til alle personer som har møtt frem til undersøkelsen og som har blodanalyser ca. 4-6 uker etter undersøkelsen ble utført.

Stasjon 4 - Blodprøve i SST-vacutainer10 ml

BLOD: Det brukes venestase til venen er punktert, siden slippes stasen opp. Etter tapping snus glasset opp/ned 5 ganger (ikke rist)

***27.11.98 **Ullevål ber om at glasset straks settes loddrett i stativ.(må ikke legges horisontalt på bordet)**
Vippe skal ikke brukes.

Glasset står til koagulasjon i **MINST 30 MINUTTER.**

Er det kaldt, må prøven stå lenger. Blodet skal være koagulert før sentrifugering. Sentrifugering foretas innen 2 timer på grunn av Glukoseverdien.

Prøvene pakkes og sendes med fryseelementer daglig til Ullevål. Forsendelses adr: se side 16.

SENTRIFUGERING

OBS de ulike typer sentrifuger har sitt eget «g»tabell oppsett

Kopi av brukerveiledningen og oversikt over «g» verdiene til sentrifugen legges ved sentrifugen Etter «g»verdien leser en av RPM (omdreining pr minn .)

Det skal brukes «g» verdi 1010.
Blir det spørsmål om forandring av sentrifugestyrke er det «g» verdien en forholder seg til ikke omdreinings-tallet.

Sentrifuger i minst 10 min etter full hastighet er oppnådd.
Sentrifugerte prøver lagres kjølig til forsendelse (SST prøvene må ikke fryse, da gel-klumpen blir lekk).

***27.11.98 Klinisk kjemisk avd. Ullevål presiserer sterkt viktigheten av ordentlig avbalansering ved sentrifugeringen.

IKKE TATT: Dersom det av forskjellige grunner ikke blir tatt blodprøve, settes allikevil vacutainer med etikett i blodkassen. Det skrives «ikke tatt blodprøve» **på målekortet. med stor skrift**
(Dette for å markere at blodprøve ikke er vekk.)

KNUST Kan blodprøven av ulike grunner ikke benyttes (knust på laget/Ullevål har tekn. problemer?),

GLASS: kan lagene ta ny blodprøve noen dager etter første us-dag. Det benyttes da nytt målekort ved forsendelsen av denne blodprøven.

Gi melding til prosjektkontoret ved å notere på dagrapporten hva som har foregått, slik at prosjektkontoret kan gjøre nødvendige tiltak. Det er ikke nødvendig å ta nye BT-målinger. (EDB-avd. samkjører)

EDTA plastrør 5 ml : **Alle personer som møter til undersøkelsen** skal det i tillegg til ovenfor nevnte blodprøve tappes ett EDTA rør, 5 ml. av.alle som møter Prøven skal ikke sentrifugeres. Pakkes i isoporesker, uten kjøleelement og sendes daglig sammen med plasmarørene til Bergen

EDTA plastrør

7 ml: De som tilhører Homosysteingruppen skal i tillegg tappes ett EDTA rør, 7 ml. Dette EDTA glasset skal i kjøleskap innen ½ time og sentrifugeres innen to timer. Plasma skal så avpippeteres umiddelbart etter sentrifugeringen over i eget plastrør Pony Vials med skrukork. Plasmarøret merkes med dertil merket etikett. Plasmarørene sendes i spesielle isoporkasser daglig sammen med EDTA 5 ml glassene.
Forsendelses adr: se «Protokoll» side 10

Bestilling av Pony Vials og isoporesker rettes til:

Kontaktperson: Marie Vik, samme adr. tlf. 55 97 57 41

Laget må selv avtale (retur av) isoporeskene fra instituttet
Instituttet har bestilt opp ett større lager.

BLOD-SMITTE: **Hvis klienten gir opplysninger om at han har hepatitt B eller er HIV-positiv, settes en gul "varsellapp" på vacutainerglasset. Det skal ikke spørres om slik blodsmitte. Alle som arbeider på våre lag skal oppføre seg som om alle fremmøtte er smittet av HIV/hepatitt.**

«OK»

Verdier som dataprogrammet ikke godtar uten sjekk

Vennløigst skriv **OK** når følgende verdier blir registrert:

HØYDE	under	130 cm	over 205 cm
VEKT	"	45 kg	" 120 kg
SYST BT	"	90	" 220
DIAST BT	"	50	" 150
PULS	"	40	" 140

MAP kan aldri bli større enn syst.BT, eller mindre enn diast.BT!

Alle «merkverdigheter», så som sterkt avvikende BT- verdier på de tre målingene (også uten besvimelse), markeres med **OK** eller klartekst.

Eks.: Måling 1: 167/120- Måling 2: 218/161- Måling3: 163/115. Eksempelet er brukt i brev fra spesiallegen hvor han skriver at det er av interesse å vite om det skjedde noe spesielt i forbindelse med undersøkelsen.

Dersom sykepleieren intuitivt skjønner at datamaskinen/Med.avd. vil bli forvirret/usikker på et svar (at det f.eks. kan være en skrive-/punchefeil), bør man skrive en «liten norsk stil» til forklaring. Skriv hvor som helst, bare ikke i datafeltene.

Anmerkninger angående bruk av Dinamap

1. Husk at den røde transportskruen under apparatet (dersom den finnes) skal skrues fast når apparatene transporteres, og skal tas ut når apparatene brukes (hensikten med transportskruen er at den fester kompressoren til underlaget). KOFFERTEN SKAL KJØRES LIGGENDE (SLIK SOM DEN BRUKES).

2. Når apparatet brukes, skal alltid alarmen være skrudd på. Tonens karakter og styrke som reguleres på baksiden av apparatet, er innstilt fra Tekn. avd.. Apparatet er innstilt silk at alarem går dersom MAP kommer under 50 eller går over 140. For å unngå for mange alarmer, kan øvre alarmgrense justeres opp til 170 etter at apparatet er satt på, ved å holde alarm- limits- bryteren på «high» inntil MAP verdien når 170. Dersom strømmen slås av, vil alarmgrense igjen automatisk komme tilbake til 50 og 140.

3. Vær forsiktig med å bøye luftslangene- spesielt hvis de er frosne.

4. Ved tekniske problemer eller dersom et apparat begynner å oppføre seg unormalt, settes det «på stallen» og man ringer Tekn. avd.

5. Alle Dinamap-apparater bør brukes av alle sykepleiere. Avdelingssykepleier bør derfor lage en rotasjonsliste som man kan følge.

STYRT LEGELISTE

***** 08.07.98 Kommunelege tilsvarer Bydelsoverlege i Bergen.**
Orienter klienten om dette i de tilfeller hvor det ikke er oppgitt ønsket lege. Meldekortene til de respondenter som ikke har oppgitt ønsket lege, men ikke har reservert seg, vil bli sendt til vedkommende BYDELSOVERLEGE.

Styrt legeliste betyr at kommunelegen i alle kommuner har fått i oppdrag før undersøkelsen starter i fylket å avklare med sine leger i kommunen hvem som sier seg villig til å foreta anbefalte etterundersøkelser etter hjerte-/kar-screeningen.

De leger som har sagt seg villige, er listeført av prosjektkontoret. Klienten kan velge lege ut fra legelisten, også lege fra andre kommuner.

Finner ikke klienten noen lege han/hun ønsker å benytte, vil eventuelt etterundersøkelses-materiale bli sendt til kommunelegen i hjemkommunen, dersom klienten ikke reserverer seg mot dette. Klienten kan da selv ta kontakt med kommunelegen, og de blir enige om hvem som skal utføre etterundersøkelsen. ikke alle kommuneleger har selv legepraksis.

Ved **å ikke gi samtykke (reserver seg)** mot at opplysninger blir sendt til noen lege, vil klienten selv få analysesvarene på sitt svarbrev. Klienten får da melding PÅ SVARBREVET om at han/hun er selv ansvarlig for å oppsøke lege om analysesvarene tilsier behov for etter-undersøkelse.
Begrunnelsen for styrt legeliste er at prosjektkontoret i den senere tiden har fått mye materiale returnert p.g.a. at legene ikke kjenner klienten, legene ikke har tid til denne type arbeid, osv.

Resultatet er at SHUS sitter med materiale som er knyttet opp til et samtykke til en bestemt lege som ikke ønsker å utføre etterundersøkelses-arbeidet.

DE LEGER SOM STÅR PÅ LEGELISTENE HAR PÅ DETTE GRUNNLAG FÅTT TILDELT LEGEKODE NUMMER.
DETTE KODENR. SKAL FØRES PÅ SPØRRESKJEMA 1, SISTE SIDEN, VED SIDEN AV SPL. KODE NR.

KLIENTENE ER SELV ANSVARLIG FOR Å TA KONTAKT MED LEGE NÅR SVARBREVET GIR MELDING OM AT DET ANBEFALES ETTERUNDERSØKELSE.

SUPPLEMENT III PR 3.7.90 (L-L)

Det har vært stilt spørsmål fra sykepleierne om det er nødvendig å ringe opp de fremmøtte om noen spørsmål er uteglemt, for å få komplett informasjon til spørreskjema og analysekort.

Utgangspunktet er at alle opplysninger er like viktige og skal påføres skjema og analysekort som avtalt.

Har noen allikevel glemt å få alle opplysninger, skal det **ikke** ringes opp til pasienten for å få komplettert skjema og analysekort.

Andre prosedyrer

Noter på dagrapport og målekortet navn og personnummer på dem som eventuelt nekter å ta blodprøve eller BT.

Spørreskjema, målekort, kvinnesamtykke samt og ett eksemplar av dagrapporten sendes samlet til prosjektkontoret. Pakken sendes som **NORGESPAKKE**

Blodkassen(ene) og ett eksemplar av en dagrapport(ene) **som angir antall blodprøver i den aktuelle blodkasse**, sendes Ullevål. Forsendelsen sendes/adresseres til:

STATENS HELSEUNDERSØKELSER
POSTENS GODSSENTER
0024 OSLO

NB: På adresselappen som følger blodkassene, øverst mellom postmerket og «Norgespakke» skrives undersøkelsessted og dato som blodprøvene er tatt.

Forsendelse av plasmarør og EDTA rør til / fra Haukeland
Her håper vi på å få forhandlet oss frem til en avtale med personell ansatt fra Bergen. Det er å håpe at mot en godtgjørelse pr dag/uke kan det bli levere/hentet materiell ved Haukeland sykehus.

Internt rapportskjema fra H/K lagene
SHUS laget sender utfylt skjema med event. tilleggs-skriv fra hvert undersøkelses sted.

Rekvirering av utstyr
(Etter tlf. samtale den 24.03.med dr. Refsum 24.03.98 MH)

fra Haukeland sykehus, v/ Halvor Bergersen, tlf. 55 97 46 78

- Pony vials plasmarør m/skrukork
- Isopor esker til forsendelse

SST rød, 10 ml bestilles fra SHUS

EDTA plastrør, 5 ml .og EDTA plastrør, 7 ml bestilles fra SHUS.

Spørreskjemaene tilhørende Tilleggsundersøkelsene
vil bli levert/sendt laget fra . HUSK, Bergen i god tid før oppstart i Fjell kommune.

Forsendelse av de ulike skjemaer som klientene fyller ut på stedet.

De få ekstra skjemaer som blir fylt ut på stedet, kan laget sende fortløpende til Haukeland i svarkonvolutt tilhørende svarskjemaene.

Fra 02.03.92

17500 deltakere

SAMTYKKE

Jeg har mottatt brosjyren sammen med innbydelsen til helse-undersøkelsen, og jeg er inneforstått med formålet med undersøkelsen.

Jeg samtykker i at resultatene fra undersøkelsen sendes den legen jeg har oppgitt på skjemaet. Dersom jeg *ikke* har oppgitt navnet på egen lege, samtykker jeg i at resultatene istedenfor sendes medisinsk faglig ansvarlig lege i min kommune.

Jeg samtykker også i at blodprøven blir nedfryst til eventuell senere forskning.

Underskrift

Fra 23.03.93

544 deltakere, ca 200 deltakere som er ilve har bare avgitt dette samtykket.

SAMTYKKE

Sammen med invitasjonsbrevet har jeg mottatt brosjyren som orienterer om helse-undersøkelsen. Jeg er derfor orientert om formålet med undersøkelsen.

1. Jeg samtykker i at mine resultater fra undersøkelsen sendes den legen jeg har oppgitt på spørreskjemaet.
2. Dersom jeg ikke har oppgitt navn på lege, samtykker jeg i at mine resultater sendes medisinsk ansvarlig lege i min kommune.
3. Jeg samtykker i at mine resultater brukes til statistikk og forskning og i forskningsøyemed kan kobles til andre registre som f.eks. kreftregister og dødsårsaksregister.

   Forutsetningen er at mitt navn og fødselsnummer fjernes før data studeres.

Vennligst stryk det/de avsnitt du eventuelt reserverer deg mot.

HUSK INFO

for fødselsårene 1925, 26, 27 og 1950, 51

Takk for at du deltok i den forrige Hordalandsundersøkelsen i 1992/93, og at du nå deltar i den nye Helseundersøkelsen i Hordaland, som har fått navnet HUSK. Den forrige undersøkelsen fikk frem mye verdifull informasjon, og satte for alvor Bergen og Hordaland på verdenskartet for forskning rundt kroniske sykdommer. Spesielt viktig var målingen av en ny risikofaktor for hjertekarsykdom: homocystein i blodet (se nedenfor).

Første fase av HUSK er den undersøkelsen du nå får tilbud om å delta i. Andre fase består i oppfølging av enkelte utvalg både på kort og lang sikt. Det er ikke satt noen spesiell tidsbegrensning for hvor lenge opplysningene kan lagres. Dette er fordi det i fremtiden kan komme ny informasjon som gjør at en vil belyse andre sider av helse og sykdom enn det som er kjent i dag. Fremtidig kobling til andre helseregistre vil kun skje etter godkjenning fra Datatilsynet, og slik at ingen opplysninger kan føres tilbake til den enkelte. Opplysningene fra de ulike delene av undersøkelsen vil kunne bli sammenstilt med hverandre, f.eks. vil en kunne se om de som har god sosial støtte har lavere blodtrykk eller blodkolesterol enn de med mindre god sosial støtte, eller om personer som har vært eller er i bestemte yrker er mer utsatt for eksem enn personer i andre yrker.

Ansvarlige for undersøkelsen - Styringsorganer

En styringsgruppe bestående av representanter for Statens Helseundersøkelser, HEMIL-senteret og Institutt for Samfunnsmedisinske fag ved Universitetet i Bergen er ansvarlig for HUSK. Fylkeslegen i Hordaland er observatør til denne gruppen. Koordineringen og den daglige styringen av prosjektet foregår fra Seksjon for forebyggende medisin, Universitetet i Bergen.

Økonomisk støtte

Til administrasjon og gjennomføring av delprosjekter er vi tildelt midler fra Norges forskningsråd, Sosial- og helsedepartementet, Kommunal- og arbeidsdepartementet, Det medisinske fakultet ved Universitetet i Bergen, L. Meltzers høyskolefond, Rådet for psykisk helse, Den Norske Kreftforening og Norsk osteoporoseforening. Vi er også tildelt støtte fra NHOs Arbeidsmiljøfond, Kavlifondet, Dr. Trygve Gythfeldt og frues forskningsfond, Røde fjær-aksjonen og farmasøytisk industri. Vi takker alle våre bidragsytere.

DELPROSJEKTER

- **Homocystein** i blodet er en ny risikofaktor for hjerte- og karsykdom. Den forrige undersøkelsen i 1992/93 gav oss verdifulle resultater. Blant annet ble det vist at noen forhold som kan føre til høyt homocysteinnivå i blodet er røyking, høyt kaffeinntak, lite mosjon og lavt inntak av frukt og grønnsaker. Andre studier tyder på at homocystein kan være en like viktig faktor som kolesterol med hensyn til risiko for hjerte- og karsykdom.

Du inviteres nå til en ny homocystein-undersøkelse. Denne tar sikte på å studere sammenhenger mellom kosthold, B-vitaminstatus og faktorer som påvirker homocysteinnivået, samt å kartlegge faktorer av betydning for endringer av homocystein. Videre vil variasjoner for gener som har betydning for omsetningen av B-vitaminer i kroppen bestemmes. Disse genene er ikke årsak til sykdom, men de kan sannsynligvis bidra til å forklare hvorfor forskjellige mennesker har ulikt behov for B-vitaminer. Disse analysene vil være av stor verdi fordi vi kan da finne ut om noen mennesker kan ha særlig nytte av et B-vitaminrikt kosthold, eller tilskudd av B-vitaminer. Blodprøven som lagres vil senere kunne undersøkes for andre faktorer knyttet til kroppens omsetning av B-vitaminer. For å måle kostens innhold av B-vitaminer og andre faktorer, ber vi deg om å fylle ut et spørreskjema om dine kostvaner, samt et skjema som bl.a. omhandler eventuell sykdom siden forrige undersøkelse. Personer med sterkt forhøyet homocystein og tegn på alvorlig mangel på B-vitaminene folat eller B-12, vil få tilbud om etterundersøkelse. For de fleste deltakerne vil det ikke være noen unormale funn, og det vil ikke bli gitt tilbakemelding.

- **Muskel-skjelett sykdommer**. Dere vil også få et tilbud om målinger av benmineraltetthet som mål på osteoporose (benskjørhet). Osteoporose er en tilstand som rammer svært mange kvinner etter som de blir eldre, og også en del menn. Den alvorligste følgen av osteoporose er benbrudd. I dette prosjektet vil sammenhengen mellom mengde mineraler i skjelettet og andre faktorer som påvirker osteoporose belyses blant annet vil kroppssammensetningen, som prosent fett, måles. Målingene vil foregå på Haukeland sykehus og er helt ufarlige.

- Det vil også gjøres en studie på forekomsten av **Sjögrens syndrom**, som er en reumatisk lidelse, med kartlegging av forskjellige faktorers betydning for denne tilstanden.

- **Hukommelse og minne.** Dette prosjektet gjelder kun for de som er født i 1925-27. Mye tyder på at homocystein og B-vitaminer i kosten kan ha betydning for hukommelse og minne etter som vi blir eldre. Gjennom et intervju med en sykepleier/hjelpepleier vil deltakernes hukommelse, minne, orienteringsevne og forståelsesevne bli belyst.

- **Lungefunksjonstest (spirometri).** Her vil deltakernes lungekapasitet bli målt ved en pusteprøve, og forekomsten av astma vil bli kartlagt.

- **Arbeidsrelaterte plager i Hordaland**. Som følge av liten kunnskap om arbeidsrelaterte plager i Norge tas ofte avgjørelser m.h.t. forebyggende tiltak på tildels manglende grunnlag. Dette prosjektet vil bl.a. undersøke forekomsten av yrkesrelatert hjerte-karsykdom, muskel-skjelettplager, vibrasjonsskader, håndeksem og forplantning.

- **Subjektiv helse, livskvalitet og søvn** skal kartlegge forekomst av og sammenheng mellom helseplager og livskvalitet, som for eksempel søvnplager.

- **Sosiale prosesser.** Her vil man forsøke å identifisere hvilke sosiale prosesser som påvirker helsen. **Angst og depresjon** vil også bli belyst.

- **Hemokromatose** er en arvelig stoffskiftesykdom som fører til jernoverskudd som kan gi organskade og sykdom. Undersøkelsen tar sikte på å kartlegge forekomst, og dernest å identifisere behandlingstrengende personer for videre oppfølging.

husk

HORDALANDSUNDERSØKELSEN '97 - '99 (HUSK)

SAMTYKKEERKLÆRING

I brosjyren "HUSK" er jeg orientert om Hordalands-undersøkelsens formål. Jeg har også sett informasjonsskrivet "HUSK INFO" som bl.a. omtaler delprosjekter, og er kjent med at undersøkelsen består av spørreskjema, blodprøve og måling av blodtrykk, høyde, vekt, liv- og hoftevidde.

Jeg er kjent med at opplysninger om meg blir behandlet strengt fortrolig og at undersøkelsen er vurdert og tilrådd av Den regionale komité for medisinsk forskningsetikk og godkjent av Datatilsynet. Det er ikke satt noen spesiell tidsbegrensning for hvor lenge opplysningene kan lagres, men jeg er klar over at jeg på hvilket som helst tidspunkt kan trekke meg fra undersøkelsen og kan reservere meg mot bruk av opplysninger om meg.

1. Jeg samtykker i at resultater fra blodprøven og andre deler av undersøkelsen, samt resultater fra eventuelle spesialundersøkelser, blir sendt til den legen jeg har oppgitt på spørreskjemaet.

2. Dersom jeg ikke har oppgitt navn på lege, eller legen min ikke deltar i undersøkelsen, samtykker jeg i at mine resultater sendes til kommunelege I.

3. Jeg samtykker i at jeg kan få tilbud om spesialundersøkelser, og at jeg kan bli kontaktet av en lege med tanke på tilbud om behandling eller for å forebygge sykdom.

4. Jeg samtykker i at mine resultater kan brukes til medisinsk forskning, eventuelt ved å sammenholde opplysninger om meg med opplysninger fra andre helse-, trygde- og sykdomsregistre, eller med mine resultater fra tidligere helseundersøkelser i Hordaland. Når disse opplysningene sammenholdes, vil mitt navn og personnummer ikke bli tatt med.

5. Jeg samtykker i at blodprøve oppbevares. All bruk av denne vil bare skje etter godkjenning fra Datatilsynet og Den regional komité for medisinsk forskningsetikk.

Vennligst stryk det/de avsnitt du reserverer deg mot.

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