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Uric acid - its role as a risk factor for the metabolic syndrome, cardiovascular and kidney disease

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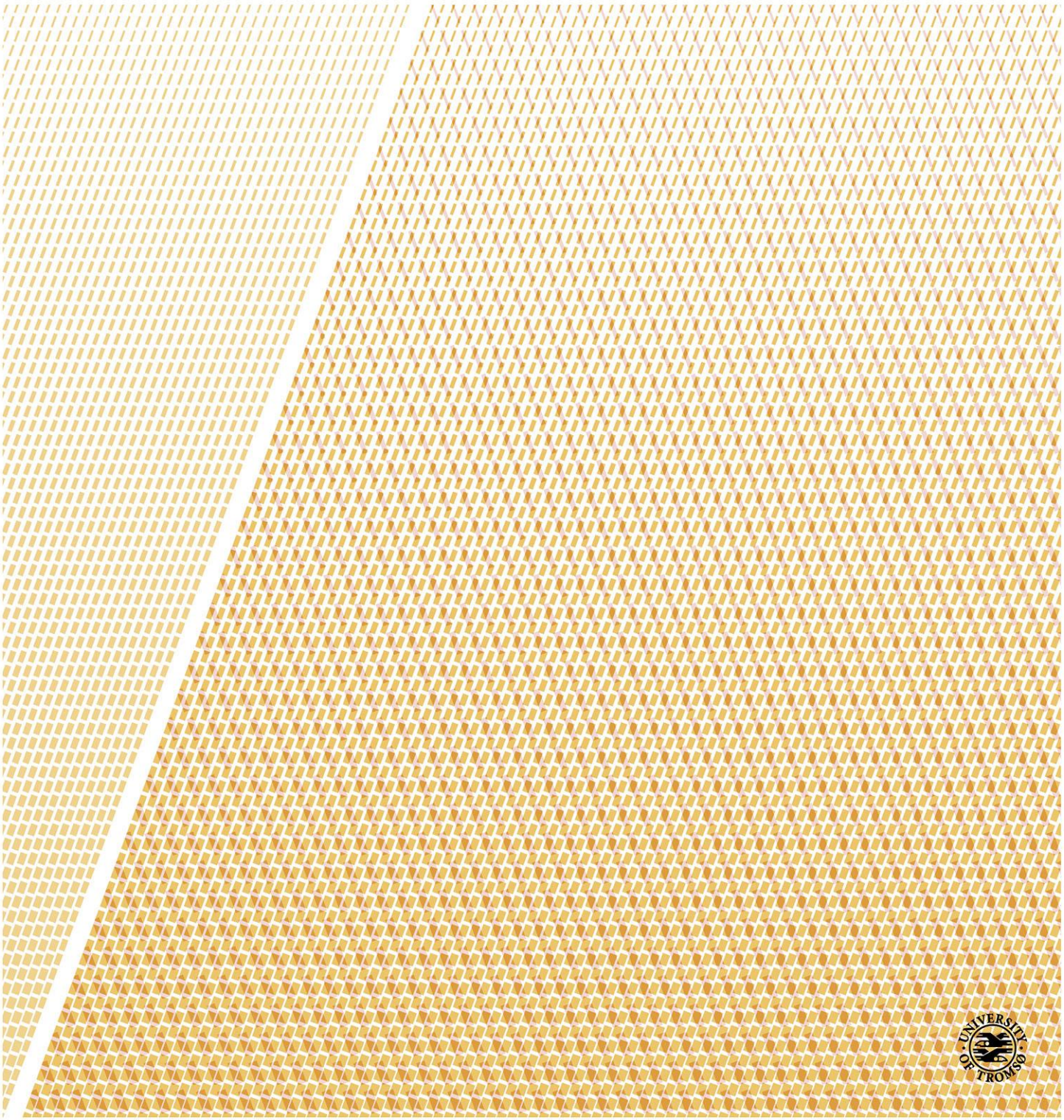


Contents

ACKNOWLEDGEMENTS

SUMMARY

Uric acid as a potential risk factor for cardiovascular and renal conditions has gained renewed attention. In this work we aimed to assess the associations between serum uric acid, metabolic syndrome, hypertension, renal dysfunction, cardiovascular events and mortality.

In paper I, 6083 participants from Tromsø 4 were stratified according to body mass index. Endpoints were the metabolic syndrome and each component of the syndrome after seven years. Increased levels of baseline serum uric acid independently predicted development of hypertension and higher fasting glycemia in the overweight, but not in the normal-weight subjects. Baseline and longitudinal serum uric acid were both predictors of future metabolic syndrome.

A prospective study that included 2637 participants who participated in Tromsø 4, 5 and 6 was described in paper II. We assessed the associations between change in serum uric acid during follow-up, baseline serum uric acid and renal dysfunction (defined as albumin-creatinine-ratio ≥1.13 mg albumin/mmol creatinine and/or estimated glomerular filtration rate < 60 ml/min/1.73 m^2). Participants were stratified according to tertiles of change in serum uric acid between baseline and follow-up 13 years later. The upper tertile, compared to the two lower tertiles, had a doubled risk of renal dysfunction after 7 years, and after 13 years the odds ratio for renal dysfunction was 2.18. The risk of developing albumin-creatinine-ratio ≥1.13 mg/mmol alone was also significantly increased. An increase in baseline serum uric acid of 59 μmol/L gave an odds ratio of 1.16 for renal dysfunction after 13 years.

In paper III, we included 5700 participants from Tromsø 4, and assessed the associations between serum uric acid and all-cause mortality after 15 years, and fatal or non-fatal myocardial infarction and ischemic stroke after 12 years. Serum uric acid was associated with all-cause mortality in men and women, even after adjustment for blood pressure, estimated

glomerular filtration rate, urinary albumin creatinine-ratio, drug intake and traditional cardiovascular risk factors. After the same adjustments, serum uric acid was associated with a 31% increased risk of stroke in men. No independent association between increment in serum uric acid and myocardial infarction was observed.

Our findings support the view that serum uric acid is associated with obesity, metabolic syndrome and hypertension, but also is a risk factor for cardiovascular and kidney disease, independently of these risk factors. Moreover, increasing values of serum uric acid over time may imply an even higher risk.

LIST OF PRESENTED PAPERS

The thesis is based on the following papers:

I. Norvik JV, Storhaug HM , Ytrehus K, Jenssen T, Zykova S, Eriksen BO and Solbu MD. Overweight modifies the longitudinal association between uric acid and some components of the metabolic syndrome: The Tromsø Study. BMC Cardiovascular Disorders 2016 May 10; 16:85.

II. Storhaug HM, Toft I, Norvik JV, Jenssen T, Eriksen BO, Melsom T, Løchen ML, Solbu MD. Uric acid is associated with microalbuminuria and decreased glomerular filtration rate in the general population during 7 and 13 years of follow-up: The Tromsø Study. BMC Nephrology 2015 Dec 11; 16:210.

III. Storhaug HM, Norvik JV, Toft I, Eriksen BO, Løchen ML, Zykova S, Solbu MD, White S, Chadban S, Jenssen T. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study. BMC Cardiovascular Disorders 2013 Dec 11;13:115.

ABBREVIATIONS

ACR	urinary albumin-creatinine ratio
BMI	body mass index
BP	blood pressure
CI	confidence interval
CHD	coronary heart disease
CKD	chronic kidney disease
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
HDL	high density lipoprotein
HR	hazard ratio
HUNT study	Nord-Trøndelag Health Study
IR	incident rate
LIFE	The Losartan Intervention For Endpoint reduction
MetS	metabolic syndrome
MDRD	Modification of Diet in Renal Disease
NCEP-ATPIII	The Third Report of the National Cholesterol Education Program (NCEP) Expert panel on Detection, Evaluation and Treatment of High

	Blood Cholesterol in Adults (Adult treatment panel III; ATP III)
NHANES	the National Health and Nutritional Examination Survey
NO	nitric oxide
OR	odds ratio
RD	renal dysfunction
RCT	randomized controlled trial
SD	standard deviation
SUA	serum uric acid
TIA	transitoric ischemic attack
UA	uric acid
WHO	World Health Organization
XDH	xanthine dehydrogenase
XO	xanthine oxidase
XOR	xanthine oxidoreductase

1. INTRODUCTION

Mortality from coronary heart disease (CHD) and stroke has decreased substantially over the last 5- 10 years. [1] However, cardiovascular disease (CVD) is still the most common cause of death globally: The 2010 Global Burden of Disease study estimated that CVD caused 15.6 million deaths worldwide. [1] When considering risk factors for CVD, a noticeable finding is that the geographic distribution of traditional risk factors is changing. The epidemic of overweight and obesity is increasing worldwide with considerable health and cost-implications.[2, 3] While body mass index (BMI) and diabetes prevalence have increased in most countries and globally, [2, 4, 5] blood pressure (BP) has declined in some high-and middle-income regions. It has, however, remained unchanged or even increased in some low-income countries.[6] Cholesterol has also declined in western countries, whereas values are increasing in East and Southeast Asia. [7] Smoking remains a notable contributor to non-communicable diseases risk.[8, 9] The above-mentioned risk factors are currently being addressed by health authorities, and effort is made to implement preventive strategies. Nevertheless, although the risk factors listed above are important, there are still unexplained etiologic factors contributing to the mortality and morbidity associated with CVD, and there is still a need to identify novel modifiable risk factors. In addition, the risk factors associated with CVD are of importance not only for CVD, but also for other conditions, and especially renal diseases. The definition of the cardio-renal syndrome [10] has enhanced the awareness of the bidirectional interactions between kidney and heart diseases.[11] Chronic kidney disease (CKD) and CVD share many of the same risk factors. Moreover, the burden of CKD has become an increasing problem in a global perspective.[12-14] A systematic analysis of mortality in Lancet in 2013 stated that CKD is rising as a non-communicable disease of global concern, but its importance has been neglected. Along with life style factors mentioned above, including change in diet and increasing obesity, a former

player has re-entered the scene. When exploring the literature concerning the etiology of CVD and CKD, the biologic substance uric acid (UA) has gained growing attention. [15]. Several researchers point on UA as a putative harmful substance in the etiology of CVD and CKD, but studies have yielded conflicting results. [16-20]

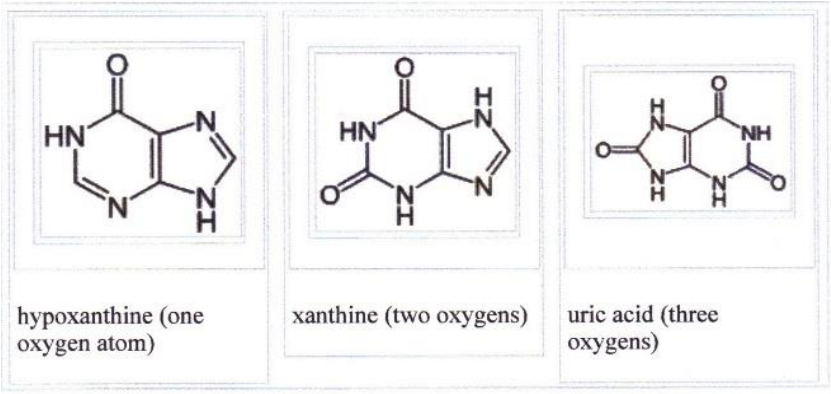
In this work, the role of UA in various conditions has been explored. We have studied the associations of serum uric acid (SUA) with development of hypertension, other components of the metabolic syndrome (MetS), renal dysfunction (RD), CVD and mortality. In the population based Tromsø Study, SUA has been measured repeatedly. Thus, in contrast to many other studies, we were able to look at the impact of change in SUA level during a period of time, in addition to the baseline value.

1.1 Background

UA is generated during the breakdown of purines from DNA, RNA, ATP and cAMP to hypoxanthine. Further breakdown to xanthine and UA (2,6,8-trihydroxypurine, $C_5H_4N_4O_3$,) (Figure 1) is done mainly in the liver by the action of the enzyme xanthine oxidoreductase (XOR), which can exist in two forms, xanthine dehydrogenase (XDH) or xanthine oxidase (XO). [19] The enzyme is mostly in its XDH form, but can be transformed into XO by proteolytic cleavage or oxidation. Reactive oxygen species are a by-product of the reaction from hypoxanthine to xanthine and from xanthine to UA. [21, 22] In humans, UA is the final product, whereas in most mammals UA is further degraded into 5-hydroxyisourate by the enzyme uricase, eventually producing allantoin, which is highly soluble and easily excreted.[23] Due to a series of mutational silencing events in its gene during hominoid evolution, humans, and their great ape relatives, do not have a functional uricase.[24] This results in urate levels that are much higher in humans; averaging between 240-366 µmol/L

(4.0-6.0 mg/dL) compared to other mammals that generally have SUA in the range 30-120 μmol/L (0.5–2.0 mg/dL).[17]

Most circulating UA is freely filtered by the kidney, with roughly 90 % of the filtered load being reabsorbed in the proximal tubule.[25] UA is also subjected to tubular secretion, and thus the renal handling of UA is complex. A smaller proportion of UA, approximately 1/3, is excreted into the intestine and further metabolized by resident gut bacteria.[26] UA is a weak diprotic acid (has two dissociable protons), and at the physiologic pH (7.4), a proton dissociates from ~99% of UA molecules, and thus most UA is present in the extracellular fluid as the anion urate. Because the ratio of urate to UA in the circulation remains constant with constant pH, the terms *urate* and *uric acid* are often used interchangeably to refer to the total pool of UA, dissociated and un-dissociated.[26] Due to the high concentration of sodium in the extracellular compartment, urate is mainly present as monosodium urate, with a low solubility limit (about 380 μmol/L). [27] When urate solubility is exceeded, monosodium urate crystals develop in and around the joints. This crystal formation is responsible of acute gout and, over time, of chronic gout; but only a small proportion of people with hyperuricemia will develop clinical gout.[15]



Hypoxanthine + H_2O + O_2 ⟷ Xanthine + H_2O_2

$$\text{Xanthine} + H_2O + O_2 \longleftrightarrow \text{Uric acid} + H_2O_2$$

Figure 1

UA is accumulated in the body due to increased production, such as with cell death, intake of alcohol or a purine rich diet.[16, 28-30] Also a diet with excess sugar increases the SUA level, because the sugar-component fructose causes increased UA production. Otherwise, accumulation of UA is caused by decreased elimination, which is the case in impaired renal function or with the use of diuretics or certain other medications.

The biologic action of UA is a paradox in the way that although it is considered the strongest circulating anti-oxidant of the body, [20] it can be pro-oxidative under certain conditions. [31, 32] In recent research there has been focus not only on crystal development as a cause of disease. Apparently, also a modest rise in SUA may be harmful. In the process of generating UA, XO also generates reactive oxygen species. It has been hypothesized that harmful mechanisms are initiated during this process, either through UA generation with increased oxidative stress, or through elevated UA per se. [15, 17-20, 33]

1.1.1 Historical perspectives

A state-of-the-art review has looked carefully at the role of UA from its discovery in the early 1800s, when it was considered a causal factor not only for gout, but also for a variety of cardiovascular and renal conditions, until its “requiem” as a risk factor was celebrated in a review article in Kidney International in 1986.[20] The fact that hyperuricemia was considered a risk factor was not surprising, as natural history showed that 25–50% of gouty subjects had hypertension, 75% were obese, 25% died with kidney failure, and 90%

developed cardiac disease, making gout the most important cardiovascular risk factor then known.[20]

Described by Hippocrates during the Golden Age of Greece, gout was originally a disease of the affluent, primarily observed in middle-aged men of the wealthy upper class ("the Patrician malady").[34] Being "disease of kings and king of diseases," gout has afflicted kings (including Alexander the Great and Henry VIII), statesmen (including Benjamin Franklin), artists (including Voltaire), and scientists (including Isaac Newton, Charles Darwin, and Leonardo da Vinci). Chronic lead intoxication from contamination of wine and food has also been implicated in the epidemics of gout that affected both the Roman Empire and Victorian England, since lead toxicity impairs the ability of the kidney to excrete UA. In 1897, in his presidential address to the American Medical Association, Dr. Davis wrote, "High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increase the tonus of the [renal] arterioles.[35]

By the mid-1900s, however, the causal nature of UA in these conditions was questioned, as it was recognized that the association of gout with CVD might simply reflect that gout and cardiovascular complications had similar risk factors (obesity, kidney disease, etc.). This was addressed in epidemiologic studies by asking whether SUA was an independent risk factor for cardiovascular and renal disease, while controlling for other known risk factors.

Some studies continued to find that SUA was an independent risk factor; however, others did not. The inconclusiveness of the data, the supposition that soluble UA was biologically inert or even an antioxidant, and the finding that the increase in SUA might be secondary to either a decrease in renal function or the presence of hyperinsulinemia, all led to the conclusion that SUA most likely was not a true cardiovascular or renal risk factor. In the 1980s, SUA was removed from some of the common laboratory panels, markedly reducing the available epidemiologic data on SUA in otherwise healthy persons and those suffering from CVD.[36]

The move was made because serious side effects from the urate lowering drug allopurinol were observed in patients with asymptomatic hyperuricemia, with an intention to reduce the risk of harm to these patients.

1.1.2 Definitions of hyperuricemia

Currently, no general consensus exists regarding how to define hyperuricemia. In an article where different definitions of hyperuricemia were explored, the authors claimed that such discrepancies preclude comparison of data from different studies and may be seen as a barrier to the understanding of gout by physicians and patients. [37] SUA is generally lower in women than in men, but in both genders distributions grossly follow Gaussian curves. [38-40] Thus, a statistical definition of hyperuricemia is possible with a SUA concentration lying more than two standard deviations (SD) above the mean. This definition, which gives higher normal values for males than for females, is being used in most laboratory reports. [40] As gout is known to follow crystallization of monosodium urate, a physicochemical definition of hyperuricemia as a concentration above the saturation point, (which is about 380 µmol/L) may also seem logical. In this view, there is no obvious reason to differentiate men from women. [40] In our studies we chose to define hyperuricemia in the same way as in the U.S National Health and Nutrition Examination Survey (NHANES) 2007–2008, as SUA ≥ 417 µmol/L (7 mg/dL) in men and ≥339 µmol/L (5.7 mg/dL) in women.[41]

1.2 Distribution of elevated SUA in the population

Epidemiologic studies show that mean SUA levels in men have increased gradually from the 1920s to the 1970s, from less than 210 µmol/L to 360-390 µmol/L.[18] High levels of SUA is prevalent in the general population; in the NHANES 2007-08 cohort hyperuricemia was present in 22 % of women, and 21 % of men.[41] In the US, the prevalence of gout more than

doubled between 1969 and 1985, [42] may have increased further over the past two decades, and parallels a significant increase in the prevalence of hyperuricemia.[41]

Age does not significantly affect SUA levels in men, but in women the levels are progressively higher in the older age groups. The rise occurs gradually, with the greatest increment in the decade between forty and fifty, an effect presumably related to the menopause. [37] Pre-menopausal women tend to have lower levels than men, probably because of the uricosuric effect of estrogens.[38]

In an article exploring the distribution of SUA levels worldwide, [39] the authors have only investigated men because of what they call « the confounding effect of estrogen in pre-menopausal women.» Examination of these data shows that e.g. most Pacific Island populations and their proposed ancestral populations have higher occurrence of hyperuricemia, and a high mean SUA level of 390 µmol/L (6.5 mg/dL). While some of this variation could relate to differences in lifestyles and environment, the authors think that ancestry also is a likely contributing factor: it is feasible that SUA concentrations may have been positively selected under certain environmental conditions. Environment also has an effect on SUA levels; a number of studies have been sampled from both urban and rural cohorts from within the same population to help understand the effects of urbanized living.[43-50] Higher SUA levels were generally observed in those inhabiting an urban environment. In general, living in an urban environment exacerbates the tendency towards elevated SUA levels, concomitant with the increased consumption of foodstuffs such as sugar-sweetened beverages and alcohol that increase urate.[28, 51, 52] However, the fact that even those living rurally and with more traditional lifestyles in Polynesia have high rates of hyperuricemia, compared to other populations worldwide, suggests a genetic predisposition, leading to the variability which we see in modern populations globally.[39, 53] It has been

suggested that the higher SUA levels in this population may explain their higher frequency of obesity and diabetes compared to other peoples throughout the world.[54]

A few studies have explored racial and ethnical differences also in other parts of the world, and found evidence for genetic influence of SUA levels in different racial/ethnic groups. [55, 56] In one study, lower SUA was found among African than Caucasian men, [57] whereas others have found higher SUA in black compared to white persons. [16] However, the first study was performed in South Africa, and the other in the US.

1.3 Uric acid as a risk factor for the MetS

MetS is a constellation of interrelated risk factors that increases the risk of CVD and type 2 diabetes.[58]

There are several definitions of the MetS. Among the most frequently used definitions is the revised National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria published by the American Heart Association. Any three (or more) out of five of the following criteria constitute the diagnosis of MetS: [59]

•Increased waist circumference (≥ 88 cm in women and ≥ 102 cm in men)

•Elevated triglycerides (≥ 1.7 mmol/L or the use of lipid-lowering drugs)

•Reduced high density lipoprotein (HDL)-cholesterol (< 1.30 mmol/L in women and < 1.03 mmol/L in men)

•Elevated BP (≥ 130 mmHg systolic BP, ≥ 85 mmHg diastolic BP or antihypertensive drug treatment)

•Elevated fasting glucose (glucose ≥ 5.6 mmol/L or on treatment for elevated glucose)

The prevalence of MetS increased significantly between NHANES 1988-1994 and NHANES 1999-2006, and one of the main reasons for this was the increase in abdominal obesity. [60] The worldwide increase in the prevalence of hyperuricemia is considered to be directly related to the increasing incidence of obesity and the MetS in developing countries, [61] as well as in developed countries.[62] Increased SUA concentration correlates strongly with obesity and the MetS. [63, 64] Historically, the elevated level of SUA observed in MetS has been attributed to hyperinsulinemia, since insulin reduces renal excretion of UA. [18, 65] However, hyperuricemia often precedes the development of hyperinsulinemia, [18, 65, 66] obesity,[67] and diabetes.[66, 68, 69] Hyperuricemia may also be present in the MetS in people who are not overweight or obese.[18] MetS occurs in up to 76 % of patients with gouty arthritis.[70, 71]

It has been suggested that UA may cause MetS by promoting a state of insulin resistance. It is well known that insulin stimulates glucose intake in skeletal muscle also via increased blood flow to these tissues through a nitric oxide (NO)-dependent pathway. UA decreases levels of NO, reduces arterial dilatation and blocks the action of insulin, resulting in increased insulin resistance and hyperinsulinemia.[72] The relationship may also be a result of the stimulating effect of insulin on urate reabsorption in the proximal tubule.[67]

1.4 Uric acid as a risk factor for hypertension

Numerous studies have reported that hyperuricemia carries an increased risk for development of hypertension independent of other risk factors.[18, 35] The strength of the relationship between SUA level and hypertension decreases with increasing patient age and duration of hypertension, suggesting that UA may be most important in younger subjects with early-onset

hypertension.[18, 35] The controversy over the role of UA in hypertension stems from the lack of plausible mechanisms and its overlap with other more conventional risk factors for hypertension such as renal disease, diabetes and obesity.[36] However, in 2001, animal experiments by Johnson and colleagues suggested a plausible cause-and-effect-relationship. Using a rat model of pharmacologically induced hyperuricemia, they showed that increased SUA levels resulted in hypertension within 2 weeks. Early hypertension was completely reversible with urate reduction, but prolonged hyperuricemia resulted in irreversible sodium-sensitive hypertension that became UA independent. These mechanistic studies supported a UA-mediated activation of the renin-angiotensin system, a system with rapid onset that can also be rapidly controlled, followed by a more gradual alteration of renal microvascular geometry and sodium handling that resulted in chronic salt-sensitive hypertension. The renal microvascular disease was shown to occur independently of hypertension and clinically resembled the renal arteriosclerosis lesion of human hypertension.[18, 20, 65] The observation that the microvascular changes still developed, even when BP was controlled by a diuretic, coupled with the demonstration of direct effects of UA on endothelial cells and vascular smooth-muscle cells, suggested that UA could cause microvascular disease independently of hypertension. [18] In experiments with cultured vascular smooth-muscle cells, UA was able to induce cellular proliferation, inflammation, oxidative stress, and activation of the local renin–angiotensin system.[18] However, these findings were made in animals.

Concerning human biology and SUA, an interesting renal biopsy study was performed in 2013: [73] In a cross-sectional study of 167 CKD patients, it was found that as the SUA level increased, the degree of renal arteriolar hyalinosis and wall thickening worsened. These results suggest that hyperuricemia may be related to renal arteriolar damage in patients with CKD.

There are a few randomized controlled trials (RCT)s that explore the effect on BP when decreasing SUA with medication. Of special interest are the RCTs where hyperuricemic

adolescents with an early stage of hypertension were randomized to SUA lowering agents versus placebo.[74] Thirty adolescents were randomized to allopurinol or placebo for four weeks; 70 % of the participants were obese. BP in the allopurinol-group decreased significantly compared to the placebo group. It is not possible to state whether the effect of allopurinol to lower BP was explained by the lowering of SUA, or by inhibition of XO with reduced production of reactive oxygen species.

To explore this further, the authors performed a similar trial in 2012.[75] Prehypertensive obese adolescents were randomized to allopurinol, the uricosuric drug probenecid or placebo. Subjects treated with either allopurinol or probenecid exhibited a significant reduction in BP, and therefore the effect was probably due to reduction in UA rather than to XO inhibition. This suggests that at least in adolescents with prehypertension, UA may cause increased BP that can be mitigated by urate lowering therapy. An additional surprising effect was that participants on urate lowering therapy ceased to gain weight. The authors summarize that allopurinol and probenecid treatment resulted in similar BP responses, which implicates UA as the biochemical mediator of increased BP.[75]

To explore change in BP after allopurinol initiation in older patients, data from the UK Clinical Practice Research Datalink was used in a propensity-matched design.[76] Data were extracted for patients with hypertension aged >65 years who were prescribed allopurinol with readings of BP pretreatment and during treatment. Data from comparable controls were extracted. The change in BP in patients with stable BP medication was the primary outcome and was compared between groups. Three hundred sixty-five patients who received allopurinol and 6678 controls were included. BP fell in the allopurinol group compared with controls. There was a trend toward greater fall in BP in the high-dose allopurinol group, but change in BP was not related to baseline UA level. The authors conclude that allopurinol use is associated with a small fall

in BP in adults and that further studies of the effect of high-dose allopurinol in adults with hypertension are needed.[76]

When exploring the literature of the associations between SUA, hypertension and the MetS, fructose intake has been extensively debated. Fructose raises UA levels rapidly via activation of the fructokinase pathway in hepatocytes. Fructokinase consumes ATP, leading to an increased load of intracellular purines requiring metabolism and disposal through XO-mediated metabolism, ending in UA.[36]

Through the 18.century there was an increasing production of sugar from sugar beets.[77] Sucrose is a disaccharide of glucose and fructose, produced from these plants, and used as table sugar and food additive. As one of the components of sucrose is fructose, increased intake of sugar, will lead to increased fructose-consumption. Although fructose is present in significant quantities in fruits, the largest single source of fructose in the diet is added sugars consumed in desserts, candies and sweetened beverages. [78]

Globally, the main source of fructose is sucrose, which constitutes >90% of the energizing sweeteners used in the world. [79] However, in the U.S it is common to use so called high fructose corn syrup, generated from maize, which is easily available, and less expensive than sugar.

Experimental data support a link between fructose intake, hyperuricemia, and increases in BP. Rats fed with high doses of fructose developed hyperuricemia, hypertension and a metabolic-like syndrome with renal hemodynamic and histologic changes, very similar to those observed with hyperuricemia. Treating these rats with the XO inhibitors allopurinol or febuxostat, lowered UA levels and prevented these changes. [18] In humans, one of the most important problems with excess fructose intake seems to be increased *de novo* lipogenesis, and thus altered blood lipid profile seems to be the most prominent feature. [79]

Sharp criticism to the fructose hypothesis has also been raised.[80] It has been claimed that too much research money has been spent on this issue when trends show that fructose consumption actually is declining, while obesity is still increasing. Moreover, the animal studies have been criticized for the fact that the rats were fed with very high doses of fructose. In a Norwegian review on the role of fructose, the author concluded that evidence is lacking that a normal consumption of fructose (approximately 50–60 g/day) increases the risk of atherosclerosis, type 2 diabetes, or obesity more than consumption of other sugars. [79] However, a high intake of fructose, particularly if combined with a high energy intake in the form of glucose/starch, may have negative health effects via de novo lipogenesis. The author concluded that more studies are needed that explore the impact of normal fructose consumption.[79]

To summarize, a major research effort has been made to describe the associations between SUA, hypertension and MetS, but there are still areas of significant uncertainty. SUA as a risk factor for hypertension has been studied extensively. However, there is a need to gain knowledge about differences between subgroups, including different age groups and various categories of obesity. As focus on individually targeted strategies is growing in modern medicine, and currently also is used in antihypertensive treatment, options may expand when the impact of SUA is further explored. Large RCTs in adolescents as well as other populations of various risk may reveal important knowledge. In addition, we still need observational data to further explore associations of importance, such as the possible impact of SUA on long-term dysmetabolic changes.

1.5 Uric acid as a risk factor for kidney disease.

CKD has emerged as a global health problem of epidemic proportions over the last few decades.[81] The prevalence of end-stage renal disease (ESRD), and the number of patients on

renal replacement therapy, is steadily increasing, and these patients have a 10-fold mortality rate.[82] Impaired kidney function increases the risk not only for ESRD and dialysis, but also for CVD. [83, 84]

In 2002, the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines defined CKD as glomerular filtration rate (GFR) <60 mL/min per 1,73 m^2 for ≥ 3 months,[13] and proposed a classification scheme based on GFR.[85] Later studies have shown that albuminuria also has an important effect on outcomes.[86] This made the Kidney Disease Improving Global Outcomes (KDIGO) Work Group on Evaluation and Management of Chronic Kidney Disease to include albuminuria in the revised 2012 classification.[13]

Even mild abnormalities in measures of renal structure and function are associated with increased risk of kidney failure or development of complications in other organ systems, especially CVD.[12]

In the article in Lancet cited above, [12] the authors describe CKD in relation to the MetS. It is known that hypertension and diabetes are important risk factors for ESRD. However, why some individuals with MetS develop albuminuria and decrease in GFR before the development of hypertension or diabetes is not known. One possibility is that underlying mechanisms, such as endothelial dysfunction and oxidative stress, might drive both kidney damage and the MetS. [12] Some authors think that diets high in added sugars (which implicates excess fructose) might have a key role in development of MetS and kidney disease by elevating UA. [87] Mild kidney disease was induced in rats fed a high fructose diet.[88] Low-grade systemic inflammation, which is present in these disorders, could also result in changes in adipokines and other substances that can affect glomerular capillary wall function.[89].

Hyperuricemia has been recognized as a risk factor for the incidence and progression of CKD, although studies have reported conflicting results (Table 1). [82, 90-100] A major methodological problem concerning UA and kidney function is that of reverse causality. UA is eliminated mainly through the kidneys, and raised UA levels could be a consequence rather than a cause of reduced kidney function.

In 2009, the result of a large study focusing on risk factors for ESRD was published.[93] As many as 177570 individuals from an integrated health care delivery system in Northern California were followed for 25 years. The 2 most potent risk factors were proteinuria and excess body weight. However, the study also identified several novel risk factors for ESRD, among them a higher level of SUA. Large prospective observational studies show that increased SUA levels predict the development and progression of CKD in various populations (Table 1).[14, 82, 92-94, 98, 101-107] Studies have also suggested that UA may be an independent predictor of the development of microalbuminuria.[70, 108]

Before SUA lowering drugs became available, more than 50% of patients with gout had some renal insufficiency, and nearly 100% had renal disease at autopsy.[18] The kidney lesions in patients with gout are characterized by advanced arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis, often with the presence of urate crystals in the outer medulla. The presence of such urate deposits gave rise to the name "gouty nephropathy" for this condition. However, the hypothesis that renal injury was caused by the deposition of urate crystals seemed incomplete, considering that the crystal deposition was focal, and thus unlikely to explain the diffuse nature of the disease. Crystals may also be found in normal kidneys in the absence of inflammation. Furthermore, the most characteristic findings, which are advanced arteriolosclerosis and glomerulosclerosis, are indistinguishable from those observed with longstanding hypertension or age-related glomerulosclerosis, may simply reflect the fact that

most patients with gout have hypertension and are older. Consequently, for the past 30 years there has been a widespread belief that UA is unlikely to be a risk factor for renal disease. [18]

However, both experimental and clinical studies suggest the possibility that an elevated level of SUA itself can lead to kidney disease without the deposition of UA crystals.[109, 110] Experimental studies in rats have shown that elevated SUA levels can cause de novo kidney disease as well as accelerate existing kidney disease.[109, 110] In rats, the mechanism of injury appears to be related to the development of preglomerular arteriolar disease that impairs the renal autoregulatory response, thereby causing glomerular hypertension. [18, 111]

As mentioned earlier, a human cross-sectional study has assessed the association between SUA and changes in renal tissue. [73] In patients with CKD it was found that with higher SUA levels, the degree of renal arteriolar hyalinosis and wall thickening worsened.

In a recently published meta-analysis that included fifteen unique cohorts, the investigators demonstrated a positive association between SUA levels and the risk of CKD, defined as eGFR <60 mL/min/1.73 m^2 at the follow-up examination, in middle-aged patients, independent of established metabolic risk factors. The risk for CKD increased by 20 % per 59 µmol/L (1 mg/dL) rise in SUA. They conclude that future randomized, high-quality RCTs, are warranted to determine whether lowering SUA levels is beneficial in CKD.[14]

Recent studies suggest that lowering levels of UA in patients with hyperuricemia may slow progression of renal disease. A study showed that the treatment of asymptomatic hyperuricemia in patients with CKD stage 3 resulted in delayed disease progression. Among patients treated with allopurinol, 16 % progressed to ESRD, compared to 46 % in the control group. [112]

Another RCT showed that treatment of asymptomatic hyperuricemia with allopurinol improved eGFR. [113]

To summarize, despite of the methodological challenges with reverse causality, SUA has been increasingly assessed as a risk factor for CKD in epidemiological studies. Some RCTs have also been performed, although they are small in design. There is a need for high-quality RCTs to replicate the findings that decreasing SUA may be beneficial for CKD patients, and prevent CKD in those having hyperuricemia. In addition, in most of the epidemiological studies performed so far, CKD has been defined on the basis of GFR alone. By including albuminuria in the definition, also subtle renal damage may be captured. Also, most studies assess SUA as a single measurement, and little is known about the impact of longitudinal change in SUA.

Table 1. Overview of epidemiologic studies assessing uric acid as a risk factor for kidney disease

Authors, year, country	Study population and design	n	Follow-up time baseline	Covariate adjustment	Limitations stated by authors	Major findings
Domronkitcaiporn et al. 2005, Thailand	Employees of the Electric Generation Authority	3499	12 years 1985	Age, sex, BMI, smoking, eGFR, proteinuria, systolic and diastolic BP, diabetes, cholesterol	MDRD formula not validated in their population. No s-albumin	OR: 1.82 (1.12, 2.98) for decreased kidney function for SUA in fourth quartile compared to first quartile
Chonchol et al. 2007, US	General population > 65 in the Cardiovascular Health Study	5808	6.9 years 1989	Age, sex, BMI, antihypertensives,allopurinol, diuretics, creatinine, systolic and diastolic BP HDL triglycerides, carotis intima thickness, hemoglobin, race	Measurement of albuminuria were not available	No increased risk for incident CKD, but for prevalent CKD
Obermayr et al. 2008, Austria	General population	21475	7 years 1990	Age, sex, eGFR, antihypertensive drugs, waist circumference, HDL, cholesterol, glucose, triglycerides, BP, exercise	MDRD formula, not gold standard, may have led to underestimation of GFR	Slighly elevated SUA (>7-8.9 mg/dL, OR:1.75 for incident CKD. Elevated SUA > 9 mg/dL, OR: 3.12 Risk for incident CKD increased roughly linearly with UA to level of 6-7 mg/dl in women and 7-8 mg/dl in men; above these levels, the risk increased rapidly.
Weiner et al, 2008, US	Atherosclerosis Risks in Communities pooled with the Cardiovascular Health Study	13338	8.5 years 1987	Age, gender, race, diabetes, systolic BP, hypertension, CVD, left ventricular hypertrophy, smoking, alcohol use, education, lipids, albumin, hematocrit, baseline eGFR	No information on baseline proteinuria and allopurinol use	Each 1 mg/dl increase in UA increased risk of CKD 7-11 %

Hsu et al 2009, US	Volunteered for health checkups	177570	25 years 1964	Age, sex, diabetes, level of education, race, BMI, elevated BP, creatinine level,urine dipstick levels of protein, glucose, and hemoglobin	Exposures were only assessed once No assess variables such as illicit drug use, use of analgesic medications, or circulating inflammatory markers.	Higher UA quartile conferred 2.14-fold increased risk of ESRD over 25 years
Sonoda et al. 2011, Japan	General population	7078	5 years 2001	Age, sex, BMI, SBP, lipids hemoglobin, smoking,	Health checkup program Albuminuria not available	Longitudinal and baseline SUA increased the OR for CKD
Ben-Dov et al, Israel	General population (Middle-aged adults)	2544	26 years 1976	Age, sex, BMI, hematocrit, creatinine, glucose, lipids, fasting glucose ASAT, serum globulins, diabetes medication thyroxin, bilirubin proteinuria	Low number of events. Might have lost some cases that were never hospitalized	Hazard ratios (HR)s 2.87 ($p = 0.003$) for acute renal failure 2.14 ($p < 0.001$) for chronic renal failure
Zhang L et al. 2012, China	General population	1410	4 years 2004	Age, sex, BMI smoking, hypertension diabetes (yes/no), albuminuria (yes/no) and baseline eGFR	UA was measured only once at baseline, and have no information of UA-lowering drugs.	Renal decline (baseline eGFR <90 and eGFR decreased ≥20% during 4 years, or eGFR decreased ≥20% during 4 years and eGFR <60 at the second visit OR 1.19 (per 1 mg/dL increase in SUA; 95% CI 1.04–1.38).

Mok et al, Korea	Health check-up male general population The Severance Cohort study	14 939	10.2 years 1994	Age, sex, BMI, hypertension, diabetes, cholesterol, smoking, alcohol drinking exercise	Recruited from individuals who went to the health promotion center to check their health status.	Increased risk of CKD when comparing the highest and lowest quartiles of SUA

1.6 Uric acid as a risk factor for CVD and mortality

The relationship between SUA and CVD is not clear. Some epidemiologic studies have reported a relationship between SUA and several cardiovascular conditions [16, 114-119] whereas others have observed no such link. [120-123] The studies have to a varying extent been able to adjust for important confounders.

The epidemiologic studies that have failed to discern any independent association of hyperuricemia with CVD are far fewer than those who show such a link.[33] In an article considering medical implications of hyperuricemia, it was claimed that the studies of healthy individuals in which correlation between hyperuricemia and cardiovascular mortality was *not* found, tended to have a low number of events per-person-years.[124]

RCTs assessing the effect of SUA lowering treatment have so far been sparse, but a few warrant some comment.

The Losartan Intervention For Endpoint reduction (LIFE) study demonstrated that SUA reduction was correlated with an improved cardiovascular outcome in patients treated with losartan compared with those taking atenolol.[68] Losartan decreases urate reabsorption in the proximal tubule and produces sustained reduction in SUA levels.[125]The LIFE study demonstrated that 29 % of the benefit of losartan was attributable to the decrease in SUA levels during treatment, even after accounting for diuretic use and renal function. The finding suggests a role of SUA lowering in prevention of CVD. However, the LIFE Study was not primarily designed to assess the impact of SUA lowering, and the study depended on multivariable analysis to come to this conclusion. Unforeseen confounding might have been present with one of the many other effects of losartan.[126]

Concerning stroke, the paradoxical effects of UA are sharply illustrated by two RCTs. In a study published in 2014, 206 women and 205 men with acute ischemic stroke were randomized to treatment with UA or placebo in combination with thrombolysis.[127] The primary outcome was the rate of excellent outcome at 90 days, defined according to a modified Rankin scale, which measures degree of disability. In women, but not in men, the administration of UA reduced infarct growth: 42 % of women had an excellent outcome compared to 29 % in the placebo group. On the other hand, another RCT published in 2014, evaluated the effect of one-year treatment with allopurinol in eighty patients with ischemic stroke or transitory ischemic attack (TIA).[128] Allopurinol lowered central BP and reduced carotid intima thickness progression compared with placebo in patients with recent ischemic stroke and TIA. These studies had opposite approaches, one study was assessing treatment during the acute stroke event, and the other investigated treatment in the post-stroke phase. Still, these examples illustrate an UA effect paradox.

Another interesting RCT was published in 2010. Allopurinol was compared with placebo in 65 patients with chronic stable angina pectoris and angiographically documented coronary artery disease. [129] Participants were randomized to high-dose allopurinol or placebo for 6 weeks before crossover. High dose allopurinol significantly improved the primary endpoint, which was the time to ST depression during a standard exercise test, and the secondary endpoints, which were total exercise time and time to chest pain, suggesting that endogenous XO activity contributes somehow to exercise-induced myocardial ischemia.

A study with data from the United Kingdom Clinical Research Practice Datalink assessed whether allopurinol treatment in hypertensive patients >65 years could be associated with less strokes and cardiac events over a 10-year period, using a propensity-matched design. [130] It was found that the patients who had been prescribed allopurinol regularly had a lower occurrence of stroke and cardiac events than those who did not receive allopurinol. The

apparent benefit was driven by treatment at higher doses. The authors conclude that RCTs, particularly at doses of ≥300 mg daily, are needed to further explore whether allopurinol improves cardiovascular outcomes in patients with hypertension.

The studies above show that SUA lowering therapy may be a promising therapeutic option in CVD, however, more trials confirming these findings are needed.

Despite growing evidence in the literature that SUA is a true risk factor for CVD, this is still controversial, and asymptomatic hyperuricemia is not an indication for prophylactic treatment. The epidemiological studies in this field are many, but with varying ability to adjust for confounders. Many of the studies also lack generalizability as they have assessed selected groups. In addition to the need for RCTs assessing the effect of SUA lowering therapy, large epidemiological studies with ability to control for confounders like eGFR and the use of diuretics are crucial.

2. AIMS OF THE THESIS

The overall aim of this project was to study the longitudinal association between SUA and traditional risk factors, as well as to assess whether SUA is an independent risk factor for cardiovascular and renal disease in a general population.

More specifically, the aims of the thesis were as follows:

1. To investigate the association between SUA and the development of hypertension and MetS in a large population-based cohort stratified for overweight.

2. To assess whether hyperuricemia is associated with development of impaired renal function. We also aimed to assess whether increase in SUA over time is a risk factor for kidney damage, defined as albuminuria and/or a decrease in eGFR after 7 and 13 years of follow-up.

3. Explore whether SUA is an independent risk factor for myocardial infarction, ischemic stroke and all-cause mortality during 12 and 15 years of follow-up.

3. STUDY POPULATION AND METHODS

3.1 The Tromsø Study

The Tromsø study is a population based cohort study with six repeated health surveys in the municipality of Tromsø, Northern Norway. The study was initiated in 1974 as a response to the high cardiovascular mortality rate in Northern Norway, particularly in men. The study was gradually expanded to include many other diseases, such as rheumatism, venous thromboembolism, neurological and mental diseases, skin diseases, stomach and bowel-related diseases, cancer, osteoporosis and kidney disease. The Institute of Community Medicine at the UiT, The Artic University of Norway is responsible for the study, and the seventh wave is currently ongoing. In Tromsø 4 in 1994/95, all inhabitants aged 25 and above were invited, and 27158 (77% of the eligible population) participated. All participants aged 55-74 years, and 5-10 % random samples of the other birth cohorts older than 24 years (10542 individuals), were invited to a second visit with extensive examination including blood and urine testing after 4-12 weeks. Attendance rate was 76 % (7965 individuals). Subjects who had previously taken part in the second visit in Tromsø 4 were eligible for a second-visit examination in Tromsø 5 (2001/02), and 5939 participated (85% of the eligible). Tromsø 6 was run in 2007/08. Subjects eligible for the second visit in Tromsø 6 were first-visit participants aged 50–62 or 75–84 years, a 20% random sample aged 63–74 years and subjects who had attended the second visit of Tromsø 4. Out of the 11 484 subjects who were eligible, 7307 (64%) attended. [131] About 80 % of the participants in Tromsø 6 had previously attended Tromsø 4.

In all three papers of the current thesis, data from the Tromsø Study were used, but with some differences. In paper I, participants from Tromsø 4 and Tromsø 5 were included. The study population consisted of 6160 participants at baseline, of whom 5496 also attended Tromsø 5. In paper II, data from all three surveys (Tromsø 4, 5 and 6) was used. This paper describes a cohort of 2637 participants who had SUA measurements in all three surveys. In paper III,

participants from Tromsø 4 were included. The participants were followed until the occurrence of the clinical endpoints myocardial infarction and ischemic stroke and/or death after 12 and 15 years, respectively. In this cohort, participants with known previous myocardial infarction, ischemic stroke or diabetes were excluded, and our cohort consisted of 5700 participants with SUA measurements in Tromsø 4.

3.2 Measurements and clinical variables

Each survey used a self-administered questionnaire with information about medication, presence of diabetes and CVD, smoking habits and physical activity (Appendix I). Anthropometric and BP measurements were standardized, and performed by trained personnel. Height and weight were measured with participants wearing light clothing and no shoes. BP was recorded with an automatic device (Dinamap Vital Sign Monitor 1846 Critikon). Three measurements were made at one-minute intervals after 2 minutes resting, and the mean of the two final recordings was used. According to the NCEP-ATPIII definition of MetS, hypertension was defined as systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg and/or current use of antihypertensive medication in article I. In article II and III, the BP cut-offs used to define hypertension were higher, systolic BP ≥ 140 mm Hg and/or diastolic BP ≥90 mmHg combined with the use of antihypertensives. Physical activity was classified as active (> 1 hour physical activity with prominent sweating or breathlessness per week) or inactive (all others). Smoking habits were classified as current smokers or not (all others).

For logistic reasons, all blood samples were non-fasting. SUA was measured by photometry with COBAS® instruments (Roche diagnostics, Switzerland) using an enzymatic colorimetric test, the uricase/ PAP method. Reference values were140-340 μmol/L (2.4-5.7 mg/dl) for females and 200-415 μmol/L (3.4-7.0 mg/dl) for males.

In paper I, we classified participants according to the revised NCEP-ATPIII criteria for the MetS. Because our data lacked fasting blood samples, we modified the definition of elevated triglycerides and elevated glucose in paper I. For the definition of elevated fasting glucose, we set the cut off at ≥ 7.8 mmol/L if time since last meal was less than four hours, and at ≥ 5.6 mmol/L if time since last meal was at least four hours. For the definition of elevated triglycerides, we set the cut-off at ≥ 2.28 mmol/L if time since last meal was less than four hours, as non-fasting triglyceride levels are on average 20% to 30% higher than fasting levels.[132] If time since last meal was ≥4 hours, the cut-off was 1.7 mmol/L.

In Tromsø 4 and 5, plasma creatinine was analysed by a modified Jaffe reaction, but since creatinine-based estimation of GFR is better validated for enzymatic creatinine measurements, 111 plasma samples from the 1994/95 survey and 142 samples from Tromsø 5 were thawed and reanalysed with an enzymatic method (Modular P/Roche). Values were fitted to a linear regression model, and recalibrated creatinine values were calculated for all participants. In the sixth Tromsø study, serum creatinine was analysed on a Hitachi Modular model using an enzymatic method that has been standardized against isotope dilution mass spectroscopy (CREA Plus, Roche Diagnostics, GmbH, Mannheim,Germany). eGFR was calculated according to the CKD-EPI equation: $eGFR = 141 \times \min(S_{Cr}/k,1)^{a} \times \max(S_{Cr}/k,1)^{-1.209} \times 0.993^{age} \times$ ([1.018 if female] and × [1.159 if black]) where S_{Cr} is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{Cr}/k and max indicates the maxiumum of S_{Cr}/k).[133].

Three separate samples of morning spot urine from three consecutive days were collected, and fresh (non-frozen) samples were analysed within 20 hours. Urinary albumin and creatinine were analysed using kits from ABX Diagnostics, Montpellier, France. Albumin-to-creatinine ratio (ACR) in mg/mmol was calculated for each day and the mean of all three was used in the analyses in article II and III. Serum total cholesterol was analysed by enzymatic

colorimetric methods with commercial kits (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). In paper II the dichotomous variable RD (Renal Dysfunction) was defined using a modification of the 2012 KDIGO CKD classification.[134] We chose the "high normal" albuminuria stage (ACR≥1.13 mg/mmol) as the cut-off value for pathological urinary albumin excretion. Participants with eGFR<60 ml/min/1.73 m² and/or ACR≥1.13 mg/mmol were considered to have RD.

3.3 Endpoint assessment

Paper III describes the prospective associations of SUA with clinical endpoints. Three different endpoints, first-ever non-fatal or fatal myocardial infarction, first-ever non-fatal or fatal ischemic stroke and all-cause mortality were evaluated.

The Tromsø Study Cardiovascular Disease Registry was responsible for assessment and validation of the cardiovascular endpoints. Adjudication of hospitalized and out-of-hospital events was done for each event by thorough review of hospital and out-of-hospital records, autopsy reports and death certificates. Event ascertainment followed a detailed protocol. For myocardial infarction, established diagnostic criteria were used to evaluate symptoms, electrocardiogram, myocardial biomarkers and/or autopsy findings, and all events that were classified as definite, probable or possible myocardial infarctions were included as endpoints in article III. Stroke was defined according to the WHO definition, only ischemic strokes were included. [135].

Individuals who had died or emigrated from Tromsø were identified through the Population Registry at Statistics Norway. The national 11-digit identification number allowed a linkage to the National Population Registry and ensured a complete follow-up status for all-cause mortality until Nov 30th, 2010 (15 years). Since the cardiovascular endpoint registry was

complete only until December 31th, 2007, follow-up time for myocardial infarction and ischemic stroke from screening was 12 years. Data were censored for emigration, and, in case of myocardial infarction and stroke, for deaths from other causes.

3.4 Statistical analyses

Covariates in each study were selected on the basis of previous scientific knowledge. We chose variables that are known or suspected confounders, mainly demographic variables, traditional cardiovascular risk factors, life style factors, relevant drug use and eGFR.

In article I and II logistic regression analyses were performed with MetS and different components, and RD as dependent variables, respectively. The analyses were adjusted for the variables mentioned above, and in in addition for baseline GFR in article II. In article III, SUA was categorized into gender-specific tertiles. Crude and age-adjusted incidence rates were calculated as events per 1000 person years at risk. Cox proportional hazard models were used to investigate associations of SUA with cardiovascular outcomes and mortality, calculated per 1 SD (87 μmol/L) increase in baseline SUA, in unadjusted, age-adjusted and multivariable adjusted analyses. The proportional hazard assumption was checked by visual inspection of the -log-log survival curves. Non-linear effects were also explored in fractional polynomial regression models.

P values < 0.05 were considered statistically significant. Most analyses were run using SPSS software version 15.0 (SPSS, INC, Chicago, Illinois) and 21 (IBM SPSS Statistics for Windows Armonk, NY). Fractional polynomial regression models were performed with STATA/MP 12.1 (Stata Corp LP, College Station, Texas).

3.5 Ethical considerations

The Regional Committee for Medical Research Ethics approved the study, and all participants gave their written consent at each survey.

4.MAIN RESULTS

4.1 Paper I

Overweight modifies the longitudinal association between uric acid and some components of the metabolic syndrome: The Tromsø Study

In this prospective cohort study, we assessed whether baseline and longitudinal change in SUA was a risk factor for development of MetS and its individual components. We included 2920 women and 2792 men who had SUA measured in Tromsø 4. The participants were stratified according to BMI. Endpoints were MetS and each component of the syndrome after seven years, according to the revised NCEP-ATP III definition. Multiple logistic regression analyses showed that higher baseline SUA was associated with higher odds of developing hypertension in overweight subjects (BMI $\geq$ 25 kg/m^2; OR per 59 µmol/L SUA increase 1.44, 95% confidence interval (CI) = 1.17-1.78, p = .001.) This association was not significant in normal-weight subjects (BMI < 25 kg/m^2), and p for interaction between overweight and SUA was .044. Overweight also modified the association between baseline SUA and the development of elevated glucose (p for interaction = .039). However, SUA was a strong predictor of MetS in all subjects (OR per 59 µmol/L SUA increase 1.32, 95% CI 1.21-1.44, p < .001). Furthermore, longitudinal SUA change was independently associated with the development of MetS in all subjects (OR per 59 µmol/L SUA increase over seven years 1.36, 95% CI 1.22-1.51, p < .001). To summarize, increased levels of baseline SUA independently predicted the development of hypertension and higher fasting glycemia in the overweight, but not the normal-weight subjects. Baseline SUA was a predictor of future MetS, and longitudinal increase in SUA over seven years was also associated with the development of MetS in all subjects.

4.2 Paper II

Uric acid is associated with microalbuminuria and decreased glomerular filtration rate in the general population during 7 and 13 years of follow-up: The Tromsø Study

In a prospective cohort study which included 2637 men and women who participated in Tromsø 4, 5 and 6, we assessed the associations between change in SUA during follow-up, baseline SUA and RD. Participants were stratified according to tertiles of change in SUA between baseline (1994/95) and follow-up 13 years later (upper tertile: SUA increasing group, two lower tertiles: SUA non-increasing group). After excluding participants with RD at baseline, we found that SUA increasers, compared to SUA non-increasers, had a doubled risk of RD after 7 years (OR 2.00, (95 % CI 1.45- 2.75)). OR for RD in SUA increasers after 13 years was 2.18 (95 % CI 1.71- 2.79). The risk of developing ACR ≥1.13 mg/mmol alone was significantly increased after 13 years (OR 1.43 (95 % CI 1.09-1.86)), but not after 7 years (OR 1.30 (95 % CI 0.90- 1.89)). An increase in baseline SUA of 59 μmol/L gave an OR for RD after 13 years of 1.16 (95 % CI 1.04-1.29). In conclusion, an increase in SUA during follow-up was associated with an increased risk of developing RD after 7 and 13 years.

4.3 Paper III

Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study

In this prospective cohort study, we included 2696 men and 3004 women who participated in Tromsø 4, and examined the association of SUA with three different endpoints: all-cause mortality after 15 years, fatal or non-fatal myocardial infarction and ischemic stroke after 12 years. In total, 1433 deaths, 659 myocardial infarctions and 430 ischemic strokes occurred during follow-up. In multivariable Cox regression analyses adjusted for several traditional and non-traditional risk factors for CVD, a 1 SD (87 μmol/L) increase in SUA gave and increased risk of all-cause mortality in both genders (HR men; 1.11 (95% CI 1.02-1.20), women; 1.16 (1.05-1.29). HRs and 95% CI for stroke were 1.31 (1.14-1.50) in men and 1.13 (0.94-1.36) in women. No independent associations were observed with myocardial infarction.

In conclusion, SUA was associated with all-cause mortality in men and women, even after adjustment for BP, eGFR, urinary ACR, drug intake and traditional cardiovascular risk factors. After the same adjustments, SUA was associated with 31% increased risk of stroke in men.

5.GENERAL DISCUSSION

5.1 Methodological considerations

5.1.1 Bias

In epidemiology, discussion of bias can be simplified under the headings of a) selection (of population), b) information (collection, analysis and interpretation of data), and c) confounding, although, this phenomenon is sometimes considered as separate from bias. [136]

5.1.2 Selection bias

Selection bias is present if the estimated association among those selected differs from the associations among the eligible.[137] Some define selection bias as a situation where *subjects* are allowed to select the study group they want to be in. [138] In our study, participants were selected if they were inhabitants of an area and belonged to a certain age group. However, self-selection may be a problem, and could threaten external validity; the attenders in health surveys tend to be more educated and have a healthier life style than non-attenders.[139] In Tromsø 4, all inhabitants of the municipality of Tromsø ≥25 years were invited, and the attendance rate (77%) is considered high among epidemiological studies. This enhances the probability that the study population is representative of the general population. In studies of randomly sampled populations, the non-response is typically 30-40 per cent, and sometimes much higher.[136] Still, in Tromsø 4, almost one out of four did not attend, and in Tromsø 6, the attendance rate was even lower; 63 %. The attendance rate was low among the age group younger than 40, and at the age of 80 and older.[131] As it is likely that non-responders differ from responders, we cannot rule out that his may have influenced the results. In addition, the vast majority of the participants were Caucasians, which limits applicability to other ethnicities.[131] Paper II presents follow-up data of participants who met at three different

waves of the Tromsø Study during 12-14 years of follow-up time. Compared to the participants who attended one or more of the follow-up surveys, the participants who only attended the Tromsø 4 Study (1994/95) had a less favorable cardiovascular risk profile. They were older, had higher SUA level, lower eGFR, higher ACR, higher BMI, and higher cholesterol. There were also more participants with hypertension, known diabetes, and a history of myocardial infarction and stroke in this cohort. All in all, the study population was healthier than the source population.

5.1.3 Information bias

Information bias occurs when the variable of interest, i.e. the main exposure, covariates or the outcome, is measured with measurement error. Measurement error in categorical variables is often referred to as misclassification. [140]

Measurements can have both random and systematic errors, [141] and both may cause biased effect estimates.[140, 142] However, random errors where there are enough observations usually produce a correct estimate of the average value.

These biases are also named non-differential or differential biases where differential bias relates to systematic error and non-differential is random and consequently affects all subgroups equally.[136]

Measurement errors in the exposures and outcomes assessed in our work will be discussed in the following:

SUA

The association between SUA and outcomes was investigated in all three articles. SUA was measured by photometry with COBAS® instruments (Roche diagnostics, Switzerland) using an enzymatic colorimetric test. Several thousand measurements were performed in each wave of the Tromsø Study by trained laboratory staff at the University Hospital, and at the Metabolic research lab, UiT. There is no reason to believe that these measurements have been exposed to systematic error. However, random errors are likely, but due to the high number of participants, this has probably not affected the results.

Change in SUA

In article I and II, change in SUA was used as an exposure variable. In article I, increase in SUA was associated with MetS. In article II, change in SUA was assessed as an exposure with decreased eGFR as an outcome. We have tested for inter-correlation between these two variables, which was satisfactory low. However, we know that increased SUA values are observed with increasing GFR, probably partly because of decreased renal elimination of UA. In this manner, the assessment and analyses of these variables are problematic and must be interpreted with caution. However; change in SUA is associated with increased ACR as well, which strengthens the finding that increasing SUA is associated with renal dysfunction.

When constructing two groups of a change variables, the phenomenon "regression to the mean" may represent a problem. This phrase was first described by Francis Galton (1822-1911), where regression means "to revert to" or "return to". This bias comes from the observation that measurements that initially lie at the extremes tend to move nearer the average on subsequent measurements. As described by the epidemiologist Bhopal: "in essence, the cause is random error."[136] In our case, if some SUA values were very low or very high, they would tend to be closer to the mean at the next measurement. This means that

some participants will be misclassified as having very high or very low SUA. In this setting, a mean value of these two measurements may better represent the true value. Consequently, in our study we cannot rule out the possibility that some subjects have been misclassified.

Hypertension

In article I hypertension defined as BP ≥ 130/85 mmHg was one of the main outcomes. There could be some problems related to this biological endpoint as exemplified by Bhopal [136]: "BP varies from moment to moment in response to activity, in a 24-hour cycle with lowered pressure in the night. There is no readily available estimate of the true summary." As a compromise, BP was taken under standard conditions, measured three times, and the average of the two last readings was used. The value is useful in clinical practice and epidemiology, but it is not an accurate summary. Long-term recordings of BP over several days (ambulatory BP) were not available. It is conceivable that this measurement error mainly would be random, but systematic error could not be ruled out. If for instance a BT-cuff used by the overweight participants read differently from the cuff used by lean participants, this could introduce bias.

Serum glucose and triglycerides

For logistic reasons, non-fasting blood samples were obtained in the Tromsø Study, which may be problematic for the interpretation of serum glucose and triglyceride values. In article I, modifications were made when classifying both variables most affected by the lack of fasting blood samples, namely glucose and triglycerides. For elevated fasting glucose we have maintained the cut-off of ≥ 5.6 mmol/L for the subjects with at least four hours since last meal, and for the persons with less than four hours since last meal, we have set the cut-off at ≥ 7.8 mmol/L, the cut-off used for impaired glucose tolerance in oral glucose tolerance tests.

However, it is likely that misclassifications may have occurred in both directions, as level of glucose not only depends on time since last meal, but also on what has been eaten and physical activity. This is a source of bias that we are unable to compensate for, and a major limitation when exploring metabolic associations. On the other hand; requesting participants to attend in a fasting state would probably had a major negative impact on the attendance rate.

Creatinine values and eGFR

In article II eGFR< 60 ml/min/1.73 m² was used as an outcome in combination with ACR, and eGFR was a covariate in article I and III. Creatinine values from Tromsø 4 and 5 were recalibrated as described, because a possible drift was observed between the originally measured values. In spite of the recalibration, a certain degree of inaccuracy cannot be ruled out.

Because serum creatinine concentration depends on muscle mass, equations to estimate GFR have been developed with the goal of overcoming this limitation. The Cockcroft-Gault [143] and Modification of diet in renal Disease (MDRD) equations have been extensively used,[144] but the first tends to overestimate GFR [145] and MDRD tends to underestimate GFR in a kidney-healthy population.[146] Thus, healthy persons may erroneously have been categorized as having CKD.[146] The CKD-EPI equation, which was published in 2009, performs better than the MDRD for GFR >60 ml/min/1.73 m², and approximately the same when GFR is less than 60 ml/min/1.73 m². Therefore, we have chosen this equation for eGFR. However, since the CKD-EPI equation also is based on serum creatinine, GFR will be biased in people with reduced muscle mass.[147]

eGFR aims to estimate the true GFR from serum creatinine, sex and age, but in the word estimate the limitation is already stated: it is not an **exact** measurement. In the cross-sectional

Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), GFR was measured by iohexol clearance and estimated by creatinine or cystatin C in a middle-aged cohort from the general population.[148] The aim of the study was to explore the validity of using eGFR as a proxy for mGFR in studies of CVD risk. The results suggested that eGFR partially depends on factors other than the true GFR. The possibility of residual confounding from these factors in studies of GFR and cardiovascular risk in persons with a GFR close to the normal range cannot be ruled out. Thus, the authors conclude that estimates of cardiovascular risk associated with small changes in eGFR must be interpreted with caution.

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Urinary ACR

In article II, ACR ≥1.13 mg /mmol was the second component of the main outcome RD. Albumin assessed in a 24-hour urine sample is the gold standard measurement for albuminuria. However, long-time urine collection is impractical and subject to significant error due to incompleteness and/or inadequate timing. Therefore, substitute measures including albumin concentration and ratio of albumin to creatinine concentrations (ACR) from a spot urine sample, have been validated and is considered satisfactory and preferable. [149, 150] By dividing the urinary albumin concentration by the creatinine concentration, differences in urinary dilution are corrected for, since creatinine excretion rate is nearly constant in each individual. However, again we are dependent on creatinine that, as described above, is influenced by the amount of muscle mass, gender, age and ethnicity.[151] Still, a strength in our study is the use of fresh urine samples, thus avoidance of prolonged storage, freezing and thawing that reduce the value of albuminuria for endpoint prediction.[152] In addition, in our material we were able to use the mean ACR value of three samples which reduces the random variation. On the other hand, variation in urinary albumin excretion over weeks was not captured by our method.

Myocardial infarction and ischemic stroke

In article III, the hard endpoints ischemic stroke and myocardial infarction were outcomes. As described, the events were adjudicated according to validated criteria by trained personnel. However, some misclassification is likely to occur. Only certain cases of myocardial infarction and ischemic strokes were included. In case of missing information, true events could erroneously have been classified as uncertain and thus not included as an endpoint. On the other hand, borderline cases could erroneously be classified as true events. Moreover, it cannot be ruled out that a few cases were treated in other hospitals and not reported to local doctors.

Covariates

Important data used in our studies was derived from questionnaires. This may have been a source of information bias. In particular, data derived from questions that may have been perceived as value-laden may have been biased. Participants may hesitate to fully answer such questions because they feel that they are too personal, or they may be uncomfortable with for instance their alcohol use or level of activity. Questions may also have been misunderstood leading to possible classification bias. Several self-reported lifestyle factors were included as covariates in all three articles. In spite of the limitations mentioned above, high validity has been found for self-reported questionnaires regarding smoking habits [153] and hard physical activity.[154] Both hard and moderate leisure time physical activity were reported in Tromsø 4, 5 and 6. Moderate activity often is over-estimated in self-administered questionnaires.[155]

Dichotomizing of variables

In our studies, we chose to dichotomize several of the exposure and outcome-variables which has a potential to introduce bias. In article I, the participants were dichotomized into BMI above or below 25 kg/m². Furthermore, each of component of the MetS is a continuous biological variable that has been dichotomized by the use of constructed cut-offs. Also in article II, the SUA change variable was categorized into SUA increasers and non-increasers, and the endpoint RD was a dichotomous constructed variable. The most obvious problem with this categorizing is the interpretation of the observations close to the cut-offs. In the statistical analyses these observations are treated as opposites, whereas they indeed are pretty close. In an article discussing "why dichotomization of continuous variables is a bad idea", the authors address this issue thoroughly. [156] First of all, dichotomizing is recognized as widespread in clinical research, and practical in the sense that one sometimes needs the distinctions normal/abnormal, cancerous/benign etc. However, simplicity achieved is gained at a cost. Information and power are inevitably lost; dichotomizing is equivalent to losing a third of the data. It also increases the possibility for false positive results. [156] These problems concerning dichotomizing might have been a problem also in our results. However, having a large sample as in our study is an advantage compared to smaller studies because statistical power is retained.

5.1.4 Type I and type II error

When evaluating the results of statistical analysis in medical research, one should always consider the possibility of type I and type II errors. A type I error is the error in rejecting a null hypothesis when in fact it is true (equal to the false positive error).[136] In making this error, one is claiming a difference between comparison groups when there is, in fact, none in the source population. Apparent differences have occurred by pure chance. In article I we found that 59 µmol/L (1 mg/dL) increase in SUA was associated with increased risk of

hypertension (OR, 1.44, p=0.001) in participants with overweight. However, statistics do have the limitation that it will always be a matter of probabilities. In the result above, we can say that there is a 99.9 probability that this result did not occur by coincidence. Still, there is a 0.1 percent possibility of a type I error, and that type of error can never be completely eliminated. To minimize type I errors, the level of significance (alpha) should be set at a low level (usually less than 5 %).

In this context, however, it should be mentioned that statistical significance and clinical relevance are two different matters. Minimal clinical differences may yield statistical significance simply due to a large sample size. Thus; the magnitudes of effects and measures should be evaluated critically. OR at 1.44, meaning a 44% increased risk (per unit SUA increase) of a common condition, such as hypertension, probably is clinically relevant. The same applies to the findings in article II and III, where increased SUA was associated with RD, stroke in men and all-cause mortality in both genders.

A type II error is failing to reject a null hypothesis when it is false, i.e. disregard an effect that is in fact present.[136] Most studies aim to have less than 10-20 percent (beta) possibility of such an error. The power of a study is the possibility that a type II error will not occur, i.e. 1 – beta. Most studies aim for a power of 80-90%.[136] Type II error is usually related to a sample size that is too small. This limits the possibility to stratify the population into subgroups for analyses. We cannot rule out that the lack of significant association between SUA increase and stroke in women was due to lack of power, i.e. a type II error.

5.1.5 Interaction

Sometimes the strength of the association between two variables differs, depending on the value of a third variable. This is usually called effect modification by epidemiologists and

interaction by biostatisticians. [138] The exposure-outcome association differs in different levels (strata) of an effect modifier. [136]

In article I, we found that the relationship between SUA and hypertension was modified by a third variable: BMI. When overweight was present, SUA was associated with hypertension. The same was the case for SUA and elevation of glucose. In overweight subjects, but not in the absence of overweight, a rise in SUA was associated with a significant increase in glucose. However, we did not find interaction between SUA and overweight for the association with MetS. This may lead to a hypothesis that there may be some biologically important mechanisms in the interplay between SUA, hypertension and overweight.

When we studied the association between change in SUA and RD in article II, there was no significant interaction between gender and SUA change during follow-up for the prediction of RD. Therefore, we ran the multivariable analyses in the entire cohort not stratified by gender, thereby increasing the statistical power. However, we ran gender specific analyses as well, and did not reveal different results; these data are not shown.

In article III, SUA was associated with all-cause mortality in both genders, and ischemic stroke in men. In our study, there was no statistically significant interaction between SUA and gender, but still these differences were revealed when performing the analyses stratified by gender. There is evidence in the literature that there may be biological differences in the way SUA affects vasculature in men and women, [157] and in cardiovascular biology in general there are important differences between men and women. A negative test for interaction does not exclude the possibility that there may be biological differences of importance. However, in article III, we cannot rule out that lack of statistical power preclude the gender differences found in these analyses, as mentioned earlier.

5.1.6 Confounding

Confounding is bias of the estimated effect of an exposure on an outcome due to the presence of a common cause of the exposure and outcome.[141] Confounding is an important issue in observational designs, and may lead to underestimation, overestimation or even change the sign of the estimated effect.[142]

Confounding can be reduced by proper adjustment. Exploring data is not sufficient to identify whether a variable is a confounder, and such evaluation of confounding may lead to bias. [141, 142, 158] Other evidence, like pathophysiological and clinical knowledge and external data, is needed. A confounder cannot be an effect of the disease or the exposure. [140, 142]

As opposed to effect modification (interaction), the exposure-outcome association of a confounder is similar in all levels (strata).

Residual confounding

The bias that remains after unsuccessful adjustment for confounders is called residual confounding. [141, 142] Residual confounding will almost always be present in observational studies.

Mediators

In contrast to the confounder, a mediator represents a step in the causal pathway between the exposure and the outcome. [141, 142] Such a variable will also be associated with both the exposure and the outcome.

Confounding in article I, II and III

In article I, SUA was associated with hypertension and elevated glucose in the overweight group and with MetS in the entire cohort.

There is a possibility for unmeasured confounding in these findings. Insulin resistance could be a confounding factor, although we adjusted for blood glucose at baseline. There is, however, evidence in the literature that a rise in SUA appears before insulin resistance.[159] Inflammation is also a possible confounder in these associations.

Recent literature in obesity pathophysiology focuses on adiponectin, an adipocytokine secreted from fat tissue. UA is able to downregulate adiponectin, and this cytokine is negatively associated with BMI and body-fat. [160, 161] Low level is associated with development of hypertension. Unfortunately, we did not measure adiponectin in our study in 1994/95.

On the other hand, it is possible that insulin resistance, inflammation and adiponectin may represent a step in the causal pathway between SUA and the outcomes, and consequently these factors may be mediators, which not necessarily should be adjusted for.

In article II we found that increasing SUA was associated with increased ACR and reduced eGFR. In previous literature, multiple risk factor adjustment has been done to a varying degree. We were able to adjust for age, baseline SUA, eGFR, ACR, BP, cholesterol, smoking, antihypertensive treatment, including diuretics, and life style factors. However, we can never rule out that we have possible unmeasured confounders that we should have been aware of. In addition, the same issue as in article I may represent a problem; some of the presumed confounding factors could in reality be mediators. In particular, elevated BP could represent a causal step between SUA rise and RD. However, basal research has shown that renal damage in the presence of hyperuricemia also occurs when BP is kept normal.[18]We ran the analyses with and without BP in the regression models and still found a significant association between SUA rise and RD (data not shown).

In article III, we found that SUA was associated with all-cause mortality in both genders and ischemic stroke in men. We did not find any significant association between SUA and myocardial infarction. In this article, a main point was to thoroughly adjust for multiple confounders that earlier studies had not been able to account for. Lack of adjustment for important confounders in the literature has been pointed out as a major problem in interpreting the association of SUA with cardiovascular endpoints. Some studies have included presumed confounders that caused SUA to loose significance; for instance, in the Framingham study, the association between SUA and mortality lost its significance when diuretics were adjusted for. We included the use of diuretics in our model, and still we found that SUA was associated with all-cause mortality.

We ran a Cox regression model with presumed confounders as independent variables in the model. We aimed to find which variables had the greatest impact on the endpoints with a theory based, stepwise inclusion of covariates into the regression model. In the literature, RD, measured as eGFR and ACR, are regarded as confounders. In our study, these variables were adjusted for. For myocardial infarction, SUA lost its significance when lipids were included as covariates. However, still residual confounding cannot be ruled out in the main results.

5.1.7 Causality

In 2005, a systematic review referred to the epidemiologist and statistician Bradford Hill when analyzing whether a causal association between SUA and CVD was likely.[126, 162] Bradford Hill is usually given credit for the modern RCT. According to Bradford Hill, there is a group of minimal conditions necessary to provide adequate evidence of a causal relationship between an incidence and a possible consequence: Temporality, strength, consistency, biological gradient, plausibility and experimental evidence.[162] However, failure to satisfy them does not disprove a causal association.

The effect has to occur after the cause, and this is the only absolute criterion. All our articles describe prospective studies, with baseline SUA as a predictor of future endpoints. However, in article I and II, we also studied longitudinal change in SUA as a major exposure variable. In article II it may be problematic that the final SUA measurement and the endpoints were assessed simultaneously, as discussed earlier. Strength, consistency and biological plausibility has also been discussed in earlier parts of the thesis. Experimental knowledge refers to the use of RCTs, which is the superior design in establishing causality. When performed adequately, this method is able to exclude confounding. Our works are observational studies, which have its limitations as described above. However, an increasing number of RCTs are performed with UA lowering therapy, showing promising effects, suggesting that SUA is a true risk factor.

5.2 Discussion of main results

5.2.1 Paper I

In article I, in contrast to other studies, we stratified the population into overweight and not overweight subjects, and made different findings between the groups. In the group with normal-weight participants, SUA was not associated with hypertension and elevated fasting glucose. However, among the overweight persons, elevation of SUA of 59 µmol/L gave a 44 % increased risk of hypertension and a 14 % increased risk of elevated fasting glucose. The associations between SUA and hypertension have been explored for more than a century. In a recent meta-analysis, 59 µmol/L (1 mg/dL) SUA increase was reported to be associated with a statistically significant elevation in incident hypertension.[35] It has been claimed that an elevated SUA is the independent risk factor for hypertension that is the most reproducible to date.[163] Although SUA and hypertension have been extensively studied, few studies have studied different strata of weight.

A multitude of studies, in an effort to explain how hyperuricemia can lead to hypertension, have proposed interlinked mechanisms such as endothelial dysfunction and reduction in endothelial NO levels,[164, 165] oxidative stress,[166] and activation of the renin-angiotensin-aldosterone-system [167] and renal microvascular lesions. [18]

Under certain circumstances, increased activity of XO, detected as increased production of UA, will lead to increased oxidative stress, which, in turn, can be detrimental in the state of reduced antioxidant capacity that accumulated fat creates. Persons with overweight may possibly be more exposed to this mechanism.[168]

Furthermore, UA can affect adipocytes by inducing upregulation of pro-inflammatory factors and downregulation of the insulin sensitizer and anti-inflammatory factor adiponectin.[161] Unfortunately, we have not measured adiponectin, but it has been shown that adiponectin is

negatively associated with BMI and body-fat.[160] Since low level of adiponectin is associated with the development of hypertension [169] and insulin resistance, [170] it could be speculated that adiponectin is part of the link between UA and hypertension and insulin resistance, and also be a part of an explanation why UA is associated with new onset hypertension and elevated glucose in the overweight but not the normal-weight subjects in our study.

Furthermore, a study found increased angiotensinogen levels in persons with hypertension and overweight (BMI $\geq$ 25 kg/m^2), compared to persons with hypertension and normal-weight (BMI < 25 kg/m^2), in the presence of hyperuricemia. [171] This could also be a mechanism by which UA is associated with obesity-related hypertension and impaired fasting glucose.

In article I we also found that baseline and increasing SUA was associated with development of MetS. An elevation of 59 µmol/L SUA gave a 32 % increased risk of MetS among both lean and overweight subjects. Earlier studies have also reported an association between SUA and MetS. [64, 172, 173] A Japanese prospective study came up with a negative result, but they had a shorter duration, and did not adjust for baseline SUA, which we did in our study. Our study also has other important strengths: the large size, solid attendance rate, long follow-up time, use of SUA as a continuous variable, and the ability to correct for confounders such as eGFR, use of diuretics and all the traditional cardiovascular risk factors. However, as described above, a major shortcoming of our study was the lack of fasting blood samples. In addition, only one single measurement of SUA was done in each survey. The fact that our study population comprised largely of healthy, middle-aged to elderly Caucasians, can be viewed as both a weakness and a strength; the results may not be generalizable to dissimilar populations, but the homogeneity of our cohort may have prevented dilution of our findings due to important diversities in baseline properties.

5.2.2 Paper II

Being in the highest tertile of SUA change, corresponding to an increase in SUA of more than 33 μmol/L over 13 years, was an independent risk factor for RD defined as increased ACR and/or a reduced eGFR. This result for eGFR was consistent whether the population had a long time follow-up of 13 years or whether the follow-up time was shorter, and the results were similar when participants with baseline RD were excluded. Although the OR for moderately reduced eGFR was higher than the OR for ACR ≥1.13 mg/mmol, longitudinally increasing SUA was significantly associated also with the development of albuminuria after 13 years. The associations between baseline SUA and the renal endpoints were not significant when the longitudinal change in SUA was not adjusted for. The reason for this is unclear, but it is possible that the association between baseline SUA and the renal endpoints within the SUA increaser-and non-increaser groups, respectively, becomes obscured when the whole cohort is studied without this group division. In our study, SUA increase was associated with worsening eGFR and ACR over time, and these two markers independently predict advanced stage CKD, CVD and mortality. [174-182] Therefore, our findings may have clinical importance.

Our study is in concordance with the results from a meta-analysis that included fifteen cohorts, as described earlier in this thesis. [14] One difference, however, was the age distribution. In our study, we found an effect in participants with a mean age of 56, whereas in the meta-analysis, the positive association between SUA and CKD was more pronounced among groups with a mean age < 60 years, and no association was observed in cohorts with a mean age ≥60 years. Thus, it is possible that our results would have been stronger if mainly younger persons were investigated.

Most studies use eGFR <60 mL/min/1.73 m^2 as the only endpoint when considering CKD. We also included ACR ≥ 1.13 mg/mmol as an outcome, and showed that increasing SUA independently predicted low grade albuminuria. A major methodological problem concerning UA and kidney function is that of reverse causality as explained on page 23 in this thesis. In order to reduce bias concerning revers causality, all patients with decreased eGFR were excluded at baseline of the analysis. We also have aimed to reduce this problem by adjusting for baseline eGFR.

Also, the fact that we found an association between SUA and development of increased albuminuria in addition to decreased eGFR, strengthens the assumption that UA may exert a harmful effect on the kidney.

A weakness of several previous epidemiological studies, as also stated by other authors, is the lack of information on diuretics. We have obtained that information in our material of almost 3000 subjects, and found that there were significantly more users of diuretics in SUA increasers. In men, 19 % of the SUA increasers used diuretics compared to 6 % of SUA non-increasers. (13 vs 6 % in women) However, when adjusting for the use of diuretics in the analyses, SUA still had a significant association with RD.

Few previous studies had information on the use of allopurinol. In our study, information about current use of allopurinol at baseline was available. However, there were few allopurinol-users (less than 0.2 % at baseline) included in the study. Moreover, the use of allopurinol was not a significant predictor in the univariate analyses and therefore not included in the multivariable models.

Other strengths of our study were the prospective design, a large cohort from the general population with a high attendance rate, and a long observation time (13 years). We also had

ACR measurements from three unfrozen urine specimens, reducing the effect of day-to-day variation.[183]

As described earlier, only persons with three SUA measurements (Tromsø 4, 5 and 6) were included in the cohort. Analyses showed that the excluded persons were less healthy at baseline, and this may have influenced the results of the study. However, it is reasonable to believe that the inclusion of these less healthy individuals would have strengthened rather than weakened the reported associations.

To summarize, this study confirms the growing evidence suggesting that SUA is a risk factor also for renal damage. Moreover, longitudinally increasing SUA may be a risk factor *per se.*

5.2.3 Paper III

In this prospective study of 5700 participants from the general population, one SD (87 μmol/L) increase in SUA was significantly associated with a 31% increased risk for ischemic stroke in men, and all-cause mortality risk was increased in both genders; 11 % in men, and 16 % in women, after multivariable adjustments. There was no association between SUA and myocardial infarction after adjustment for lipids. Interaction between SUA and gender in the association with stroke was not observed in our study.

The association between SUA and ischemic stroke has been found in previous studies. [114, 184, 185] However, the Framingham study failed to show an independent association of SUA with stroke.[186] A systematic review and meta-analysis from 2009 of 16 prospective cohort studies, found that the elevated SUA level is associated with a modest but statistically significant increased risk of stroke incidence and mortality.[185] In our study, we did not find an association in women; SUA lost its significance when BP and BMI were adjusted for. This

result is in contrast to the large Swedish AMORIS [114] study, which found UA to be more strongly related to stroke in women than in men. In the AMORIS study, more than 400000 participants were followed, and more than 11000 strokes were registered, and thus this study is unique due to its size. A limitation of the AMORIS study, was the lack of information about the use of antihypertensive drugs. In our study, 430 ischemic strokes occurred, and thus we might have lacked the power to show significant associations in women. When we look at the figure of the incidence rates in our study (Figure 3 in article 3), the incidence of events are increasing with increasing tertiles of SUA in both genders, but there were fewer events among women. Statistical analysis did not yield significant associations, which could be due to too few events among women.

Another explanation for the gender differences in our study might be actual biological differences in these associations. Differences in risk estimates for stroke between genders may relate to gender-specific differences in vascular biology. Vlachopoulos et al. [157] reported that in newly diagnosed hypertensive persons, UA was associated with increased aortic stiffness in both genders, but a negative association with arterial wave reflection was observed only in women. Such differences in vascular function could influence the tendency to develop stroke. In an article from 2016, however, the risk of stoke with increments in SUA in women increased by 15% for each 59 µmol/L increase in plasma UA (95% CI 3%-28%), but was no longer significant after adjustment for cardiovascular risk factors, particularly history of hypertension. [187]

It has been suggested that UA may have harmful effects on platelet function, [188] and cause endothelial dysfunction. In one study it was shown that UA could induce expression of CRP in human vascular endothelial and smooth muscle cells, inhibit endothelial cell proliferation and migration and impair NO production. [189] Vannorsdall et al. reported that even a mild

elevation of SUA was associated with cerebral ischemia. One hundred eighty study participants aged 20 to 96 years completed neuropsychological testing, laboratory blood studies, and a brain MRI scan. [190] It was suggested that impaired vascular tone and endothelial dysfunction could contribute to ischemic changes, because they permit cerebrospinal fluid to cross the blood-brain barrier and cause areas of edema.[190]

In the AMORIS study, the authors referred to the urate redox shuttle theory [191]: UA may turn into a pro-oxidant risk factor once the environment becomes atherosclerotic with plaque formation within the arterial wall, or it may become elevated as a response to an up-regulated XO activity with deleterious peroxidation and other processes affecting plaque formation and stability.[192, 193]

Quite opposite to this, it has been shown that treatment with UA in combination with thrombolysis was of benefit to patients suffering from acute stroke, as described earlier. [127] UA is one of the most important endogenous antioxidants in the human brain, and high circulating UA concentration could play a role against the deleterious effect of free radicals produced upstream in the synthesis of UA.[194]

We observed a significant association of SUA with all-cause mortality, with a modest increase in mortality risk in both genders. In the Framingham study, [186] no association was observed with all-cause mortality after adjustments for age, BP, smoking, BMI, total cholesterol, intake of alcohol and medication. On the other hand, the NHANES I study [16] reported a 13% increased mortality risk in women in fully adjusted analyses, but only with non-significant associations in men. The fact that the SUA level in women tends to increase during the fifth to the seventh decade due to postmenopausal reduction in UA excretion [195, 196] and being flat or slightly declining in men, [186] may influence the gender specific association with endpoints.

No independent association between increment in SUA and myocardial infarction was observed in the present study. Total- and HDL-cholesterol abolished the effect of SUA on future myocardial infarction.

The Framingham Study[186] is one of the largest studies on the association of SUA with CVD in the general population. Our study differs from the Framingham Study in many ways, and as mentioned earlier, the mean age in the Tromsø study was relatively high. Mean age was 47 years in the Framingham cohort compared with 60 years in the Tromsø cohort, and thus mortality rate was lower in the Framingham study (12.4 per 1000 person years compared to 18.9 per 1000 person years). The observation time in our study was longer than in most previous studies, and this may explain why we were able to detect associations in a study population where high-risk subjects had been excluded.

A recent study published in 2016 examined the controversy regarding the association between hyperuricemia and CHD. [197] This was a systematic review and dose-response meta-analysis of 29 prospective cohort studies (n = 958410 participants, including our study on SUA and cardiovascular endpoints and mortality). In contrast to our results with no association between SUA and myocardial infarction, hyperuricemia in the meta-analysis was associated with increased risk of CHD morbidity (adjusted RR 1.13; 95% CI 1.05-1.21). As in our study, increased mortality risk was found, however the meta-analysis specified CHD mortality while we explored all-cause mortality. For each increase of 1 mg/dl in UA level, the pooled multivariate RR of CHD mortality was 1.13 (95% CI 1.06 -1.20). The authors also found that hyperuricemia may increase the risk of CHD events, particularly CHD mortality in females[197] which we did not find in our study.

Taken together, the meta-analysis showed some differences and some similarities compared to our study, but the studies included had some heterogeneity, and as studies from all over the

world was included, ethnical and environmental differences also could have been of significance.

6. CONCLUSIONS AND PERSPECTIVES

In accordance with previous studies, our research supports the suggested interplay between UA, obesity, MetS and hypertension. Further studies should examine the exact causal relationship. With regards to renal damage, not only SUA per se, but also *increase* in SUA seems to be of importance. We conclude that SUA is an independent risk marker of all-cause mortality in both genders, ischemic stroke in men and that gender-specific analyses should be given priority in future studies.

Other approaches could also be of importance in assessing the impact of UA:

•Our studies have gained information on renal function with repeated measurements over many years. Still, we use eGFR, and not exact GFR measurements. However, exact information on renal function has been gained by the RENIS-T6 group, and in the RENIS Follow-up Study. In the future, we hope to study the association between SUA and age-related change in measured GFR in a collaboration project with the RENIS researchers.

•As described initially, SUA is generated from xanthine and hypoxanthine up-stream, and excreted in the urine and feces. By studying the serum concentrations and urinary excretion of metabolites and precursors more thoroughly, causes of hyperuricemia among individuals could be differentiated. In theory, this could lead to a more targeted strategy for SUA reduction in each individual.

•SUA reduction in RCTs in adolescents was briefly described above. Hyperuricemia among the youngest is usually combined with overweight and is an area of utterly importance. Early

intervention may prevent this group from developing serious health problems later in life. In Fit Futures, a special survey of adolescents run by the Tromsø study, many participants were overweight. Blood samples have been collected, and assessment of SUA, and possibly a targeted follow-up for the participants at risk, may be highly valuable.

•Adiponectin is among the new markers that may be of importance in obesity, inflammation and SUA. In the future, it would be interesting to explore associations more thoroughly. Currently Tromsø 7 is running, which hopefully will yield new opportunities in such assessment.

• Some of our data was based upon biological samples and questionnaires collected 21–22 years ago, with endpoint registration only 7 years later (Met S and hypertension in article I). Both lifestyles and pharmacological treatments have changed during these years, and it would be of interest and importance to confirm these finding in future studies.

•As the knowledge in this field has expanded, RCTs on lowering SUA in subgroups at high risk should be performed, which may give firm answers to the role of SUA in cardiovascular and renal conditions.

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Helseundersøkelsen i Tromsø

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. I tillegg skal undersøkelsen øke kunnskapen om kreftsykdommer og andre alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Vi ber deg derfor svare på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø **Statens helseundersøkelser**

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du purring.

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dag Mnd År

Dato for utfylling av skjema: ..... 18 ...../...../.....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 - 28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑
- Gode ..... ❑
- Vanskelige ..... ❑
- Meget vanskelige ..... ❑

Hvor mange av de første 3 årene av ditt liv
- bodde du i by? ..... 30 _____ år
- hadde dere katt eller hund i hjemmet? ..... 31 _____ år

Hvor mange av de første 15 årene av ditt liv
- bodde du i by? ..... 32 _____ år
- hadde dere katt eller hund i hjemmet? ..... 34 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.		Ja	Nei	Antall
Ektefelle/samboer	36	❑	❑	
Andre personer over 18 år	37	❑	❑	_____
Personer under 18 år	40	❑	❑	_____

Hvor mange av barna har plass i barnehage? ..... 43 _____

Hvilken type bolig bor du i?
- Enebolig/villa ..... 45 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor stor er din boenhet? ..... 46 _____ m^2

I omtrent hvilket år ble boligen bygget? ..... 49 _____

		Ja	Nei
Er boligen isolert etter 1970?	53	❑	❑
Bor du i underetasje/kjeller?	54	❑	❑
Hvis "Ja", er gulvbelegget lagt på betong?	55	❑	❑

Hvordan er boligen hovedsakelig oppvarmet?
- Elektrisk oppvarming ..... 56 ❑
- Vedfyring ..... ❑
- Sentralvarmeanlegg oppvarmet med:
  - Parafin ..... ❑
  - Elektrisitet ..... ❑

		Ja	Nei
Er det heldekkende tepper i stua?	60	❑	❑
Er det katt i boligen?	61	❑	❑
Er det hund i boligen?	62	❑	❑

ARBEID

Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid?
- For det meste stillesittende arbeid? ..... 63 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Kan du selv bestemme hvordan arbeidet ditt skal legges opp?
- Nei, ikke i det hele tatt ..... 64 ❑ 1
- I liten grad ..... ❑ 2
- Ja, i stor grad ..... ❑ 3
- Ja, det bestemmer jeg selv ..... ❑ 4

		Ja	Nei
Har du skiftarbeid, nattarbeid eller går vakter?	65	❑	❑

Har du noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.		Ja	Nei
Sjåfør	66	❑	❑
Bonde/gårdbruker		❑	❑
Fisker		❑	❑

EGNE SYKDOMMER

Har du noen gang hatt:
Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen.
*Hvis det har skjedd flere ganger, hvor gammel var du **siste** gang?*

	Ja	Nei	Alder
Lårhalsbrudd 69	❑	❑	_____
Brudd ved håndledd/underarm 72	❑	❑	_____
Nakkesleng (whiplash) 75	❑	❑	_____
Skade som førte til sykehusinnleggelse 78	❑	❑	_____
Sår på magesekken 81	❑	❑	_____
Sår på tolvfingertarmen 84	❑	❑	_____
Magesår-operasjon 87	❑	❑	_____
Operasjon på halsen 90	❑	❑	_____

Har du eller har du hatt:
Sett ett kryss for hvert spørsmål.

	Ja	Nei
Kreftsykdom 93	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis	❑	❑
Benskjørhet (osteoporose) 98	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren	❑	❑
Nyrestein 103	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue	❑	❑
Matvareallergi 108	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? ..110 ____ ganger

	Ja	Nei
Har du hatt dette siste 14 dager? 112	❑	❑

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:
Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 113	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 119	❑	❑	❑	❑	❑	❑
Kreftsykdom 125	❑	❑	❑	❑	❑	❑
Astma 131	❑	❑	❑	❑	❑	❑
Mage/tolvfingertarm-sår 137	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 143	❑	❑	❑	❑	❑	❑
Psykiske plager 149	❑	❑	❑	❑	❑	❑
Allergi 155	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 161	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 167	____	____	____	____	____	____

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 177	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 178	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 179	❑	❑
Har du hatt episoder med piping i brystet? 180	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 181	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 185	❑	❑

Hvor ofte er du plaget av søvnløshet?

Aldri, eller noen få ganger i året 186	❑ 1
1-2 ganger i måneden	❑ 2
Omtrent en gang i uken	❑ 3
Mer enn en gang i uken	❑ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?

Ingen spesiell tid 187	❑ 1
Særlig i mørketiden	❑ 2
Særlig i midnattsoltiden	❑ 3
Særlig vår og høst	❑ 4

	Ja	Nei
Har du det siste året vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 188	❑	❑

Hvor ofte er du plaget av hodepine?

Sjelden eller aldri 189	❑ 1
En eller flere ganger i måneden	❑ 2
En eller flere ganger i uken	❑ 3
Daglig	❑ 4

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

Ikke i det hele tatt 190	❑ 1
Bare i liten grad	❑ 2
En del	❑ 3
Ganske mye	❑ 4

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:
*Sett **0** hvis du **ikke** har hatt slik kontakt.*

	Antall ganger siste år
Hos vanlig lege/legevakt 191	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 197	_____
Innlagt i sykehus	_____
Hos bedriftslege	_____
Hos fysioterapeut 203	_____
Hos kiropraktor	_____
Hos akupunktør	_____
Hos tannlege 209	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
*Sett **0** hvis du **ikke** har brukt midlene.*

Legemidler
- Smertestillende ....215 _____ mnd.
- Sovemedisin .... _____ mnd.
- Beroligende midler .... _____ mnd.
- Medisin mot depresjon ....221 _____ mnd.
- Allergimedisin .... _____ mnd.
- Astmamedisin .... _____ mnd.

Kosttilskudd
- Jerntabletter ....227 _____ mnd.
- Kalktabletter eller benmel .... _____ mnd.
- Vitamin D-tilskudd .... _____ mnd.
- Andre vitamintilskudd ....233 _____ mnd.
- Tran eller fiskeoljekapsler .... _____ mnd.

Har du de siste 14 dager brukt følgende legemidler eller kosttilskudd?
*Sett **ett** kryss for **hvert** spørsmål.*

	Ja	Nei
Legemidler		
Smertestillende medisin 237	❑	❑
Febersenkende medisin	❑	❑
Migrenemedisin	❑	❑
Eksemsalve	❑	❑
Hjertemedisin (ikke blodtrykksmedisin)	❑	❑
Kolesterolsenkende medisin 242	❑	❑
Sovemedisin	❑	❑
Beroligende medisin	❑	❑
Medisin mot depresjon	❑	❑
Annen nervemedisin	❑	❑
Syrenøytraliserende midler 247	❑	❑
Magesårsmedisin	❑	❑
Insulin	❑	❑
Tabletter mot diabetes (sukkersyke)	❑	❑
Tabletter mot lavt stoffskifte (thyroxin)	❑	❑
Kortisontabletter 252	❑	❑
Annen medisin	❑	❑
Kosttilskudd		
Jerntabletter	❑	❑
Kalktabletter eller benmel	❑	❑
Vitamin D-tilskudd	❑	❑
Andre vitamintilskudd 257	❑	❑
Tran eller fiskeoljekapsler	❑	❑

VENNER

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ....259 ____ gode venner
Tell ikke med de du bor sammen med, men ta med andre slektninger!

Hvor mange av disse gode vennene har du kontakt med minst en gang i måneden? ....261 ____

	Ja	Nei
Føler du at du har nok gode venner? 263	❑	❑

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?
- Aldri, eller noen få ganger i året ....264 ❑ 1
- 1-2 ganger i måneden .... ❑ 2
- Omtrent en gang i uken .... ❑ 3
- Mer enn en gang i uken .... ❑ 4

KOSTVANER

Hvis du bruker smør eller margarin på brødet, hvor mange skiver rekker en liten porsjonspakning vanligvis til? Vi tenker på slik porsjonspakning som du får på fly, på kafé o.l. (10-12 gram).

Den rekker til omtrent ....265 _____ skiver

Hva slags fett blir vanligvis brukt til **matlaging** (ikke på brødet) i din husholdning?
- Meierismør ....266 ❑
- Hard margarin .... ❑
- Bløt (Soft) margarin .... ❑
- Smør/margarin blanding .... ❑
- Oljer ....270 ❑

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss!

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 271	❑	❑	❑	❑ 275

Hvor mye (i **antall** glass, kopper, poteter eller brødskiver) spiser eller drikker du vanligvis **daglig** av følgende matvarer?
*Kryss av for **alle** matvarene.*

	0	Færre enn 1	1-2	3-4	5-6	Mer enn 6
Helmelk (søt eller sur) (glass) 276	❑	❑	❑	❑	❑	❑
Lettmelk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Skummet melk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Te (kopper)	❑	❑	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑	❑	❑
Poteter 281	❑	❑	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød)	❑	❑	❑	❑	❑	❑
Brødskiver med						
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑	❑	❑
– magert kjøttpålegg (f.eks. skinke)	❑	❑	❑	❑	❑	❑
– fetere kjøttpålegg (f.eks. salami)	❑	❑	❑	❑	❑	❑
– gulost 286	❑	❑	❑	❑	❑	❑
– brunost	❑	❑	❑	❑	❑	❑
– kaviar	❑	❑	❑	❑	❑	❑
– syltetøy og annet søtt pålegg	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Hvor mange **ganger i uka** spiser du vanligvis følgende matvarer?
*Kryss av for **alle** matvarene.*

	Aldri	Færre enn 1	1	2-3	4-5	Omtrent daglig
Yoghurt 290	❑	❑	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑	❑	❑
Middag med						
– rent kjøtt	❑	❑	❑	❑	❑	❑
– pølser/kjøttpudding/-kaker	❑	❑	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer) 295	❑	❑	❑	❑	❑	❑
– mager fisk (f.eks. torsk)	❑	❑	❑	❑	❑	❑
– fiskeboller/-pudding/-kaker	❑	❑	❑	❑	❑	❑
– grønnsaker	❑	❑	❑	❑	❑	❑
Majones, remulade o.l.	❑	❑	❑	❑	❑	❑
Gulrøtter 300	❑	❑	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑	❑	❑
Appelsiner, mandariner o.l.	❑	❑	❑	❑	❑	❑
Sukkerholdige leskedrikker	❑	❑	❑	❑	❑	❑
Sukkerfrie («Light») leskedrikker	❑	❑	❑	❑	❑	❑
Sjokolade	❑	❑	❑	❑	❑	❑
Vafler, kaker o.l. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALKOHOL

Hvor ofte pleier du å drikke	øl?	vin?	brennevin?
Aldri, eller noen få ganger i året	❑ 308	❑	❑ 1
1-2 ganger i måneden	❑	❑	❑ 2
Omtrent 1 gang i uken	❑	❑	❑ 3
2-3 ganger i uken	❑	❑	❑ 4
Omtrent hver dag	❑	❑	❑ 5 310

Omtrent hvor ofte har du i løpet av siste år drukket alkohol tilsvarende minst 5 halvflasker øl, en helflaske vin eller 1/4 flaske brennevin?

- Ikke siste år ..... 311 ❑ 1
- Noen få ganger ..... ❑ 2
- 1 - 2 ganger per måned ..... ❑ 3
- 1 - 2 ganger i uken ..... ❑ 4
- 3 eller flere ganger i uken ..... ❑ 5

I omtrent hvor mange år har ditt alkoholforbruk vært slik du har svart i spørsmålene over? ..... 312 _____ år

SLANKING

Omtrent hvor mange ganger har du bevisst prøvd å slanke deg? Sett **0** hvis ingen forsøk.

- – før 20 år ..... 314 _____ ganger
- – senere ..... 316 _____ ganger

Hvis du har slanket deg, omtrent hvor mange kilo har du på det meste gått ned i vekt?

- – før 20 år ..... 318 _____ kg
- – senere ..... 320 _____ kg

Hvilken vekt ville du være tilfreds med (din "trivselsvekt")? ..... 322 _____ kg

UFRIVILLIG URINLEKKASJE

Hvor ofte har du ufrivillig urinlekkasje?

- Aldri ..... 325 ❑ 1
- Ikke mer enn en gang i måneden ..... ❑ 2
- To eller flere ganger i måneden ..... ❑ 3
- Ukentlig eller oftere ..... ❑ 4

Dine kommentarer:

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 326 _____ år

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... 328 _____ år

Når du ser bort fra svangerskap og barselsperiode, har du noen gang vært blødningsfri i minst 6 måneder? 330	Ja ❑	Nei ❑

Hvis "Ja", hvor mange ganger? ..... 331 _____ ganger

Hvis du fremdeles har menstruasjon eller er gravid:

Hvilken dato startet din siste menstruasjon? ..... 333 dag/ mnd/ år ___/___/___

Bruker du vanligvis smertestillende legemidler for å dempe menstruasjonsplager? 339	Ja ❑	Nei ❑

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Er du gravid nå? 342	Ja ❑	Nei ❑	Usikker ❑

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? 343	Ja ❑	Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 344	❑	❑
Eggehvite i urinen 346	❑	❑

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.

Barn:	Fødselsår:	Antall måneder med amming:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

PREVENSJON OG ØSTROGEN

Bruker du, eller har du brukt:	Nå	Før	Aldri
P-pille (også minipille) 372	❑	❑	❑
Hormonspiral	❑	❑	❑
Østrogen (tabletter eller plaster) 374	❑	❑	❑
Østrogen (krem eller stikkpiller)	❑ 1	❑ 2	❑ 3

Hvis du bruker p-pille, hormonspiral eller østrogen; hvilket merke bruker du nå?

376 .....

Hvis du bruker eller har brukt p-pille:

Alder da du begynte med P-piller? ..... 380 _____ år

Hvor mange år har du tilsammen brukt P-piller? ..... 382 _____ år

Dersom du har født, hvor mange år brukte du P-piller før første fødsel? ..... 384 _____ år

Hvis du har sluttet å bruke P-piller:

Alder da du sluttet? ..... 386 _____ år

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsen i Tromsø

Helseundersøkelsen i Tromsø

for dem som er 70 år og eldre.

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. De skal også øke kunnskapen om kreftsykdommer og alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Endelig skal de gi kunnskap om hvorledes den eldste delen av befolkningen har det. Vi ber deg derfor svare på spørsmålene nedenfor.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø

Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du purring.

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dato for utfylling av skjema: ..... 18 Dag ...../ Mnd ...../ År .....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 -28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑ 1
- Gode ..... ❑ 2
- Vanskelige ..... ❑ 3
- Meget vanskelige ..... ❑ 4

Hvor gamle ble dine foreldre?

- Mor ble ..... 30 _____ år
- Far ble ..... 32 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.	Ja	Nei	Antall
Ektefelle/samboer 34	❑	❑	
Andre personer over 18 år 35	❑	❑	_____
Personer under 18 år 38	❑	❑	_____

Hvilken type bolig bor du i?

- Enebolig/villa ..... 41 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor lenge har du bodd i boligen du bor i nå? ..... 42 _____ år

	Ja	Nei
Er boligen tilpasset til dine behov? 44	❑	❑
Hvis "Nei", er det problemer med:		
Plassen i boligen 45	❑	❑
Ujevn, for høy eller for lav temperatur 46	❑	❑
Trapper 47	❑	❑
Toalett 48	❑	❑
Bad/dusj 49	❑	❑
Vedlikehold 50	❑	❑
Annet (spesifiser) 51	❑	❑
Ønsker du å flytte til en eldrebolig? 52	❑	❑

TIDLIGERE ARBEID OG ØKONOMI

Hvordan vil du beskrive det arbeidet du hadde de siste 5-10 årene før du ble pensjonist?

- For det meste stillesittende arbeid? ..... 53 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarbeid, husmor, undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Har du hatt noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.	Ja	Nei
Sjåfør 54	❑	❑
Bonde/gårdbruker 55	❑	❑
Fisker 56	❑	❑

Hvor gammel var du da du ble pensjonert? ..... 57 _____ år

Hva slags pensjon har du?

- Minstepensjon ..... 59 ❑
- Tilleggspensjon ..... 60 ❑

Hvordan er din økonomi nå?

- Meget god ..... 61 ❑ 1
- God ..... ❑ 2
- Vanskelig ..... ❑ 3
- Meget vanskelig ..... ❑ 4

HELSE OG SYKDOM

Er helsen din blitt forandret det siste året?

- Ja, dårligere ..... 62 ❑ 1
- Nei, uforandret ..... ❑ 2
- Ja, bedre ..... ❑ 3

Hvordan synes du at helsen din er nå i forhold til andre på samme alder?

- Mye dårligere ..... 63 ❑ 1
- Litt dårligere ..... ❑ 2
- Omtrent lik ..... ❑ 3
- Litt bedre ..... ❑ 4
- Mye bedre ..... ❑ 5

EGNE SYKDOMMER

Har du noen gang hatt:

Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen. Hvis det har skjedd flere ganger, hvor gammel var du siste gang?

	Ja	Nei	Alder
Lårhalsbrudd 64	❑	❑	_____
Brudd ved håndledd/underarm 67	❑	❑	_____
Nakkesleng (whiplash) 70	❑	❑	_____
Skade som førte til sykehusinnleggelse 73	❑	❑	_____
Sår på magesekken 76	❑	❑	_____
Sår på tolvfingertarmen 79	❑	❑	_____
Magesår-operasjon 82	❑	❑	_____
Operasjon på halsen 85	❑	❑	_____

Har du eller har du hatt:

Sett ett kryss for hvert spørsmål.	Ja	Nei
Kreftsykdom 88	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Parkinsons sykdom	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis 93	❑	❑
Benskjørhet (osteoporose)	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren 98	❑	❑
Gjentatt, ufrivillig urinlekkasje	❑	❑
Grønn stær	❑	❑
Grå stær	❑	❑
Slitasjegikt (artrose)	❑	❑
Leddgikt 103	❑	❑
Nyrestein	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue 108	❑	❑
Matvareallergi	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? 111 ____ ganger

	Ja	Nei
Har du hatt dette de siste 14 dager? 113	❑	❑

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:

Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 114	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 120	❑	❑	❑	❑	❑	❑
Kreftsykdom 126	❑	❑	❑	❑	❑	❑
Høyt blodtrykk 132	❑	❑	❑	❑	❑	❑
Astma 138	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 144	❑	❑	❑	❑	❑	❑
Slitasjegikt (artrose) 150	❑	❑	❑	❑	❑	❑
Psykiske plager 156	❑	❑	❑	❑	❑	❑
Alderdomssløvhet 162	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 168	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 174	__	__	__	__	__	

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 184	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 185	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 186	❑	❑
Har du hatt episoder med piping i brystet? 187	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 188	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde 191	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 192	❑	❑
Har du gått ned i vekt siste året? 193	❑	❑
Hvis "Ja":		
Hvor mange kilo? 194	_____ kg	

Hvor ofte er du plaget av søvnløshet?

- Aldri, eller noen få ganger i året ..... 196 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?

- Ingen spesiell tid ..... 197 ❑ 1
- Særlig i mørketiden ..... ❑ 2
- Særlig i midnattsoltiden ..... ❑ 3
- Særlig vår og høst ..... ❑ 4

	Ja	Nei
Pleier du å ta en lur på dagen? 198	❑	❑
Føler du at du vanligvis får nok søvn?	❑	❑

Er du plaget av:	Nei	Litt	I stor grad
Svimmelhet 200	❑	❑	❑
Dårlig hukommelse	❑	❑	❑
Kraftløshet	❑	❑	❑
Forstoppelse 203	❑	❑	❑

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

- Ikke i det hele tatt ..... 204 ❑
- Bare i liten grad ..... ❑
- En del ..... ❑
- Ganske mye ..... ❑

LEGEMLIGE FUNKSJONER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre?	Ja	Med noe hjelp	Nei
Gå innendørs i samme etasje 205	❑	❑	❑
Gå i trapper	❑	❑	❑
Gå utendørs	❑	❑	❑
Gå ca. 500 meter	❑	❑	❑
Gå på toalettet	❑	❑	❑
Vaske deg på kroppen 210	❑	❑	❑
Bade eller dusje	❑	❑	❑
Kle på og av deg	❑	❑	❑
Legge deg og stå opp	❑	❑	❑
Spise selv	❑	❑	❑
Lage varm mat 215	❑	❑	❑
Gjøre lett husarbeid (f.eks. oppvask)	❑	❑	❑
Gjøre tyngre husarbeid (f.eks. gulvvask)	❑	❑	❑
Gjøre innkjøp	❑	❑	❑
Ta bussen	❑	❑	❑

	Ja	Vanskelig	Nei
Kan du høre vanlig tale (evt. med høreapparat)? 220	❑	❑	❑
Kan du lese (evt. med briller)? 221	❑	❑	❑

Er du avhengig av noen av disse hjelpemidlene?

	Ja	Nei
Stokk 222	❑	❑
Krykke	❑	❑
Gåstol (rullator)	❑	❑
Rullestol	❑	❑
Høreapparat	❑	❑
Trygghetsalarm 227	❑	❑

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært: *Sett 0 hvis du ikke har hatt slik kontakt.*	Antall ganger siste år
Hos vanlig lege/legevakt 228	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 234	_____
Innlagt i sykehus	_____
Hos fysioterapeut	_____
Hos kiropraktor 240	_____
Hos akupunktør	_____
Hos tannlege	_____
Hos fotterapeut 246	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

Har du hjemmehjelp?	Ja	Nei
Privat 252	❑	❑
Kommunal	❑	❑

Har du hjemmesykepleie? ..... ❑ ❑

Er du fornøyd med helse- og hjemmetjenesten i kommunen?	Ja	Nei	Vet ikke
Prinsippet med fast lege 255	❑	❑	❑
Hjemmesykepleien	❑	❑	❑
Hjemmehjelpen	❑	❑	❑

Er du trygg på at du kan få hjelp av helse- og hjemmetjenesten hvis du trenger det?

- Trygg ..... 258 ❑ 1
- Ikke trygg ..... ❑ 2
- Svært utrygg ..... ❑ 3
- Vet ikke ..... ❑ 4

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
Sett 0 hvis du ikke har brukt midlene.

Legemidler

- Smertestillende ..... 259 _____ mnd.
- Sovemedisin ..... _____ mnd.
- Beroligende midler ..... _____ mnd.
- Medisin mot depresjon ..... 265 _____ mnd.
- Allergimedisin ..... _____ mnd.
- Astmamedisin ..... _____ mnd.
- Hjertemedisin (ikke blodtrykksmedisin) ..... 271 _____ mnd.
- Insulin ..... _____ mnd.
- Tabletter mot diabetes (sukkersyke) ..... _____ mnd.
- Tabletter mot lavt stoffskifte (thyroxin) ..... 277 _____ mnd.
- Kortisontabletter ..... _____ mnd.
- Midler mot forstoppelse ..... _____ mnd.

Kosttilskudd

- Jerntabletter ..... 283 _____ mnd.
- Vitamin D-tilskudd ..... _____ mnd.
- Andre vitamintilskudd ..... _____ mnd.
- Kalktabletter eller benmel ..... 289 _____ mnd.
- Tran eller fiskeoljekapsler ..... _____ mnd.

FAMILIE OG VENNER

Har du nær familie som kan gi deg hjelp og støtte når du trenger det? 293	Ja	Nei
	❑	❑

Hvis "Ja": Hvem kan gi deg hjelp?

- Ektefelle/samboer ..... 294 ❑
- Barn ..... ❑
- Andre ..... ❑

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ..297 ____ **gode venner**
Tell ikke med dem du bor sammen med, men ta med andre slektninger!

	Ja	Nei
Føler du at du har nok gode venner? 299	❑	❑

Føler du at du hører med i et fellesskap (gruppe av mennesker) som stoler på hverandre og føler forpliktelse overfor hverandre (f.eks. i politisk parti, religiøs gruppe, slekt, naboskap, arbeidsplass eller organisasjon)?

- Sterk tilhørighet ..... 300 ❑ 1
- Noe tilhørighet ..... ❑ 2
- Usikkert ..... ❑ 3
- Liten eller ingen tilhørighet ..... ❑ 4

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?

- Aldri, eller noen få ganger i året ..... 301 ❑ 1
- 1-2 ganger i måneden ..... ❑ 2
- Omtrent en gang i uken ..... ❑ 3
- Mer enn en gang i uken ..... ❑ 4

KOSTVANER

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? ..... 302 _____ Antall

Hvor mange ganger i uken spiser du varm middag? ..... 304 _____

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss.

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 306	❑	❑	❑	❑ 310

Hva slags fett blir til vanligvis brukt til *matlaging* (ikke på brødet) i din husholdning?

- Meierismør ..... 311 ❑
- Hard margarin ..... ❑
- Bløt (Soft) margarin ..... ❑
- Smør/margarin blanding ..... ❑
- Oljer ..... 315 ❑

Hvor mye (i antall glass, poteter eller brødskiver) spiser/drikker du vanligvis daglig av følgende matvarer?
Kryss av for alle matvarene.

	Ingen	Mindre enn 1	1-2	3 og mer
Melk alle sorter (glass) 316	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑
Poteter	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød) ...	❑	❑	❑	❑
Brødskiver med				
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑
– gulost	❑	❑	❑	❑
– kaviar 322	❑ 1	❑ 2	❑ 3	❑ 4

Hvor mange ganger i uka spiser du vanligvis følgende matvarer?
Kryss av for alle matvarene.

	Aldri	Sjeldnere enn 1	1	2 og mer
Yoghurt 323	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑
Middag med				
– rent kjøtt	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer)	❑	❑	❑	❑
– mager fisk (f.eks. torsk) 328	❑	❑	❑	❑
– grønnsaker (rå eller kokte)	❑	❑	❑	❑
Gulrøtter (rå eller kokte)	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑
Appelsiner, mandariner o.l. 333	❑ 1	❑ 2	❑ 3	❑ 4

TRIVSEL

Hvordan trives du med å bli gammel - alt i alt?

- Godt ..... 334 ❑ 1
- Ganske bra ..... ❑ 2
- Opp og ned ..... ❑ 3
- Dårlig ..... ❑ 4

Hvordan ser du på livet fremover?

- Lyst ..... 335 ❑ 1
- Ikke så verst ..... ❑ 2
- Nokså bekymret ..... ❑ 3
- Mørkt ..... ❑ 4

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 336 _____ år

Hvor gammel var du da menstruasjonen sluttet? ..... 338 _____ år

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.
Hvis du har født mer enn 6 barn, noter fødselsår og antall måneder med amming for dem nederst på siden.

Barn:	Fødselsår:	Antall måneder med amming:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? ..... 366 Ja ❑ Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 367	❑	❑
Eggehvite i urinen 369	❑	❑

ØSTROGEN-MEDISIN

Bruker du, eller har du brukt, østrogen-medisin?

	Nå	Før	Aldri
Tabletter eller plaster 371	❑	❑	❑
Krem eller stikkpiller 372	❑	❑	❑

Hvis du bruker østrogen, hvilket merke bruker du nå?

..... 373

Dine kommentarer:

Takk for hjelpen! Husk å postlegge skjemaet idag!
Helseundersøkelsen i Tromsø

10. MOSJON OG FYSISK AKTIVITET

10.1 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

10.2 Angi bevegelse og kroppslig anstrengelse i din 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 som passer best)

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? ☐ 1

Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka? ☐ 2
(Her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m.)

Driver mosjonsidrett, tyngre hagearbeid e.l.? ☐ 3
(Merk at aktiviteten skal vare minst 4 timer i uka)

Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka? ☐ 4

11. FAMILIE OG VENNER

11.1 Bor du sammen med:

	JA	NEI
Ektefelle/samboer?	☐	☐

11.2 Hvor mange gode venner har du? *Antall venner* ☐☐

Regn med de du kan snakke fortrolig med og som kan gi deg hjelp dersom du trenger det. Tell ikke med de du bor sammen med, men ta med andre slektninger.

11.3 Hvor stor interesse viser folk for det du gjør?
(Sett bare ett kryss)

Stor interesse	Noe interesse	Litt interesse	Ingen interesse	Usikkert
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11.4 Hvor mange foreninger, lag, grupper, kirkesamfunn e.l. deltar du i på fritiden? *Antall* ☐☐
(Skriv 0 hvis ingen)

11.5 Føler du at du kan påvirke det som skjer i lokalsamfunnet der du bor? *(Sett bare ett kryss)*

Ja, i stor grad	Ja, en del	Ja, i liten grad	Nei	Har ikke forsøkt
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

12. SYKDOM I FAMILIEN

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

	JA	NEI	VET IKKE
	☐	☐	☐

12.2 Kryss av for de slektningene som har eller har hatt noen av sykdommene: *(Sett kryss for hver linje)*

	Mor	Far	Bror	Søster	Barn	Ingen av disse
Hjerneslag eller hjerneblødning	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder	☐	☐	☐	☐	☐	☐
Astma	☐	☐	☐	☐	☐	☐
Kreftsykdom	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke)	☐	☐	☐	☐	☐	☐

12.3 Hvis noen slektninger har diabetes, i hvilken alder fikk de diabetes (hvis for eks. flere søsken, før opp den som fikk det tidligst i livet):

Vet ikke, ikke aktuelt	Mors alder	Fars alder	Brors alder	Søsters alder	Barns alder
☐	☐☐	☐☐	☐☐	☐☐	☐☐

13. BRUK AV MEDISINER

Med medisiner mener vi her medisiner kjøpt på apotek.
Kosttilskudd og vitaminer regnes ikke med her.

13.1 Bruker du?

	Nå	Før, men ikke nå	Aldri brukt
Medisin mot høyt blodtrykk	☐	☐	☐
Kolesterolsenkende medisin	☐	☐	☐

13.2 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?
(Sett ett kryss pr. linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende uten resept	☐	☐	☐	☐
Smertestillende på resept	☐	☐	☐	☐
Sovemedisin	☐	☐	☐	☐
Beroligende medisin	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐
Annen medisin på resept	☐ 1	☐ 2	☐ 3	☐ 4

13.3 For de medisinene som du har krysset av for i pkt. 13.1 og 13.2, og som du har brukt i løpet av de siste 4 ukene:

Angi navnet og hvilken grunn det er til at du tar/har tatt disse (sykdom eller symptom):
(Kryss av for hvor lenge du har brukt medisinen)

Navn på medisinen: *(ett navn pr. linje):*	Grunn til bruk av medisinen:	Hvor lenge har du brukt medisinen? Inntil 1 år	Ett år eller mer
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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

14. RESTEN AV SKJEMAET SKAL BARE BESVARES AV KVINNER

14.1 Hvor gammel var du da du fikk menstruasjon aller første gang? *Alder i år* ☐☐

14.2 Hvis du ikke lenger får menstruasjon, hvor gammel var du da den sluttet? *Alder i år* ☐☐

14.3 Er du gravid nå?

Ja	Nei	Usikker	Over fruktbar alder
☐ 1	☐ 2	☐ 3	☐ 4

14.4 Hvor mange barn har du født? *Antall barn* ☐☐

14.5 Bruker du, eller har du brukt?
(Sett ett kryss for hver linje)

	Nå	Før, men ikke nå	Aldri
P-pille/minipille/p-sprøyte	☐	☐	☐
Hormonspiral *(ikke vanlig spiral)*	☐	☐	☐
Østrogen *(tabletter eller plaster)*	☐	☐	☐
Østrogen *(krem eller stikkpiller)*	☐	☐	☐

14.6 Hvis du bruker/har brukt reseptpliktig østrogen:
Hvor lenge har du brukt dette? *Antall år* ☐☐

14.7 Hvis du bruker p-pille, minipille, p-sprøyte, hormonspiral eller østrogen; hvilket merke bruker du?

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Helse-undersøkelsen

Personlig innbydelse

Ikke skriv her:

5.3 (Kommune) ☐☐☐☐ (Fylke) ☐☐ (Land) ☐☐☐☐

9.3 (Virksomhet) ☐☐☐☐☐ 9.4 (Yrke) ☐☐☐☐☐ 14.7 (Merke) ☐☐ ☐☐☐☐

1. EGEN HELSE

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

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

1.2 Har du, eller har du hatt?:

	JA	NEI	Alder første gang
Astma	☐	☐	
Høysnue	☐	☐	
Kronisk bronkitt/emfysem	☐	☐	
Diabetes (sukkersyke)	☐	☐	
Benskjørhet (osteoporose)	☐	☐	
Fibromyalgi/kronisk smertesyndrom	☐	☐	
Psykiske plager som du har søkt hjelp for	☐	☐	
Hjerteinfarkt	☐	☐	
Angina pectoris (hjertekrampe)	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	

1.3 Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året? JA ☐ NEI ☐

1.4 Får du smerter eller ubehag i brystet når du:

	JA	NEI
Går i bakker, trapper eller fort på flat mark?	☐	☐

1.5 Hvis du får slike smerter, pleier du da å:

Stoppe? ☐ 1 | Saktne farten? ☐ 2 | Fortsette i samme takt? ☐ 3

1.6 Dersom du stopper, forsvinner smertene da etter mindre enn 10 minutter? JA ☐ NEI ☐

1.7 Kan slike smerter opptre selv om du er i ro? JA ☐ NEI ☐

2. MUSKEL OG SKJELETTPLAGER

2.1 Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 4 ukene?
(Varighet angis bare hvis du har hatt plager)

	Ikke plaget	En del plaget	Sterkt plaget	Varighet: Inntil 2 uker	Varighet: 2 uker eller mer
Nakke/skuldre	☐	☐	☐	☐	☐
Armer, hender	☐	☐	☐	☐	☐
Øvre del av ryggen	☐	☐	☐	☐	☐
Korsryggen	☐	☐	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐	☐	☐
Andre steder	☐	☐	☐	☐	☐
	1	2	3	1	2

2.2 Har du noen gang hatt:

	JA	NEI	Alder siste gang
Brudd i håndledd/underarm?	☐	☐	
Lårhalsbrudd?	☐	☐	

3. ANDRE PLAGER

3.1 Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?
(Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐
	1	2	3	4

4. BRUK AV HELSETJENESTER

4.1 Hvor mange ganger de siste 12 månedene har du selv brukt:
(Sett ett kryss for hver linje)

	Ingen	1-3 ganger	4 eller flere
Allmennpraktiserende lege	☐	☐	☐
Bedriftslege	☐	☐	☐
Psykolog eller psykiater *(privat eller på poliklinikk)*	☐	☐	☐
Annen spesialist *(privat eller på poliklinikk)*	☐	☐	☐
Legevakt *(privat eller offentlig)*	☐	☐	☐
Sykehusinnleggelse	☐	☐	☐
Hjemmesykepleie	☐	☐	☐
Fysioterapeut	☐	☐	☐
Kiropraktor	☐	☐	☐
Tannlege	☐	☐	☐
Alternativ behandler	☐	☐	☐

5. OPPVEKST OG TILHØRIGHET

5.1 Hvor lenge har du samlet bodd i fylket? ☐☐ år
(Sett 0 hvis mindre enn et halvt år)

5.2 Hvor lenge har du samlet bodd i kommunen? ☐☐ år
(Sett 0 hvis mindre enn et halvt år)

5.3 Hvor bodde du det meste av tiden før du fylte 16 år?
(kryss av for ett alternativ og spesifiser)

Samme kommune ☐ 1

Annen kommune i fylket ☐ 2 Hvilken: _____

Annet fylke i Norge ☐ 3 Hvilket: _____

Utenfor Norge ☐ 4 Land: _____

5.4 Har du flyttet i løpet av de siste fem årene?

Nei ☐ 1 | Ja, en gang ☐ 2 | Ja, flere ganger ☐ 3

6. VEKT

6.1 Anslå din vekt da du var 25 år gammel: ☐☐☐ **hele kg**

7. MAT OG DRIKKE

7.1 Hvor ofte spiser du vanligvis disse matvarene?
(Sett ett kryss pr. linje)

	Sjelden /aldri	1-3 g. pr.mnd	1-3 g. pr.uke	4-6 g. pr.uke	1-2 g. pr.dag	3 g. el. mer pr.dag
Frukt, bær	☐	☐	☐	☐	☐	☐
Ost *(alle typer)*	☐	☐	☐	☐	☐	☐
Poteter	☐	☐	☐	☐	☐	☐
Kokte grønnsaker	☐	☐	☐	☐	☐	☐
Rå grønnsaker/salat	☐	☐	☐	☐	☐	☐
Feit fisk *(f.eks. laks, ørret, makrell, sild)*	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

7.2 Hva slags fett bruker du oftest? *(Sett ett kryss pr. linje)*

	Bruker ikke	Meieri-smør	Hard margarin	Myk/lett margarin	Oljer	Annet
På brødet	☐	☐	☐	☐	☐	☐
I matlagingen	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

7.3 Bruker du følgende kosttilskudd:

	Ja, daglig	Iblant	Nei
Tran, trankapsler, fiskeoljekapsler?	☐	☐	☐
Vitamin- og/eller mineraltilskudd?	☐	☐	☐

7.4 Hvor mye drikker du vanligvis av følgende?
(Sett ett kryss pr. linje)

	Sjelden /aldri	1-6 glass pr.uke	1 glass pr.dag	2-3 glass pr.dag	4 glass el. mer pr.dag
Helmelk, kefir, yoghurt	☐	☐	☐	☐	☐
Lettmelk, cultura, lettyoghurt	☐	☐	☐	☐	☐
Skummet melk (sur/søt)	☐	☐	☐	☐	☐
Ekstra lettmelk	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Vann	☐	☐	☐	☐	☐
Farris, Ramløsa e.l.	☐	☐	☐	☐	☐
Cola-holdig leskedrikk	☐	☐	☐	☐	☐
Annen brus/leskedrikk	☐	☐	☐	☐	☐
	1	2	3	4	5

7.5 Drikker du vanligvis brus/cola: Med sukker ☐ 1 Uten sukker ☐ 2

7.6 Hvor mange kopper kaffe og te drikker du daglig? *Antall kopper*
(Sett 0 for de typene du ikke drikker daglig)

Filterkaffe ☐☐

Kokekaffe/trykkanne ☐☐

Annen kaffe ☐☐

Te ☐☐

7.7 Omtrent hvor ofte har du i løpet av det siste året drukket alkohol?
(Lettøl og alkoholfritt øl regnes ikke med)

Har aldri drukket alkohol	Har ikke drukket alkohol siste år	Noen få ganger siste år	Omtrent 1 gang i måneden
☐ 1	☐ 2	☐ 3	☐ 4
2-3 ganger pr. måned	**ca. 1 gang i uka**	**2-3 ganger i uka**	**4-7 ganger i uka**
☐ 5	☐ 6	☐ 7	☐ 8

Til dem som har drukket siste år:

7.8 Når du har drukket alkohol, hvor mange glass eller drinker har du vanligvis drukket? *Antall* ☐☐

7.9 Omtrent hvor mange ganger i løpet av det siste året har du drukket så mye som minst 5 glass eller drinker i løpet av ett døgn? *Antall ganger* ☐☐

7.10 Når du drikker, drikker du da vanligvis: *(Sett ett eller flere kryss)*

Øl ☐ Vin ☐ Brennevin ☐

8. RØYKING

8.1 Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? *Antall hele timer* ☐☐

8.2 Røykte noen av de voksne hjemme da du vokste opp? JA ☐ NEI ☐

8.3 Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? JA ☐ NEI ☐

8.4 Har du røykt/røyker du daglig? Ja, nå ☐ Ja, tidligere ☐ Aldri ☐
Hvis ALDRI: Hopp til spørsmål 9 (UTDANNING OG ARBEID)

8.5 Hvis du røyker daglig nå, røyker du:

	JA	NEI
Sigaretter?	☐	☐
Sigarer/sigarillos?	☐	☐
Pipe?	☐	☐

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

8.7 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* ☐☐

9. UTDANNING OG ARBEID

9.1 Hvor mange års skolegang har du gjennomført? *Antall år* ☐☐
(Ta med alle år du har gått på skole eller studert)

9.2 Er du i inntektsgivende arbeid?

Ja, full tid ☐ 1 | Ja, deltid ☐ 2 | Nei ☐ 3

9.3 Beskriv virksomheten på det arbeidsstedet (avdelingen) der du utførte inntektsgivende arbeid i lengst tid de siste 12 mnd. *(F.eks. regnskapsbyrå, ungdomsskole, barneavd. på sykehus, snekkerverksted, bilverksted, bank, dagligvarehandel e.l.)*

Virksomhet: _____
Hvis pensjonert, skriv tidligere hovedvirksomhet og yrke. Gjelder også 9.4

9.4 Hvilket yrke/tittel har eller hadde du på dette arbeidsstedet? *(F.eks. sekretær, lærer, industriarbeider, barnepleier, møbelsnekker, avdelingsleder, selger, sjåfør e.l.)*

Yrke: _____

9.5 Arbeider du i ditt hovedyrke som selvstendig, som ansatt eller som familiemedlem uten fast avtalt lønn?

Selvstendig ☐ | Ansatt ☐ | Familiemedlem ☐

9.6 Mener du at du står i fare for å miste ditt nåværende arbeid eller inntekt de nærmeste 2 årene? JA ☐ NEI ☐

9.7 Mottar du noen av følgende ytelser?

	JA	NEI
Sykepenger (er sykmeldt)	☐	☐
Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon	☐	☐
Rehabiliterings-/attføringspenger	☐	☐
Uførepensjon (hel eller delvis)	☐	☐
Dagpenger under arbeidsledighet	☐	☐
Sosialhjelp/-stønad	☐	☐
Overgangsstønad for enslige forsørgere	☐	☐

E11. BRUK AV HELSETJENESTER

Hvor mange ganger de siste 12 månedene har du selv brukt:
(Sett ett kryss for hver linje)

	Ingen	1-3 ganger	4 eller flere
Allmennpraktiserende lege	☐	☐	☐
Spesialist *(privat eller på poliklinikk)*	☐	☐	☐
Legevakt *(privat eller offentlig)*	☐	☐	☐
Sykehusinnleggelse	☐	☐	☐
Hjemmesykepleie	☐	☐	☐
Fysioterapeut	☐	☐	☐
Kiropraktor	☐	☐	☐
Kommunal hjemmehjelp	☐	☐	☐
Tannlege	☐	☐	☐
Alternativ behandler	☐	☐	☐

Er du trygg på at du kan få hjelp av helseog hjemmetjenesten hvis du trenger det?

JA	NEI	Vet ikke
☐ 1	☐ 2	☐ 3

E12. FAMILIE OG VENNER

Bor du: Hjemme? ☐ 1 Institusjon/bofellesskap? ☐ 2

Bor du sammen med:

	JA	NEI
Ektefelle/samboer?	☐	☐
Andre personer?	☐	☐

Hvor mange gode venner har du?
Regn med de du kan snakke fortrolig med og som kan gi deg hjelp når du trenger det. Tell ikke med de du bor sammen med, men ta med barn og andre slektninger. ..... *Antall venner* ☐☐

Hvor stor interesse viser folk for det du gjør?
(Sett bare ett kryss)

Stor interesse	Noe interesse	Litt interesse	Ingen interesse	Usikkert
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Hvor mange foreninger, lag, grupper, kirkesamfunn e.l. deltar du i ? *Antall* ☐☐
(Skriv 0 hvis ingen)

E13. OPPVEKST OG TILHØRIGHET

Hvor lenge har du samlet bodd i fylket? ☐☐ år

Hvor lenge har du samlet bodd i kommunen? ☐☐ år

Hvor bodde du det meste av tiden før du fylte 16 år?
(Kryss av for ett alternativ og spesifiser)

Samme kommune ..... ☐ 1
Annen kommune i fylket ..... ☐ 2 Hvilken: _____
Annet fylke i Norge ..... ☐ 3 Hvilket: _____
Utenfor Norge ..... ☐ 4 Land: _____

Har du flyttet i løpet av de siste fem årene?

Nei	Ja, en gang	Ja, flere ganger
☐ 1	☐ 2	☐ 3

E14. BRUK AV MEDISINER

Med medisiner mener vi her medisiner kjøpt på apotek. Kosttilskudd og vitaminer regnes ikke med her.

Bruker du?
(Sett ett kryss for hver linje)

	Nå	Før, men ikke nå	Aldri brukt
Medisin mot høyt blodtrykk	☐	☐	☐
Kolesterolsenkende medisin	☐	☐	☐
Medisin mot osteoporose (benskjørhet)	☐	☐	☐
Insulin	☐	☐	☐
Tabletter mot sukkersyke	☐	☐	☐

Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?
(Sett ett kryss for hver linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende uten resept	☐	☐	☐	☐
Smertestillende på resept	☐	☐	☐	☐
Sovemedisin	☐	☐	☐	☐
Beroligende medisin	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐
Annen medisin på resept	☐	☐	☐	☐
	1	2	3	4

Angi navnet på de medisinene du bruker nå, og hva grunnen er til at du tar medisinene (sykdom eller symptom):
(Kryss av for hvor lenge du har brukt medisinen)

Navn på medisinen: (ett navn pr. linje):	Grunn til bruk av medisinen:	Hvor lenge har du brukt medisinen? Inntil 1 år	Ett år eller mer
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

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

E15. RESTEN AV SKJEMAET SKAL BARE BESVARES AV KVINNER

Hvor gammel var du da du fikk menstruasjon aller første gang? *Alder i år* ☐☐

Hvor gammel var du da menstruasjonen sluttet? *Alder i år* ☐☐

Hvor mange barn har du født? *Antall barn* ☐☐

Bruker du, eller har du brukt østrogenmedisin? *I antall år totalt*

	Aldri	Før	Nå	
Tabletter eller plaster	☐	☐	☐	☐☐
Krem eller stikkpiller	☐	☐	☐	☐☐

Hvis du bruker østrogen; hvilket merke bruker du nå?

_____

Har du noen gang brukt P-pille? JA ☐ NEI ☐

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E

Helse-undersøkelsen

Personlig innbydelse

Ikke skriv her:

E13 (Kommune)	(Fylke)	(Land)	E15 (Merke)	
☐☐☐☐	☐☐	☐☐☐☐	☐☐	☐☐

E1. 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
Astma	☐	☐	
Kronisk bronkitt/emfysem	☐	☐	
Diabetes (sukkersyke)	☐	☐	
Benskjørhet (osteoporose)	☐	☐	
Fibromyalgi/kronisk smertesyndrom	☐	☐	
Psykiske plager som du har søkt hjelp for	☐	☐	
Hjerteinfarkt	☐	☐	
Angina pectoris (hjertekrampe)	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	

Får du smerter eller ubehag i brystet når du:

	JA	NEI
Går i bakker, trapper eller fort på flat mark?	☐	☐

Hvis du får slike smerter, pleier du da å:

Stoppe?	Saktne farten?	Fortsette i samme takt?
☐ 1	☐ 2	☐ 3

	JA	NEI
Dersom du stopper, forsvinner smertene da etter mindre enn 10 minutter?	☐	☐
Kan slike smerter opptre selv om du er i ro?	☐	☐

E2. SYKDOM I FAMILIEN

Har en eller flere av dine foreldre eller søsken hatt:

	JA	NEI	Vet ikke
Hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?	☐	☐	☐

Kryss av for de slektningene som har eller har hatt noen av sykdommene: *(Sett kryss for hver linje)*

	Mor	Far	Bror	Søster	Barn	Ingen av disse
Hjerneslag eller hjerneblødning	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder	☐	☐	☐	☐	☐	☐
Astma	☐	☐	☐	☐	☐	☐
Kreftsykdom	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke)	☐	☐	☐	☐	☐	☐

Hvis noen slektninger har diabetes, i hvilken alder fikk de diabetes (hvis for eks. flere søsken, før opp den som fikk det tidligst i livet):

Vet ikke, ikke aktuelt	Mors alder	Fars alder	Brors alder	Søsters alder	Barns alder
☐					

E3. PLAGER

Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)? *(Sett ett kryss for hver linje)*

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐ 1	☐ 2	☐ 3	☐ 4

E4. TENNER, MUSKEL OG SKJELETT

Hvor mange tenner har du mistet/trukket? *Antall tenner*
(Se bort fra melketenner og visdomstenner)

Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 4 ukene?

	Ikke plaget	En del plaget	Alvorlig plaget
Nakke/skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

Har du noen gang hatt:

	JA	NEI	Alder siste gang
Brudd i håndledd/underarm?	☐	☐	
Lårhalsbrudd?	☐	☐	

Har du falt i løpet av det siste året? *(Sett bare ett kryss)*

Nei	Ja, 1-2 ganger	Ja, mer enn 2 ganger
☐ 1	☐ 2	☐ 3

E5. MOSJON OG FYSISK AKTIVITET

Hvordan har din fysiske aktivitet vært det siste året?
Tenk deg et ukentlig gjennomsnitt for året.
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

E6. VEKT

Anslå din vekt da du var 25 år gammel: ☐☐☐ **hele kg**

E7. UTDANNING

Hvor mange års skolegang har du gjennomført? *Antall år* ☐☐
(Ta med alle år du har gått på skole eller studert)

E8. MAT OG DRIKKE

Hvor ofte spiser du vanligvis disse matvarene?
(Sett ett kryss for hver linje)

	Sjelden /aldri	1-3 g. pr.mnd	1-3 g. pr.uke	4-6 g. pr.uke	1-2 g. pr.dag	3 g. el. mer pr.dag
Frukt, bær	☐	☐	☐	☐	☐	☐
Ost *(alle typer)*	☐	☐	☐	☐	☐	☐
Poteter	☐	☐	☐	☐	☐	☐
Kokte grønnsaker	☐	☐	☐	☐	☐	☐
Rå grønnsaker/salat	☐	☐	☐	☐	☐	☐
Feit fisk *(f.eks. laks, ørret, makrell, sild)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Bruker du kosttilskudd:

	Ja, daglig	Iblant	Nei
Tran, trankapsler, fiskeoljekapsler	☐	☐	☐
Vitamin- og/eller mineraltilskudd	☐	☐	☐

Hvor mye drikker du vanligvis av følgende?
(Sett ett kryss for hver linje)

	Sjelden /aldri	1-6 glass pr.uke	1 glass pr.dag	2-3 glass pr.dag	4 glass el. mer pr.dag
Helmelk, kefir, yoghurt	☐	☐	☐	☐	☐
Lettmelk, cultura, lettyoghurt	☐	☐	☐	☐	☐
Skummet melk (sur/søt)	☐	☐	☐	☐	☐
Ekstra lettmelk	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Vann	☐	☐	☐	☐	☐
Brus, mineralvann	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Hvor mange kopper kaffe og te drikker du daglig?
(Sett 0 for de typene du ikke drikker daglig) *Antall kopper*

Filterkaffe	☐☐
Kokekaffe/trykkanne	☐☐
Annen kaffe	☐☐
Te	☐☐

Omtrent hvor ofte har du i løpet av det siste året drukket alkohol? *(Lettøl og alkoholfritt øl regnes ikke med)*

Har aldri drukket alkohol	Har ikke drukket alkohol siste år	Noen få ganger siste år	Omtrent 1 gang i måneden
☐ 1	☐ 2	☐ 3	☐ 4
2-3 ganger pr. måned	**ca. 1 gang i uka**	**2-3 ganger i uka**	**4-7 ganger i uka**
☐ 5	☐ 6	☐ 7	☐ 8

Til dem som har drukket siste år:

Når du har drukket alkohol, hvor mange glass eller drinker har du vanligvis drukket? *Antall* ☐☐

Omtrent hvor mange ganger i løpet av det siste året har du drukket så mye som minst 5 glass eller drinker i løpet av ett døgn? *Antall ganger* ☐☐

E9. RØYKING

Hvor lenge er du vanligvis daglig tilstede i et røykfylt rom? *Antall hele timer* ☐☐

	JA	NEI
Røykte noen av de voksne hjemme da du vokste opp?	☐	☐
Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år?	☐	☐

	Ja, nå	Ja, tidligere	Aldri
Har du røykt/røyker du daglig?	☐	☐	☐

Hvis du ALDRI har røykt daglig;
Hopp til spørsmål E11 (FUNKSJON OG TRYGGHET)

Hvis du røyker daglig nå, røyker du:	JA	NEI
Sigaretter?	☐	☐
Sigarer/sigarillos?	☐	☐
Pipe?	☐	☐

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* ☐☐

E10. FUNKSJON OG TRYGGHET

Ville du følt deg trygg ved å ferdes alene på kveldstid i nærområdet der du bor?

Ja	Litt utrygg	Svært utrygg
☐ 1	☐ 2	☐ 3

Når det gjelder førlighet, syn og hørsel, kan du: *(Sett ett kryss for hver linje)*

	Uten problemer	Med litt problemer	Med store problemer	Nei
Gå en 5 minutters tur i noenlunde raskt tempo?	☐	☐	☐	☐
Lese vanlig tekst i aviser, evt. med briller?	☐	☐	☐	☐
Høre hva som blir sagt i en normal samtale?	☐ 1	☐ 2	☐ 3	☐ 4

Har du på grunn av varige helseproblemer vansker med å: *(Sett ett kryss for hver linje)*

	Ingen vansker	Noen vansker	Store vansker
Bevege deg rundt i egen bolig?	☐	☐	☐
Komme deg ut av boligen på egen hånd?	☐	☐	☐
Delta i foreningsliv eller andre fritidsaktiviteter?	☐	☐	☐
Bruke offentlige transportmidler?	☐	☐	☐
Utføre nødvendige daglige ærend?	☐	☐	☐

Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

- ☐ Meget god
- ☐ God
- ☐ Verken god eller dårlig
- ☐ Dårlig
- ☐ Meget dårlig

2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

- ☐ Mye bedre
- ☐ Litt bedre
- ☐ Omtrent lik
- ☐ Litt dårligere
- ☐ Mye dårligere

3 **Har du eller har du hatt?**

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐	☐	
Angina pectoris *(hjertekrampe)*	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	
Hjerteflimmer *(atrieflimmer)*	☐	☐	
Høyt blodtrykk	☐	☐	
Beinskjørhet *(osteoporose)*	☐	☐	
Astma	☐	☐	
Kronisk bronkitt/emfysem/KOLS	☐	☐	
Diabetes	☐	☐	
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	
Lavt stoffskifte	☐	☐	
Nyresykdom, unntatt urinveisinfeksjon	☐	☐	
Migrene	☐	☐	

4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?**

☐ Ja ☐ Nei

5 **Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?**

- ☐ Aldri, eller noen få ganger
- ☐ 1-3 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn 1 gang i uken

6 **Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?** (Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐

BRUK AV HELSETJENESTER

7 **Har du i løpet av de siste 12 måneder vært hos:** Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege	☐	☐	
Psykiater/psykolog	☐	☐	
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	
Fysioterapeut	☐	☐	
Kiropraktor	☐	☐	
Annen behandler *(homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l)*	☐	☐	
Tannlege/tannpleier	☐	☐	

8 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Ja	Nei	Ant ggr
Innlagt på sykehus	☐	☐	
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk	☐	☐	
Ved annen sykehuspoliklinikk	☐	☐	

9 **Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?**

☐ Ja ☐ Nei

BRUK AV MEDISINER

10 **Bruker du, eller har du brukt, noen av følgende medisiner?** (Sett ett kryss for hver linje)

	Aldri brukt	Nå	Før	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Medisin mot hjertesykdom	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Medisin mot beinskjørhet *(osteoporose)*	☐	☐	☐	
Insulin	☐	☐	☐	
Diabetesmedisin *(tabletter)*	☐	☐	☐	
Stoffskiftemedisinene Thyroxin/levaxin	☐	☐	☐	

11 **Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?** (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende reseptfrie	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

12 **Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode.** (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

13 **Hvem bor du sammen med?** (Sett kryss for hvert spørsmål og angi antall)

	Ja	Nei	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

14 **Kryss av for de slektninger som har eller har hatt**

	Foreldre	Barn	Søsken
Hjerteinfarkt	☐	☐	☐
Hjerteinfarkt før fylte 60 år	☐	☐	☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐
Hjerneslag/hjerneblødning	☐	☐	☐
Beinskjørhet *(osteoporose)*	☐	☐	☐
Magesår/tolvfingertarmsår	☐	☐	☐
Astma	☐	☐	☐
Diabetes	☐	☐	☐
Demens	☐	☐	☐
Psykiske plager	☐	☐	☐
Rusproblemer	☐	☐	☐

15 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

16 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

17 **Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?**

☐ Aldri, eller noen få ganger i året
☐ 1-2 ganger i måneden
☐ Omtrent 1 gang i uken
☐ Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

18 **Hva er din høyeste fullførte utdanning?** (Sett ett kryss)

☐ Grunnskole, framhaldsskole eller folkehøyskole
☐ Yrkesfaglig videregående, yrkesskole eller realskole
☐ Allmennfaglig videregående skole eller gymnas
☐ Høyskole eller universitet, mindre enn 4 år
☐ Høyskole eller universitet, 4 år eller mer

19 **Hva er din hovedaktivitet?** (Sett ett kryss)

☐ Yrkesaktiv heltid
☐ Yrkesaktiv deltid
☐ Arbeidsledig
☐ Hjemmeværende
☐ Pensjonist/trygdet
☐ Student/militærtjeneste

20 **Mottar du noen av følgende ytelser?**

- ☐ Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
- ☐ Sykepenger (er sykemeldt)
- ☐ Rehabiliterings-/attføringspenger
- ☐ Uføreytelse/pensjon, hel
- ☐ Uføreytelse/pensjon, delvis
- ☐ Dagpenger under arbeidsledighet
- ☐ Overgangstønad
- ☐ Sosialhjelp/-stønad

21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

- ☐ Under 125 000 kr
- ☐ 125 000-200 000 kr
- ☐ 201 000-300 000 kr
- ☐ 301 000-400 000 kr
- ☐ 401 000-550 000 kr
- ☐ 551 000-700 000 kr
- ☐ 701 000 -850 000 kr
- ☐ Over 850 000 kr

22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**

- ☐ Ja
- ☐ Nei

FYSISK AKTIVITET

23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks postbud, pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

24 **Angi bevegelse og kroppslig anstrengelse i din 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 som passer best)

- ☐ Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
- ☐ Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka

25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uken
- ☐ En gang i uken
- ☐ 2-3 ganger i uken
- ☐ omtrent hver dag

26 **Hvor hardt mosjonerer du da i gjennomsnitt?**

- ☐ Tar det rolig uten å bli andpusten eller svett.
- ☐ Tar det så hardt at jeg blir andpusten og svett
- ☐ Tar meg nesten helt ut

27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**

- ☐ Mindre enn 15 minutter
- ☐ 15-29 minutter
- ☐ 30 minutter – 1 time
- ☐ Mer enn 1 time

ALKOHOL OG TOBAKK

28 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2-4 ganger hver måned
- ☐ 2-3 ganger pr. uke
- ☐ 4 eller flere ganger pr.uke

29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 eller flere

30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ aldri
- ☐ sjeldnere enn månedlig
- ☐ månedlig
- ☐ ukentlig
- ☐ daglig eller nesten daglig

31 **Røyker du av og til, men ikke daglig?**

- ☐ Ja
- ☐ Nei

32 **Har du røykt/røyker du daglig?**

- ☐ Ja, nå
- ☐ Ja, tidligere
- ☐ Aldri

33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**

Antall år ☐☐

34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**

Antall sigaretter ☐☐

35 **Hvor gammel var du da du begynte å røyke daglig?**

Antall år ☐☐

36 **Hvor mange år til sammen har du røykt daglig?**

Antall år ☐☐

37 **Bruker du, eller har du brukt, snus eller skrå?**

- ☐ Nei, aldri
- ☐ Ja, men jeg har sluttet
- ☐ Ja, av og til
- ☐ Ja, daglig

KOSTHOLD

38 **Spiser du vanligvis frokost hver dag?**

☐ Ja ☐ Nei

39 **Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag?** (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter ☐☐

40 **Hvor mange ganger i uken spiser du varm middag?**

Antall ☐☐

41 **Hvor ofte spiser du vanligvis disse matvarene?**
(Sett ett kryss pr linje)

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Kjøtt *(ikke kvernet)*	☐	☐	☐	☐	☐
Kvernet kjøtt *(pølser, hamburger o.l)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk	☐	☐	☐	☐	☐
Feit fisk *(f.eks.laks, ørret, makrell, sild, kveite,uer)*	☐	☐	☐	☐	☐

42 **Hvor mye drikker du vanligvis av følgende?**
(Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker med sukker	☐	☐	☐	☐	☐

43 **Hvor mange kopper kaffe og te drikker du daglig?**
(sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe	☐☐
Kokekaffe/presskanne	☐☐
Annen kaffe	☐☐
Te	☐☐

44 **Hvor ofte spiser du vanligvis fiskelever?**
(For eksempel i mølje)

☐ Sjelden/aldri ☐ 1-3 g i året ☐ 4-6 g i året
☐ 7-12 g i året ☐ Oftere

45 **Bruker du følgende kosttilskudd?**

	Daglig	Iblant	Nei
Tran, trankapsler	☐	☐	☐
Omega 3 kapsler *(fiskeolje,selolje)*	☐	☐	☐
Kalktabletter	☐	☐	☐

SPØRSMÅL TIL KVINNER

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Usikker

47 **Hvor mange barn har du født?**

Antall ☐☐

48 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.**
(Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **Har du i forbindelse med svangerskap hatt for høyt blodtrykk?**

☐ Ja ☐ Nei

50 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

51 **Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?**

☐ Ja ☐ Nei

52 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

53 **Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?**

☐ Ja ☐ Nei

54 **Hvis Ja, hvilke(t) barn**

Barn 1	Barn 2	Barn 3	Barn 4	Barn 5	Barn 6
☐	☐	☐	☐	☐	☐

55 **Hvor gammel var du da du fikk menstruasjon første gang?**

Antall år ☐☐

56 **Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?**

P-pille, hormonspiral eller lignende ☐ Ja ☐ Nei
Hormonpreparat for overgangs-alderen ☐ Ja ☐ Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

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