Faculty of Health Sciences
Institute of Medical Biology

# Uric acid and adiponectin in cardiovascular disease

*Results from the Tromsø Study*

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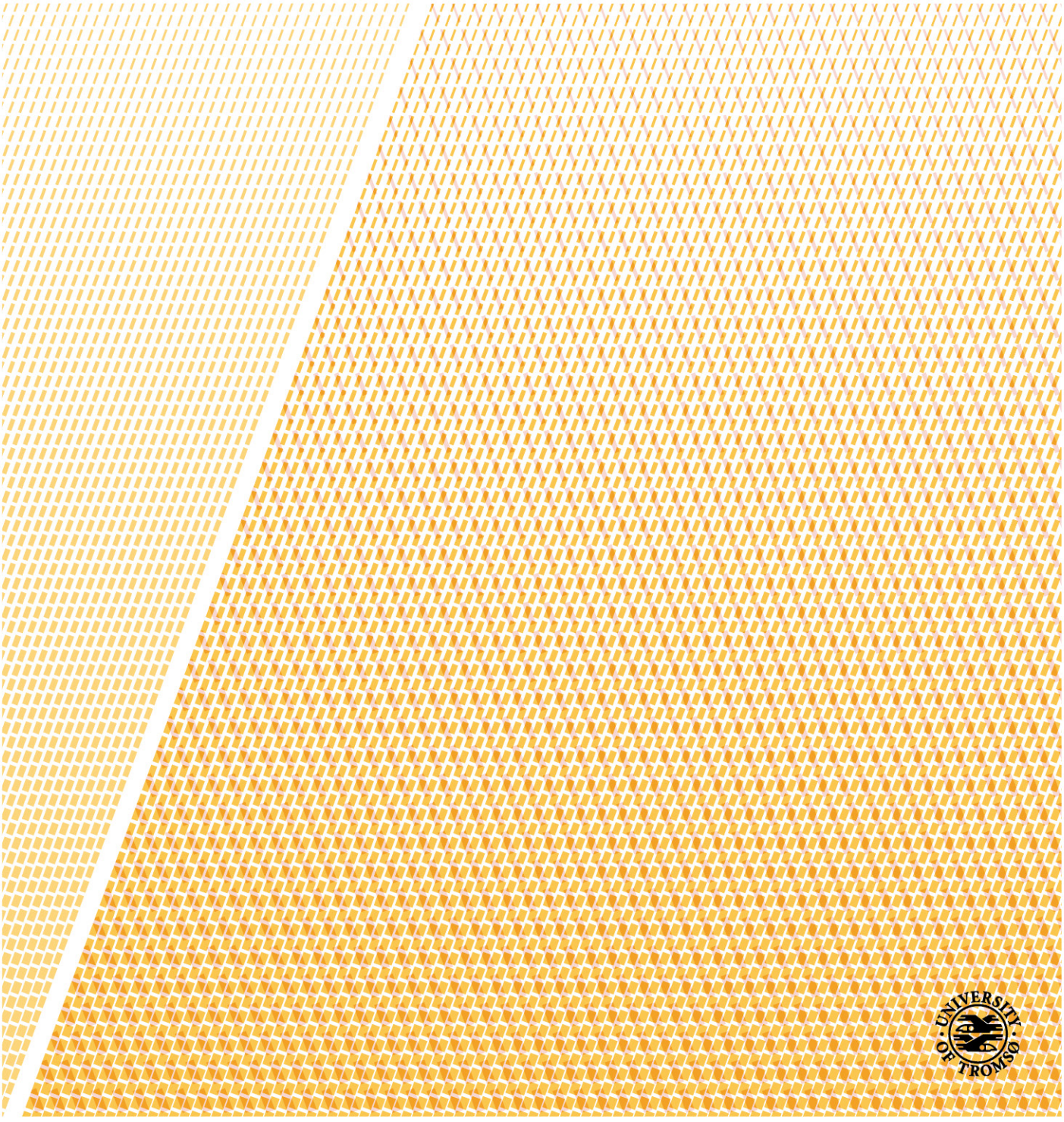
*A dissertation for the degree of Philosophiae Doctor – March 2017*



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# Summary

Uric acid, a product of metabolism, was discovered a quarter of a millennium ago and has been known to be a possible cardiovascular risk factor for well over a century. A much newer discovery, adiponectin, was discovered only a little more than 20 years ago as a protein hormone secreted by adipose tissue and has attracted substantial attention for its association with cardiovascular disease. This thesis will examine the modifying action of overweight on the relationship between uric acid levels and metabolic syndrome, the association between uric acid levels and adverse cardiovascular events and mortality in subjects with or without diastolic dysfunction, and the sex-specific association between adiponectin levels and diastolic dysfunction. In addition, this thesis will determine whether a relevant interaction between uric acid and adiponectin exists with respect to diastolic dysfunction.

Paper 1, a seven-year prospective study with over 6,000 participants, examines whether overweight modifies the association between the uric acid levels and metabolic syndrome. In overweight but not normal-weight subjects, the baseline uric acid levels predicted the development of elevated blood pressure and elevated fasting glucose levels. The baseline uric acid levels and changes in the uric acid levels over seven years predicted metabolic syndrome and most of its components.

A 19-year prospective study of 1,460 women and 1,480 men with endpoints of all-cause mortality, incident myocardial infarction and incident ischaemic stroke is described in Paper 2. Uric acid levels were a predictor of all-cause mortality in subjects with echocardiographic markers of diastolic dysfunction but not in subjects without these markers. Uric acid levels were a stronger predictor of incident ischaemic stroke in subjects with severely enlarged atria than in subjects with normal-sized atria.

Paper 3 describes a cross-sectional study of 1,165 women and 896 men and the sex-specific relationship between adiponectin levels and diastolic dysfunction. Lower adiponectin levels were associated with greater odds of echocardiographic indices of diastolic dysfunction in women but lower odds of diastolic dysfunction in men. Additionally, lower adiponectin levels were associated with a higher left ventricular mass in women only. An interaction between uric acid and adiponectin levels was not observed for any marker of diastolic dysfunction.

These findings support an association between uric acid levels and increased cardiovascular risk, with detrimental effects observed in subjects who already present a state of metabolic derangement and an elevated risk, such as overweight persons and subjects with diastolic dysfunction. Furthermore, adiponectin levels, and thus adipose tissue function, may provide a clue to why heart failure with preserved ejection fraction shows a female preponderance.

# List of presented papers

This thesis is based on the following papers:

1 Norvik JV, Storhaug HM, Ytrehus K, Jenssen TG, Zykova, SN, Eriksen BO, and Solbu MD. Overweight Modifies the Longitudinal Association between Uric Acid and some Components of the Metabolic Syndrome: The Tromsø Study. *BMC Cardiovasc Disord*. 2016;16(1):85.

2 Norvik JV, Schirmer H, Ytrehus K, Storhaug HM, Jenssen TG, Eriksen BO, Mathiesen EB, Løchen ML, Wilsgaard T, and Solbu MD. Uric Acid Predicts Mortality and Ischaemic Stroke in Subjects with Diastolic Dysfunction: The Tromsø Study 1994-2013. (Accepted for publication by ESC Heart Failure).

3 Norvik JV, Schirmer H, Ytrehus K, Jenssen TG, Zykova SN, Eggen AE, Eriksen BO, and Solbu MD. Low Adiponectin is Associated with Diastolic Dysfunction in Women: a Cross-sectional Study from The Tromsø Study. (Submitted for publication November 2016).

# List of abbreviations

| | |
|---|---|
| AHA | American Heart Association |
| BMI | body mass index |
| CI | confidence interval |
| CKD-EPI | The Chronic Kidney Disease Epidemiology Collaboration |
| DD | diastolic dysfunction |
| ΔUA | change in the uric acid levels |
| E/A ratio | ratio of peak early left ventricular (LV) filling (E-wave) and peak late LV filling (A-wave) |
| EDT | E-wave deceleration time |
| e’ | early myocardial peak velocity of the mitral annulus |
| E/e’ ratio | E-wave and e’ wave ratio |
| eGFR | estimated glomerular filtration rate |
| Hba1c | haemoglobin a1c |
| HDL | high-density lipoprotein |
| HF | heart failure |
| HFpEF | heart failure with preserved ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| HMW | high molecular weight |
| HR | hazard ratio |
| IDF | International Diabetes Federation |
| IVRT | isovolumetric relaxation time |
| LA | left atrium |
| LV | left ventricle |
| MetS | metabolic syndrome |
| NCEP-ATP III | National Cholesterol Education Program Adult Treatment Panel III |
| NHANES | National Health and Nutrition Examination Survey |
| NHLBI | National Heart, Lung, and Blood Institute |
| NO | nitric oxide |
| OR | odds ratio |
| RCT | randomized controlled trial |
| RAAS | renin-angiotensin-aldosterone-system |
| ROS | reactive oxygen species |
| RWT | relative wall thickness |
| SD | standard deviation |
| UA | uric acid |
| WHO | World Health Organization |
| XDH | xanthine dehydrogenase |
| XO | xanthine oxidase |
| XOR | xanthine oxidoreductase |

# 1 Introduction and background

According to the World Health Organization (WHO), 56 million people died in 2012[1]. Of these individuals, 38 million died from a noncommunicable disease, diseases not passed on from person to person. Among the deaths due to noncommunicable disease, more than 46%, 17.5 million deaths, resulted from cardiovascular disease, the leading cause of death worldwide. WHO defines premature death as death occurring before the age of 70, and the concept is a major consideration for evaluations of the impact of a cause of death on a population[1]. Cardiovascular disease is responsible for 37% of all premature deaths due to noncommunicable diseases, as shown in Figure 1.

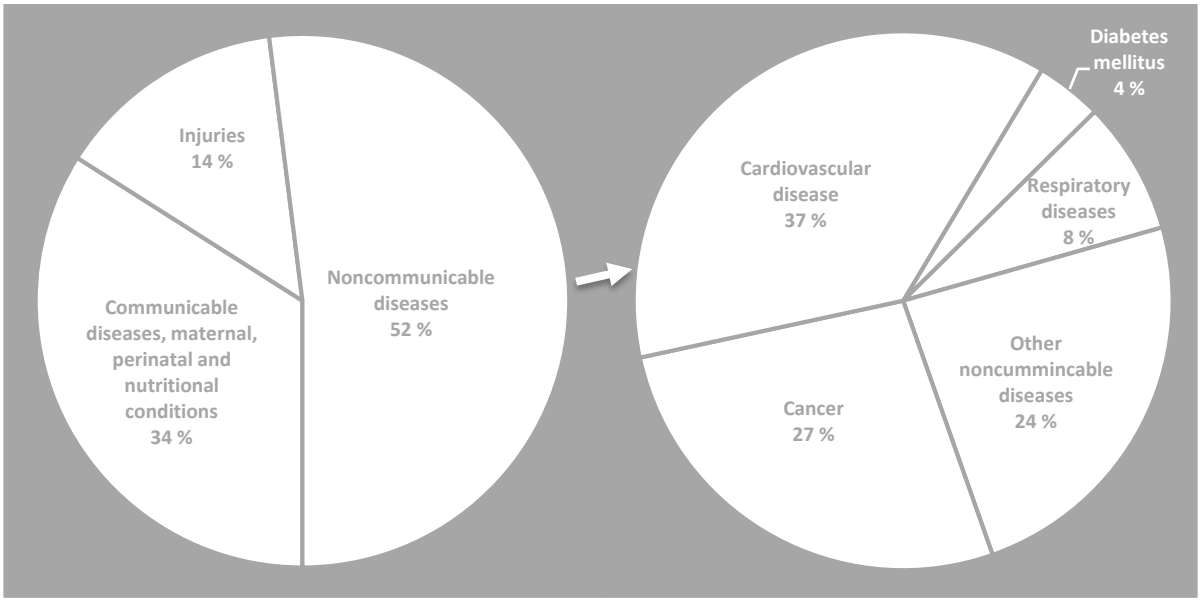


*Figure 1. Left: Proportion of global deaths for individuals under the age of 70 years by cause of death. Right: Proportion of global noncommunicable deaths for individuals under the age of 70 years by cause of death.*

The WHO has a stated goal of reducing premature mortality due to cardiovascular diseases, cancer, respiratory diseases or diabetes mellitus by 25% by the year 2025[2]. Although the number of deaths arising from cardiovascular disease has decreased dramatically over the last 40 years in Norway, particularly in the group < 70 years of age, it is still the leading cause of death in this country[3]. One study examining the decline in acute coronary heart disease in Tromsø between 1994 and 2008 attributed 66% of the decrease to reductions in population risk factors, such as cessation of smoking and reduction of blood pressure and cholesterol levels[4]. An increase in the populations who are overweight or have diabetes mellitus type 2 has hampered the decrease in coronary heart disease[4]. There is, however, desire and room for the improvement of risk estimation, and the American Heart Association (AHA) recommends conducting research to fill gaps in knowledge about cardiovascular risk assessment and outcomes[5].

Metabolic syndrome (MetS), which is strongly associated with overweight and obesity, is a cluster of risk factors for cardiovascular disease[6]. Uric acid (UA) has long been linked with MetS[7] and cardiovascular disease[8], but the possible modulatory effect of overweight on the relationship between UA levels and MetS components has not been examined.

Diastolic dysfunction (DD) is a pathological state characterized by abnormal cardiac relaxation, stiffness or filling and is closely associated with heart failure (HF) with preserved ejection fraction (HFpEF)[9]. Overweight and obesity are prevalent in subjects with HFpEF[10]. DD itself[11] and HFpEF[12] are associated with increased mortality. A medical treatment with a proven benefit for HFpEF is not available[13]. The effect of UA levels on mortality and cardiovascular events in subjects with DD has not been thoroughly studied.

Adiponectin is a hormone secreted mainly by adipocytes[14], and low serum adiponectin levels are generally associated with cardiovascular disease[15] and obesity[16]. Sex-specific differences in adiponectin levels have been observed in that women in general have higher plasma concentrations[17]. HFpEF exhibits a female preponderance, and the basis for this preponderance is a stated direction for future research[10]. The association between DD and adiponectin levels, as well as the sex-specific differences related to this association, warrant investigation. UA may affect adipocytes by inducing the downregulation of adiponectin[18], and the association between the UA and adiponectin levels in DD is not known.

Cardiovascular disease is the main cause of death worldwide, and the global goal is to reduce cardiovascular mortality. Investigations of modifiable risk factors for and biomarkers of cardiovascular disease will contribute to our ability to achieve this goal. In the present thesis, we specifically address, for the first time, the interrelationships between UA levels, MetS, adiponectin levels, indices of DD and the future development of cardiovascular disease and mortality in a large, middle-aged to elderly cohort from the general population,

# 2 Metabolic syndrome

### 2.1.1 Definitions

Physicians have been aware for decades of an established set of interrelated risk factors for cardiovascular disease and diabetes that tend to cluster. In 1923, the Swedish medical doctor Eskil Kylin observed a syndrome that was associated with an increased risk of cardiovascular disease and was characterized by hypertension, hyperglycaemia, and hyperuricaemia, which is one of the first descriptions of the clustering of these risk factors[19]. Modern studies of this phenomenon began after the 1988 Banting Lecture to the American Diabetes Association, during which Gerald M. Reaven introduced insulin resistance as the major factor in the syndrome, coining it “syndrome X”[20]. Consequently, this syndrome was renamed “insulin-resistance syndrome” in 1992[21]. The label “metabolic syndrome”, which is currently the most common name for this syndrome, was first proposed in 1981[22] and was the term used by a consultant group for the WHO in 1998 in an initial attempt to formalize diagnostic criteria for the syndrome[7]. In this definition, insulin resistance is a prerequisite for the diagnosis of MetS, in addition to two or more additional risk factors, including hypertension, elevated triglyceride levels, central or general obesity and microalbuminuria. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) published their definition of MetS[23]. The NCEP-ATP III criteria did not have any single feature as a prerequisite for the diagnosis. Rather, the presence of three or more of the following factors was required for diagnosis: elevated waist circumference, elevated triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol levels, elevated blood pressure and elevated fasting glucose levels. In 2005, AHA and the National Heart, Lung, and Blood

Institute (NHLBI), as well as the International Diabetes Federation (IDF) attempted to reach a common definition for MetS. Although the AHA/NHBLI criteria were almost identical to the NCEP-ATP III criteria[24], the IDF definition included central obesity as a precondition in addition to any two or more of the other four criteria from the NCEP-ATP III classification as a requirement for the diagnosis of MetS[25]. Nevertheless, in 2009, the groups reached a consensus, and IDF, NHLBI, AHA, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity released a joint scientific statement[6]. This definition of MetS did not have any one required feature, and three or more of five factors were established as requirements for diagnosis. These criteria were the same as the revised NCEP-ATP III criteria published by AHA/NHBLI, with the exception of population-specific waistline cut-off points, and are the basis for the definition of MetS used throughout this dissertation. Some researchers disagreed regarding the cut-off points for waist circumference. For Europids, the IDF recommended a threshold of ≥ 80 cm for women and ≥ 94 cm for men; the AHA/NHLBI recommended a threshold of ≥ 88 cm for women and ≥ 102 cm for men. The latter cut-offs are used to diagnose MetS in this thesis. However, due to lack of fasting blood samples, the AHA/NHBLI cut-off points have been modified in the present work. The AHA/NHBLI definition of MetS and the modified AHA/NHBLI definition employed here are summarized in Table 1.

*Table 1. Three or more of the following five criteria constitute a diagnosis of metabolic syndrome.*

| **Measure** | **AHA/NHBLI** | **MetS definition paper 1** |
|---|---|---|
| **Elevated waist circumference** | ≥ 88 cm in women, ≥ 102 cm in men | ≥ 88 cm in women, ≥ 102 cm in men |
| **Elevated triglyceride levels** | ≥ 1.7 mmol/L or on fibrates or nicotinic acid | ≥ 1.7 mmol/L if the time since the last meal is ≥ 4 hours or ≥ 2.28 mmol/L if the time since the last meal is < 4 hours or the subject uses fibrates or nicotinic acid |
| **Reduced HDL cholesterol levels** | < 1.3 mmol/L in women, < 1.0 mmol/L in men or use of fibrates or nicotinic acid | < 1.3 mmol/L in women, < 1.0 mmol/L in men or use of fibrates or nicotinic acid |
| **Elevated Blood pressure** | systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or use of antihypertensive treatment | systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or use of antihypertensive treatment |
| **Elevated Fasting glucose levels** | ≥ 5.6 mmol/L or use of a glucose-lowering treatment | ≥ 5.6 mmol/L if the time since the last meal is ≥ 4 hours or ≥ 7.8 mmol/L if the time since the last meal is < 4 hours or the subject uses a glucose-lowering treatment |

### 2.1.2 Prevalence

One investigator estimated the prevalence of MetS to range from < 10% to 84%, depending on the region, demographics of the population studied and definition of MetS used[19]. For example, the waist circumference cut point employed by the IDF would encompass more people than the definition from AHA/NHBLI. Based on estimates from the IDF, the worldwide prevalence was approximately 20-25%[26]. In the National Health and Nutrition Examination Survey (NHANES) 2003-2006, approximately 34% of US adults aged ≥ 34 years had MetS[27]. In one study, the prevalence of MetS in Northern Norway in 2003-2004 was reported to be approximately 18% when the AHA/NHBLI cut-off was used for waist circumference and approximately 26% when the IDF cut point was used[28]. The prevalence of MetS significantly increased between NHANES 1988-1994 and NHANES 1999-2006, and one of the main reasons for this change was the surge in abdominal obesity[29]. The syndrome is common, and its prevalence is increasing worldwide[6].

### 2.1.3 Metabolic syndrome as a risk factor

The reason why diagnostic criteria were created for MetS was for the early identification of persons at risk of developing diabetes and cardiovascular disease and, consequently, for promoting lifestyle changes or initiating medical treatment. Although a few studies failed to observe an association between MetS and cardiovascular disease, most studies identified a strong relationship between MetS and cardiovascular disease[30], which is not surprising because all the components of MetS have long been known as major cardiovascular risk factors[30]. This relationship leads to the question of whether MetS offers diagnostic value beyond the individual component risk factors that comprise the syndrome. One 11-year prospective study with more than 12,000 participants showed that subjects with MetS had an increased risk of cardiovascular disease, although the diagnosis of MetS did not suggest a greater risk than the risk explained by the presence of its individual components[31]. Moreover, MetS has been suggested to be a weaker tool for predicting the risk of cardiovascular disease than the traditional Framingham criteria[30]. However, many view MetS as a real and progressive pathophysiological state with risk factors that are causally interrelated[32]. One meta-analysis examining 87 studies with a total of nearly one million subjects found that persons with MetS had double the risk of cardiovascular disease and cardiovascular mortality, with a median follow-up time of 12.3 years[8]. Furthermore, subjects with MetS have a five-fold increased risk of developing type 2 diabetes mellitus[6]. The CardioMetabolic Health Alliance recognizes that additional factors that are not incorporated in the MetS are related to the syndrome and are associated with adverse outcomes[32]. Therefore, the identification of features associated with MetS, such as an easily and inexpensively modifiable risk factor, is a worthwhile endeavour.

## 2.2 Diastolic dysfunction

### 2.2.1 Definitions

Diastole is the interval between aortic valve closure and mitral valve closure[38]. Impairment of left ventricular (LV) relaxation, LV compliance and filling pressures may result in impaired LV filling or suction capacity and cause DD[9,33] . DD is closely associated with HFpEF, a clinical syndrome with symptoms (such as dyspnoea and fatigue) that may be accompanied by signs (such as elevated jugular venous pressure, pulmonary crepitation and peripheral oedema) of

heart failure (HF), and a normal or slightly reduced LV ejection fraction[9]. DD can worsen over time and poses a risk for HFpEF[34]. In the 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF, the diagnosis of HFpEF requires symptoms with or without signs of HF and LV ejection fraction ≥ 50% (plus elevated natriuretic peptide levels, if available), plus at least one additional criterion: a relevant structural heart disease (LV hypertrophy or left atrial (LA) enlargement) or other indices of DD[9]. The indices of DD used in this dissertation are based on these guidelines and previously published data and are listed in Table 2[35–37].

*Table 2. Echocardiographic indices of diastolic dysfunction.*

| **Index** | **Normal values** | **Diastolic dysfunction Paper 2** | **Diastolic dysfunction Paper 3** |
|---|---|---|---|
| **E/A ratio** | Paper 2: 0.75-1.5<br>Paper 3: 0.75-2.0 | < 0.75 or > 1.5 | < 0.75 or > 2.0 |
| **EDT** | 140-220 ms | < 140 ms or > 220 ms | < 140 ms or > 220 ms |
| **IVRT** | Paper 2: > 60 ms<br>Paper 3: 60-110 ms | ≤ 60 ms | < 60 ms or > 110 ms |
| **LA size** | < 2.2 cm/m$^2$ | Moderately enlarged 2.2-2.79 cm/m$^2$ or severely enlarged ≥ 2.8 cm/m$^2$ | Moderately enlarged 2.2-2.79 cm/m$^2$ or severely enlarged ≥ 2.8 cm/m$^2$ |
| **E'-wave** | ≥ 9 cm/s | Not applicable | < 9 cm/s |
| **E/e' ratio** | < 8 | Not applicable | ≥ 8 |
| **LV remodelling** | LV mass ≤ 95 g/m² in women, ≤ 115 g/m² in men, and RWT ≤ 0.42 | Not applicable | Concentric remodelling: LV mass ≤ 95 g/m² in women or ≤ 115 g/m² in men, and RWT > 0.42; concentric hypertrophy: LV mass > 95 g/m² in women or > 115 g/m² in men, and RWT > 0.42; eccentric hypertrophy: LV mass > 95 g/m² in women or > 115 g/m² in men, and RWT < 0.42 |

Abbreviations: E/A ratio, E-wave/A-wave ratio; EDT, E-wave deceleration time; IVRT, isovolumetric relaxation time; LA, left atrium; E/e' ratio, E-wave/e'-wave ratio; LV, left ventricle; RWT, relative wall thickness.

The indices of DD can be acquired through regular transthoracic echocardiography in the clinic. Three of the indices, E/A ratio, EDT and IVRT, are acquired by placing the Doppler probe in the mitral ostium and registering the velocity of the LV inflow from the LA during diastole[33,38]. A schematic of a transmitral flow profile is shown in Figure 2.

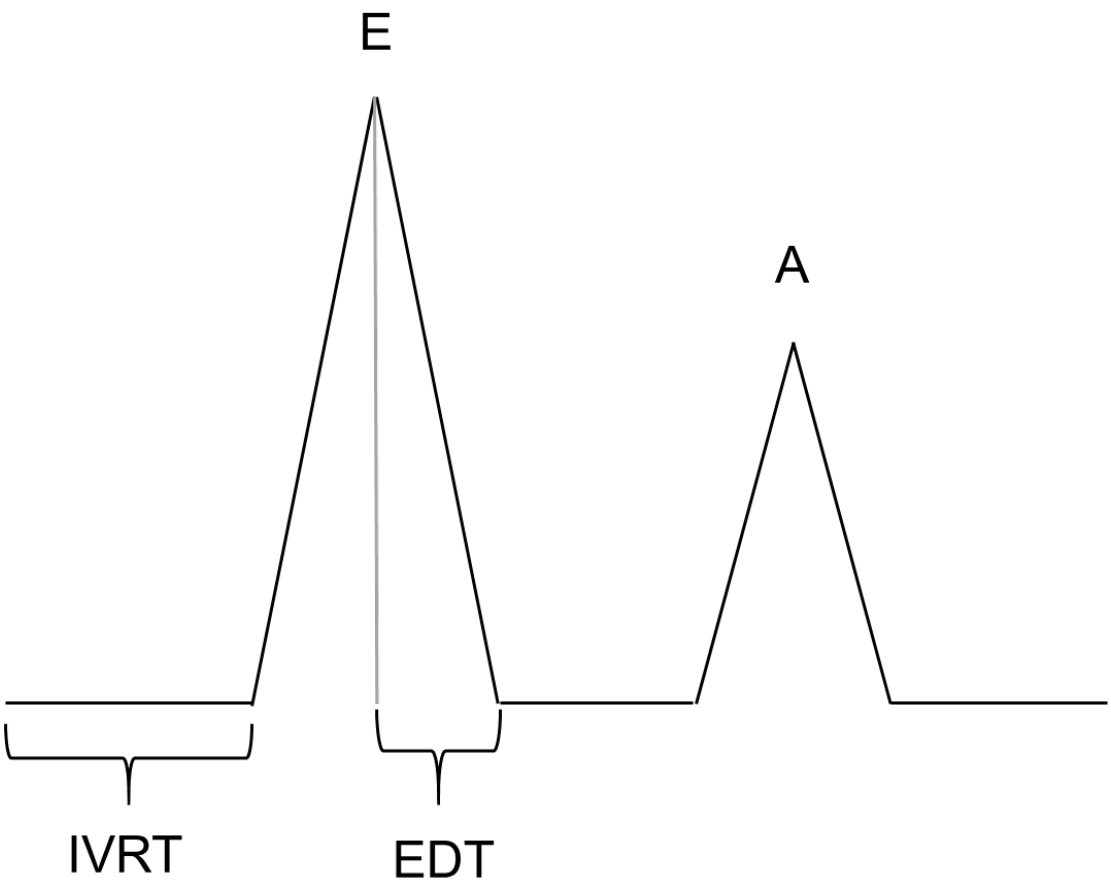


*Figure 2. Schematic of transmitral flow. Abbreviations: A, A-wave; E, E-wave; EDT; E-wave deceleration time; IVRT, isovolumetric relaxation time.*

Diastolic flow across the mitral valve has two peaks: the E-wave, showing the early, passive filling of the LV, and the A-wave, showing the late, active filling as a result of atrial contraction[33,38]. The E-wave reflects the pressure gradient between the LA and the LV during early diastole, is affected by the rate of LV relaxation and the LA pressure[33,38]. The A-wave reflects the pressure gradient between the LA and the LV during late diastole, and is affected by LA contractile function and LV compliance[33,38]. A reduced ratio of the velocity of the E-wave and the A-wave, the E/A ratio, is associated with impaired LV relaxation, and an increased E/A ratio is associated with restrictive filling[33,38]. The E-wave (EDT) deceleration time is the duration of the interval between peak early diastolic filling, the apex of the E-wave, and the end of the E-wave[33,38]. The isovolumetric relaxation time (IVRT) is the duration of the interval between the closing of the aortic valve and the opening of the mitral valve[33,38]. A decreased EDT or IVRT indicates restrictive LV physiology, and an increased EDT or IVRT indicates impaired LV relaxation[33,38]. The LA size reflects the effects of increased LV filling pressures over time[33,38]. The three Doppler measurements described above are acquired by reflection of signals from moving blood cells, in contrast to tissue Doppler imaging, which is

based on reflections from moving myocardium[33]. The e'-wave a recording of the moving myocardium approximately 1 cm apical of the mitral valve during early diastolic filling[33]. This thesis uses the average velocity of the e'-waves captured near the septal and lateral leaflets of the mitral valve. Reduced e'-wave is associated with impaired LV relaxation[38]. An elevated ratio of the E-wave and the e'-wave is associated with increased LV filling pressures[38]. Pathological LV remodeling is associated with associated with LV stiffness and DD[38].

### 2.2.2 Epidemiology and prognosis

In developed countries, the prevalence of HF is approximately 1-2% of the adult population and ≥ 10% of people > 70 years of age[9]. Approximately half of patients with HF have HFpEF[39]. Some researchers have reported an approximately 1% annual increase in the prevalence of HFpEF in the population with HF[40]. In contrast to patients with HF with reduced ejection fraction (HFrEF), patients with HFpEF tend to be older, more frequently are women and more often present a history of hypertension[9]. The reasons for the female preponderance of HFpEF are unknown[10]. Atrial fibrillation, obesity, diabetes mellitus and hyperlipidaemia are other disorders that are highly prevalent in the population with HFpEF[39]. The EURObservational Research Programme: the Heart Failure Pilot Survey (ESC_HF Pilot) conducted a prospective 1-year survey among 136 cardiology centres in 12 countries with over 5,000 enrolled patients with HF and confirmed that HF is a major health problem[12]. The all-cause mortality rate after one year was 13.4% for patients with acute HFpEF and 5.9% for patients with chronic, stable HFpEF, and the overall hospitalization rates for the population with HF were 43.9% for patients with acute HF and 31.9% for patients with chronic HF. The study did identify somewhat lower mortality rates for patients with HFpEF than for patients with HFrEF. Other researchers have previously suggested that the prognosis is comparable[41]. DD not accompanied by HF is associated with increased all-cause mortality and is often asymptomatic[11]. In contrast to HFrEF, a medical treatment with a proven benefit for HFpEF or DD is not available[42], and therapy focuses on alleviating symptoms and treating comorbidities, such as hypertension, volume overload and atrial fibrillation[9]. Overall, a disease-specific understanding of HFpEF is lacking, and thus more knowledge about modifiable risk factors associated with HFpEF is needed. Indeed, investigations designed to elucidate the contributions of metabolic disturbances are warranted, given the high prevalence of obesity, dyslipidaemia, diabetes mellitus, and MetS in subjects with HFpEF. In addition, research is needed to shed light on its female preponderance[10].

## 2.3 Uric acid

### 2.3.1 Production and metabolism

UA is the end stage of purine metabolism in humans and is the breakdown product of molecules such as nucleic acids (DNA and RNA) and adenosine triphosphate (ATP). Humans and most primates are almost the only mammals with high serum UA levels because the gene encoding the uricase enzyme became a pseudo-gene during evolution[43]. Some researchers have hypothesized that the gene became non-functional in early hominids approximately 15 million years ago as a consequence of the shift in diet due to climate change[44]. This change may have provided some survival advantage during times of food shortage because an elevated UA level may augment the storage of energy from fructose in fruits as fat[44]. Uricase metabolizes UA into allantoin, which is freely excreted in the urine;

therefore, most mammals have low UA levels - approximately 60 µmol/L. In contrast, UA is not as easily excreted, and normal humans have serum UA levels approaching – and often exceeding – the theoretical limit of UA solubility in serum (approximately 400 µmol/L)[45]. UA metabolism is displayed schematically in Figure 3. Xanthine oxidoreductase (XOR) degrades hypoxanthine to xanthine and xanthine into UA, and exists in two forms, xanthine dehydrogenase (XDH) and xanthine oxidase (XO)[46]. XOR mostly occurs in its XDH form, but proteolytic cleavage or oxidation transforms the enzyme to xanthine oxidase (XO)[47]. In its XO form, reactive oxygen species (ROS) are a by-product of the degradation of hypoxanthine to xanthine and xanthine to UA[46].

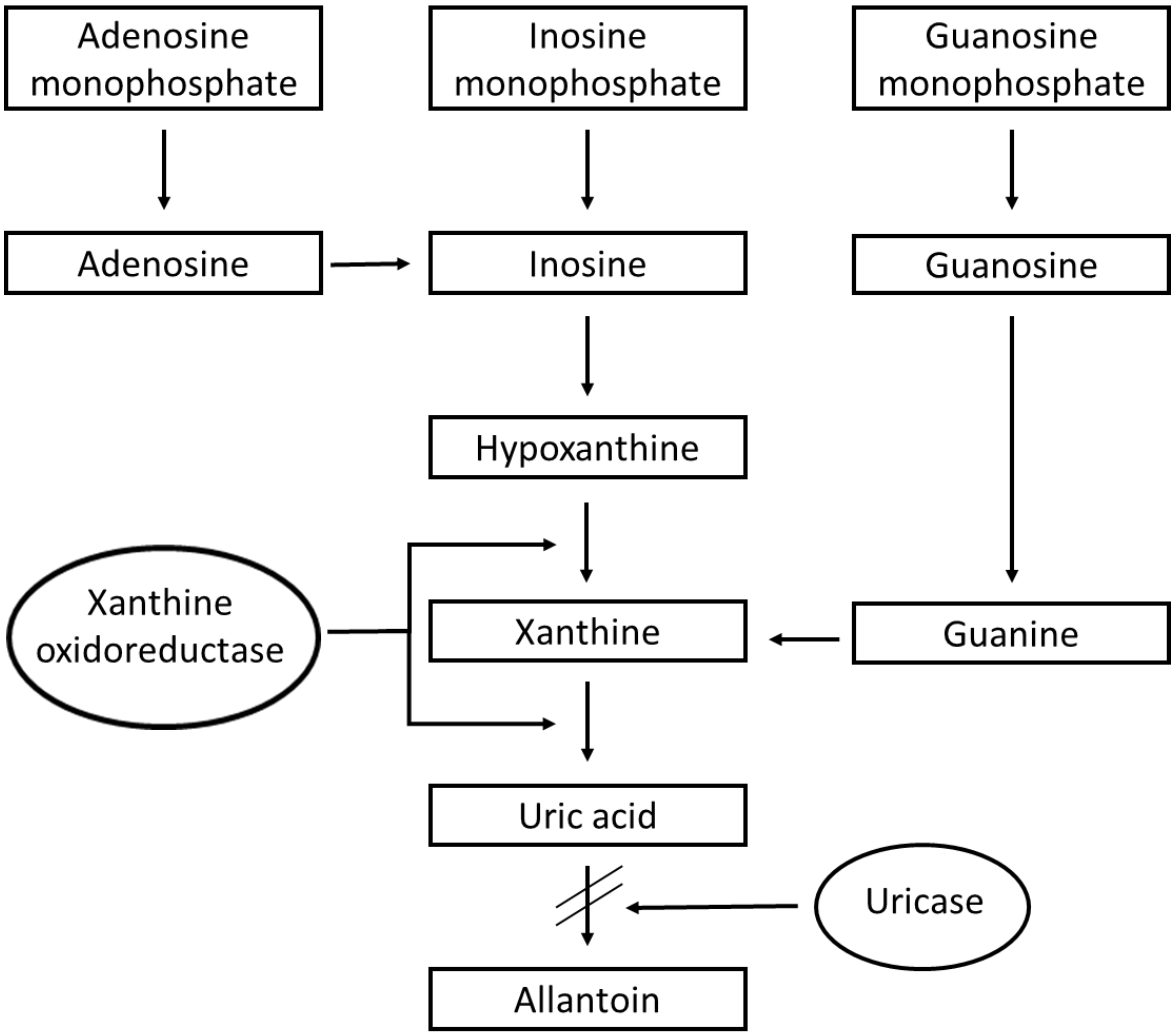


*Figure 3. Diagram of purine metabolism. Humans lack uricase, and hence uric acid is the end product.*

### 2.3.2 Hyperuricaemia

Approximately one-third of the total body UA is obtained exogenously, originating from dietary purines (particularly from purine-rich foods such as red meats, organ meats and shellfish), and the remainder is endogenously produced[46]. Ethanol will greatly increase production because of ATP turnover during metabolism, as will fructose intake[46]. Approximately one-third of UA excretion occurs via the gastrointestinal tract, and the two-thirds occurs by urinary excretion[46]. Consequently, high levels of serum UA, hyperuricaemia, is caused by overproduction of UA or reduced excretion, the latter being the most frequent

occurrence[48]. Traditional risk factors for hyperuricaemia are alcohol consumption, diuretic and low-dose aspirin use, a Western diet, a sedentary lifestyle, obesity, male gender and age[49–51]. The classification of hyperuricaemia varies between studies and countries; in some studies, hyperuricaemia has "arbitrarily" been defined as approximately > 389 µmol/L in women and > 416 µmol/L in men[46]. The NHANES studies has defined hyperuricaemia as > 339 µmol/L in women and > 416 µmol/L in men[51]. Table 3 lists the reference values for the serum UA levels provided by the laboratory at the University Hospital of North Norway. The reason for the different UA levels for pre- and post-menopausal women is a possible influence of oestrogen on UA reabsorption in the renal proximal tubule[52].

*Table 3. Reference values for uric acid at the University Hospital of North Norway.*

| | |
|---|---|
| **Women 18-49 years** | 155-350 µmol/L |
| **Women ≥ 50 years** | 155-400 µmol/L |
| **Men ≥ 18 years** | 230-480 µmol/L |

Sustained hyperuricaemia above the limit of UA solubility in serum (and thus the limit of monosodium urate crystal formation) is a prerequisite for gout[53], which is the most common of the three major urate crystal deposition-related disorders: gout, urate nephropathy and nephrolithiasis. These disorders are currently the only diseases caused by hyperuricaemia for which there is an indication for medical treatment in Europe and the USA; recommendations for the treatment of asymptomatic hyperuricaemia are not available[54]. The NHANES 2007-2008 examined US adults and found that the prevalence of hyperuricaemia was 21.6% in women and 21.2% in men[51]. Similar prevalences have been reported in studies conducted in Thailand[55], Japan[56] and China[57]. However, a minority of people with hyperuricaemia suffer from gout. In one study, only 22% of persons with UA levels > 535 µmol/L developed gout during a 5-year period[58]. The prevalence of hyperuricaemia is increasing, as evidenced by the increase in the incidence of gout since the 1960s[53], which increases as UA levels increase[58]. This increase is believed to be related to the increases in populations with adiposity and hypertension, as well as the increased use of diuretics and low-dose aspirin[51].

### 2.3.3 Uric acid as a risk factor

Although treatments for hyperuricaemia are not recommended unless it causes a crystal deposition-related disorder, UA has been implicated in several other conditions not related to crystal disposition. The consequences of hyperuricaemia were first recorded in 2640 BC when the Egyptians identified gout[59]. UA was discovered in 1776 by the Swedish chemist Carl Wilhelm Scheele[60], and in 1859, Sir Alfred Baring Garrod stated that the deposition of UA is the cause of gouty inflammation[59]. As early as the 1870s, the British physician Frederick A. Mahomed linked hyperuricaemia to hypertension[60], and it has since been associated with several other disorders that are not caused by crystal disposition, such as obesity, chronic kidney disease, preeclampsia, diabetes, MetS and cardiovascular disease[61].

UA has the strongest association with hypertension with regards to cardiovascular risk; some researchers have claimed that hyperuricaemia is currently the most reproducible independent risk factor for hypertension[62]. A meta-analysis of 18 prospective studies with more than 55,000 participants found that hyperuricaemia is associated with an increased risk of hypertension with a pooled relative risk of 1.13 per 59 µmol/L increase in the UA levels[63]. Numerous studies have defined UA as a risk factor for cardiovascular disease. NHANES 1971-1992 identified increased UA levels as a risk factor for ischaemic heart disease mortality and total cardiovascular mortality in both men and women and a risk factor for all-cause mortality in women[64]. A prospective study of more than 400,000 subjects with a follow-up time of approximately 12 years identified UA as a risk factor for myocardial infarction, stroke and congestive HF[65]. A publication from the Tromsø Study examined UA levels in a 15-year prospective study and found that UA levels were associated with all-cause mortality and ischaemic stroke[66]. A Finnish study of more than 1,400 men with a follow-up time of approximately 12 years stated that UA levels were a strong predictor of cardiovascular death and all-cause mortality[67]. However, several studies have disputed the hypothesis that UA levels are a cardiovascular risk factor, most notably the Framingham Heart Study with 6,763 participants, in which UA levels were not an independent risk factor for coronary heart disease, cardiovascular death or all-cause mortality after a complete adjustment of the models[68]. The authors argued that UA was associated with other factors associated with cardiovascular disease and death (i.e., confounders), particularly the use of diuretics, and not the outcomes per se. This discrepancy highlights the major controversy regarding this topic: is UA a causal risk factor for cardiovascular disease or is it merely linked to other factors associated with cardiovascular disease?

With regards to MetS, the 1998 WHO definition noted that although hyperuricaemia had been suggested to be a component of MetS, it was not required for diagnosis[7]. However, a position statement on MetS by the American College of Endocrinology in 2003 did identify UA as a component of the syndrome[69], but no major guideline currently establishes UA as a major factor of MetS. Nonetheless, in 2015, The CardioMetabolic Think Tank published a new care model for patients with MetS, in which they proposed MetS subtypes and recognized hyperuricaemia as a possible pathophysiological foundation for one subtype, along with other risk factors that are not featured in the guideline criteria for MetS[32]. According to NHANES 1988-1994, the prevalence of MetS was substantially increased as UA levels increased and the prevalence exceeding 70% in subjects with UA levels > 590 µmol/L[70]. A meta-analysis based on 11 prospective studies and nearly 60,000 subjects discovered that higher UA levels led to an elevated risk of MetS based on a linear dose-response relationship, with a relative risk of 1.30 per 59 µmol/L increase in the UA level[71]. However, researchers have not determined whether UA is a predictor of the development of MetS in all subjects or in subgroups of the population.

## 2.4 Adiponectin

### 2.4.1 History, production and action

Adiponectin, a protein that is specifically produced by adipocytes, was discovered in 1995 and was coined Acrp30 (adipocyte complement-related protein of 30 kDa)[72]. It belongs to a group of protein hormones known as adipokines that are produced by adipose tissue[14].

Adipokines regulate energy metabolism, insulin sensitivity, inflammation, atherosclerosis and cell proliferation[14]. Biologically important members include, among others, tumour necrosis factor-α, interleukin-6, interleukin-10, omentin, leptin and adiponectin[73]. Adiponectin is present at high levels in healthy humans and comprises approximately 0.01% of the total plasma protein[74]. The normal range is approximately 5-10 µg/mL, and women generally have higher levels than men[17], and adiponectin shows a negative correlation with testosterone[75]. Three subtypes of adiponectin receptors (AdipoR1, AdipoR2, and T-cadherin) have been identified, present in skeletal muscle, liver, vasculature and several other places[76] Adiponectin is not routinely measured in the clinic. Adiponectin has been shown to be an insulin-sensitizing protein that protects the vasculature and has anti-inflammatory properties[77]. Adiponectin is separated into three complexes: a low molecular weight form, a middle molecular weight form, and a high molecular weight (HMW) form. The dissimilarity in adiponectin levels between men and women may be solely due to a higher level of the HWM form in women than in men[78].

### 2.4.2 Adiponectin as a risk factor

Low levels of adiponectin are associated with the development of insulin resistance[79], hypertension[80], metabolic syndrome[81] and a higher risk of myocardial infarction[15]; adiponectin is also negatively correlated with body mass index (BMI) and body fat[16]. These observations comply with the traditional view that high adiponectin levels are favourable in terms of cardiac health. However, several studies have challenged this view. In one study, a high adiponectin level was a predictor of mortality in patients with HFrEF and a marker of HF severity[82]. This study is part of a growing body of evidence showing that although adiponectin is generally viewed as protective, higher levels are observed in patients with chronic HF and increase with disease severity, particularly in the presence of cardiac cachexia[83]. A meta-analysis of 15 prospective studies and 1 nested case control study with more than 14,000 patients with established cardiovascular disease found that increased baseline adiponectin levels were associated with an elevated risk of all-cause mortality and cardiovascular mortality[84]. Some investigators have suggested that this increased risk is due to an upregulation of the adiponectin levels to compensate for increased oxidative stress and inflammation[85]. High adiponectin levels are also associated with chronic kidney disease and a reduced glomerular filtration rate (GFR), possibly due to low clearance rates[86] or as a compensatory mechanism for adiponectin resistance or chronic inflammation[87]. However, not all investigations have identified an association between adiponectin levels and cardiovascular disease. A meta-analysis of 16 prospective studies including approximately 24,000 patients did not identify a relationship between adiponectin levels and incident coronary heart disease or stroke[88]. Some studies have examined the relationship between adiponectin levels and DD. In one study of 77 healthy subjects, the adiponectin levels were negatively correlated with two of the markers of DD applied in this thesis, e' and LV mass, in linear regression analyses[89]. The Framingham Offspring Study examined the relationship between the adiponectin levels and cardiac remodelling and discovered a lower LV mass in patients in the higher adiponectin quartiles[90]. However, the authors did not observe an association between the adiponectin levels and LA size when the models were fully adjusted.

UA has been postulated to affect adipocytes by downregulating the adiponectin levels[18], and a biologically relevant interaction between uric acid and adiponectin may exist. However, any

association between adiponectin and UA in disease may be confounded by a reduced GFR, in which both UA and adiponectin levels are known to be elevated, and the analyses must therefore control for kidney function.

# 3 Aims of the thesis

We aimed to examine the relationship between the plasma levels of UA and adiponectin with the often-coexisting pathological states of MetS and DD, which are connected by risk factors such as overweight, hypertension, diabetes mellitus and chronic kidney disease. The aims of the thesis were:

- To examine the relationship between UA levels and MetS, specifically the modulatory effect of overweight on the relationship.
- To study the effect of UA levels on the association between indices of DD and adverse outcomes.
- To investigate the association between adiponectin levels and DD and determine whether this association is sex specific.
- To ascertain whether there is an interaction between UA and adiponectin for the association with DD.

# 4 Study population and methods

## 4.1 The Tromsø Study

Tromsø is the largest city of Northern Norway and its municipality had 73,480 inhabitants by January 1 2016, with 65,189 of the people within the city limits[91]. The Tromsø Study is a series of surveys conducted on the inhabitants of the municipality of Tromsø since 1974[92], and is a population-based prospective study on a mostly healthy, middle-aged to elderly, Caucasian population[93,94]. This study was initiated as a measure to prevent the high mortality of cardiovascular diseases in men in Northers Norway, and seven surveys of the study series have been completed 6-7 years apart[92,94]. From the second wave in 1979-98 and onwards, women were included in the surveys[94]. The surveys all include questionnaire data, sampling of biological specimens and clinical measurements[93]. The study was initiated, and is run and owned, by the University of Tromsø[93]. It was originally funded by The University of Tromsø – The Arctic University of Norway, and still is, but receives today considerable contributions from the National Screening Services, the Research Council of Norway, Northern Norway Regional Health Authority, Norwegian Council on Cardiovascular Diseases and Norwegian Foundation for Health and Rehabilitation[92]. This thesis uses data from the fourth, fifth and sixth waves of the Tromsø Study, which were conducted in 1994-95, 2001-02 and 2007-08, respectively.

### 4.1.1 The Tromsø 4 study population

The fourth wave of the Tromsø Study series was the largest, was conducted in 1994-95, and all inhabitants of Tromsø ≥ 25 years were invited to participate. A total of 27,158 persons participated in this study, amounting to a 77% eligibility rate after exclusion of the individuals who died or moved from the municipality between the time of the invitation and the time of the survey. Among these individuals, all women and men aged 55–74 years, as well as

smaller (5–8%) random samples of the other age groups < 85 years, were invited to an extended examination. This special study included echocardiography and UA measurements among other measurements, and 7,665 subjects participated (75% of the eligible subjects).

### 4.1.2 The Tromsø 5 study population

For the Tromsø Study of 2001-02, all subjects from the special study of Tromsø 4 plus a smaller sample from the 30, 40, 45, 60 or 75-year-old age groups were invited, and 8,130 were enrolled (76% of eligible subjects). At 89%, the enrolment rate was high among persons who had previously participated in Tromsø 4 seven years prior to this study, and this group was invited to an extended, special examination. A total of 5,939 subjects agreed to participate in the special survey (85% of eligible subjects).

### 4.1.3 The Tromsø 6 study population

The sixth survey of the Tromsø Study was conducted in 2007-08, and four distinct groups were invited: subjects who participated in the special study of Tromsø 4, a 10% random sample of persons aged 30-39, a 40% random sample of subjects aged 43-59 years, and all individuals aged 40-42 or 60-87 years. A total of 12,984 subjects were enrolled (66% of the invited population). In addition, all subjects from the special study of Tromsø 4 who were aged 50-62 or 75-84 years, plus a 20% random sample of subjects aged 63-74 years old, were invited to participate in a special examination. Among the 11,484 eligible subjects, 7,307 persons participated (64% participation rate). The special study included adiponectin measurements and echocardiography.

### 4.1.4 The study populations assessed in the papers in this thesis

Paper 1 examines the subjects that attended the special studies from both Tromsø 4 and Tromsø 5. We excluded subjects with missing serum UA analyses (n = 405), prevalent diabetes at baseline (n = 282; defined as Hba1c ≥ 6.5%, non-fasting glucose ≥ 10.0 mmol/L, under anti-diabetic treatment or self-reported diabetes), and underweight subjects (n = 82, BMI < 18.5 kg/m$^2$). The final study cohort consisted of 6,083 subjects at baseline.

The population evaluated in Paper 2 consisted of the individuals who participated in the special study from Tromsø 4. Of these individuals, 7,445 persons had serum UA measurements, and 3,272 were randomly selected for echocardiography. A total of 3,068 subjects underwent both UA measurements and echocardiography. We excluded the individuals with diabetes at baseline (n = 128). Thus, the final cohort consisted of 2,940 subjects.

Paper 3 examined the people who participated in the special survey from Tromsø 6. Among these individuals, 2,243 people were randomly selected and underwent echocardiography. We again excluded the subjects with prevalent diabetes at baseline (n = 182), resulting in 2,061 subjects who were enrolled in the final cohort.

## 4.2 Measurements and clinical variables

All subjects completed a self-administered questionnaire that provided information on their current use of medication, diabetes, smoking habits, alcohol consumption, and physical activity. Experienced nurses performed the anthropometric measurements. Blood pressure was recorded in triplicate, and we used the mean of the second and third measurements. We

classified physical activity as active (≥ 1 hour of physical activity with prominent perspiration or breathlessness per week) or inactive (all others), and smoking habits were classified as current smokers and non-smokers.

### 4.2.1 Blood samples

Serum UA levels were measured by spectrophotometry with COBAS instruments (Roche diagnostics, Switzerland) using an enzymatic colorimetric test known as the uricase/phenol-amino-phenazone (PAP) method. Serum specimens from participants in Tromsø 6 were stored at -70°C, thawed and analysed for the total adiponectin levels in 2012. Adiponectin levels were analysed using an ELISA (DY1065 kit from R&D Systems, Inc., Minneapolis, MN).

Originally, the plasma creatinine levels in participants in Tromsø 4 and Tromsø 5 were analysed using a modified Jaffe reaction, an indirect colorimetric method of measuring creatinine levels[95]. However, because of a possible drift in the results between baseline and follow-up, 111 plasma samples from participants in Tromsø 4 and 142 samples from participants in the Tromsø 5 studies were thawed and reanalysed in 2006 using an enzymatic method (Modular P/Roche Diagnostics). These results were then fitted to a linear regression model, and the creatinine levels for all participants in those two surveys were recalibrated. In Tromsø 6, the plasma creatinine levels were measured using an enzymatic method that has been standardized using isotope dilution mass spectrometry (CREA Plus, Roche Diagnostics, GmbH, Mannheim, Germany). We calculated the estimated glomerular filtration rate (eGFR) for the subjects included in Paper 1 and Paper 2 according to The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[96]. Because cystatin C measurements were available for the participants in Tromsø 6, we calculated the eGFR for the participants in Paper 3 according to the CKD-EPI creatinine-cystatin C equation, which is superior to the CKD-EPI formula[97].

Since blood samples were obtained from non-fasting subjects in all surveys, the MetS definition applied in Paper 1 was modified to compensate for the non-fasting glucose and triglyceride levels, as described above (Table 1) and discussed below.

### 4.2.2 Echocardiography

The echocardiography procedures in Tromsø 4 were performed with a Vingmed CFM 750 (Vingmed Sound A/S, Horten, Norway) combined with a 3.25-MHz mechanical and 2.5-MHz Doppler probe.

The echocardiography procedures in Tromsø 6 were performed with an Acuson Sequoia C512 Ultrasound System (Siemens Medical Solutions. Mountain View, California, USA) with a combined 3.5-MHz second harmonic ultrasound and 2.5-MHz Doppler probe.

We calculated LV mass using the cube formula at end-diastole (LV mass = 0.8 x [1.04 x {interventricular septum thickness + LV internal diameter + posterior wall thickness}$^3$ – {LV internal diameter}$^3$] + 0.6 g)[98]. We calculated the relative wall thickness (RWT) as (relative wall thickness = [2 x posterior wall thickness]/LV internal diameter at end-diastole)[98].

We indexed the LA size and LV mass by the body surface area calculated using the Du Bois formula (body surface area = [weight {kg}$^{0.425}$ × height {cm}$^{0.725}$] x 0.007184) in both Paper 2 and Paper 3[35].

Due to technological advancements and new guidelines, there were discrepancies between the indices of DD studied in Paper 2 and Paper 3. Tissue Doppler was not available in Tromsø 4, and therefore Paper 2 does not include any markers of DD based on Tissue Doppler measurements. The European Society of Cardiology published new guidelines for echocardiographic LV diastolic assessments in the time between the submission of Papers 2 and 3, which affected the indices of DD applied in Paper 3. Specifically, the upper normal limit for the E/A ratio was increased from 1.5 in Paper 2 to 2.0 in Paper 3, and an upper limit for IVRT was added, according to the new guidelines[9]. In addition, the subjects with an IVRT of exactly 60 ms were in Paper 3 within the normal range. In contrast to Paper 3, Paper 2 did not use LV mass as a marker of DD. The indices of DD for both papers are listed in Table 2.

## 4.3 Assessment of endpoints

Paper 2 utilizes the endpoints all-cause mortality, first-ever fatal or non-fatal myocardial infarction and first-ever fatal or non-fatal ischaemic stroke for the 2,940 subjects in the study. The endpoints were identified by linkage to the diagnosis registry at the University Hospital of North Norway and the National Causes of Death Registry. An independent endpoint committee evaluated hospital and out-of-hospital journals, autopsy records and death certificates to adjudicate each event. The committee identified myocardial infarctions and ischaemic strokes by examining the diagnosis registries at the University Hospital of North Norway (outpatient diagnoses included) and the National Causes of Death Registry through a search for the International Classification of Diseases, Ninth Revision (ICD-9) codes 410-414, 427, 428, 430-438, and 798-799 and ICD-10 codes I20-I25, I46-I48, I50, I60-I69, R96, R98, and R99. The events were classified using the Modified World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) and MONICA Risk, Genetics, Archiving and Monograph (MORGAM) manuals. Information on emigration from the municipality, from Norway, and date of death was obtained from the National Registry of Norway. The endpoint registry was completed through December 31, 2013 (19 years) for all-cause mortality and through December 31, 2012 (18 years) for myocardial infarction and ischaemic stroke. For all-cause mortality data, we censored for emigration from Norway. For myocardial infarction and ischaemic stroke, we censored for migration out of the municipality or Norway, and death from other causes than incident myocardial infarction and incident ischaemic stroke, respectively.

## 4.4 Statistical analysis

Baseline data are presented as the means ± standard deviations (SD) for continuous variables and as numbers and percentages for categorical variables. Student's t-test and the chi square test were used to examine the differences between the continuous and categorical variables in two groups. In Paper 1, logistic regression analyses were used to examine the relationship between the UA levels and the components of MetS and the syndrome itself. We tested for the interaction between UA and overweight using two-way cross products between the continuous UA variable and an indicator variable of BMI < 25 kg/m$^2$ vs. BMI ≥ 25 kg/m$^2$ for each component of MetS and the syndrome as a whole. Cox

proportional hazard models were used in Paper 2 to assess the association between the UA levels and the clinical endpoints at different levels of DD. We tested for the interaction between UA and each echocardiographic marker of DD using two-way cross products between the continuous UA variable and indicator variables of each echocardiographic marker of DD. In Paper 3, logistic regression and fractional polynomial models were applied to examine the sex-specific differences in the association between the adiponectin levels and DD. We tested for interaction between sex and adiponectin for the association with DD indices using two-way cross products between sex and adiponectin as a continuous variable and as an indicator variable (low sex-specific tertile vs. two upper tertiles). A two-sided P-value of < 0.05 was considered significant. We performed all analyses with SPSS software (IBM Corp., released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp and IBM Corp., Released 2015, IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp), with the exception of the polynomial fractional analyses in Paper 3, which were conducted with Stata software (StataCorp., 2015, Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## 4.5 Ethical considerations

The Regional Committee for Medical Research Ethics approved the study, and all participants provided written consent for participation in each survey.

# 5 Main results

## 5.1 Paper 1: Overweight modifies the longitudinal association between the uric acid levels and some components of metabolic syndrome: The Tromsø Study

The main finding of this paper was that elevated UA levels were associated with the development of elevated blood pressure in overweight subjects (BMI ≥ 25 kg/m$^2$) over a span of seven years (odds ratio [OR] of 1.44 per 59 µmol/L UA increase at baseline, 95% confidence interval [CI] = 1.17-1.77, P = 0.001). In individuals with a normal weight (BMI < 25 kg/m$^2$), UA levels were not associated with the development of elevated blood pressure, and the P-value for the interaction between the UA level and the dichotomized BMI variable was 0.04. This finding was the same for the development of elevated fasting glucose levels over seven years. In the overweight subjects, UA levels were associated with the development of this MetS component (OR of 1.20 per 59 µmol/L increase in the UA levels, 95% CI = 1.10–1.32, P < 0.001), but not in individuals with a normal weight, and the P-value for the interaction between the UA level and the BMI cut-off was 0.01. These results are presented in Figure 4, along with the association between the UA levels and other components of MetS and the syndrome itself.

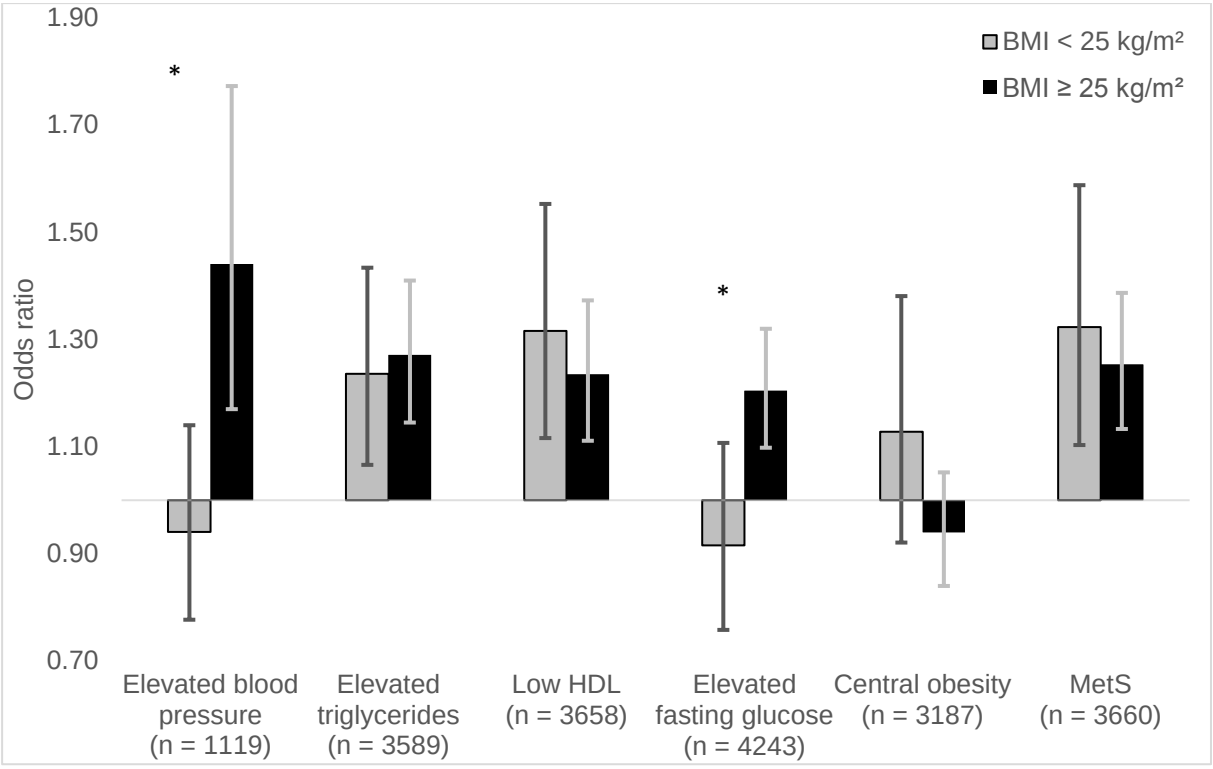


*Figure 4. Multivariate binary logistic regression models and baseline uric acid levels as a predictor of MetS and its components after seven years, stratified into normal-weight and overweight groups by BMI. The OR is reported as a 59 µmol/L increase in the uric acid level. Whiskers represent the 95% confidence interval. The group includes subjects without each component of MetS of interest or MetS at baseline. Covariates: sex, age, systolic blood pressure, total cholesterol, current smoking, physical activity, HbA1c, eGFR, alcohol consumption, use of diuretics, and waist circumference at baseline. * P-value for the interaction with the BMI cut-off < 0.05. Abbreviations: eGFR, estimated glomerular flitration rate; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; BMI, body mass index; MetS, metabolic syndrome.*

Although a significant difference between the overweight and normal-weight groups was not observed, the figure clearly shows that the UA level was associated with the development of MetS after seven years. Among the group of subjects without MetS at baseline (n = 3,660), 611 individuals developed MetS seven years later, and the UA levels predicted the outcome (OR of 1.29 per 59 µmol/L increase in the UA levels, 95% CI = 1.18–1.41, P < 0.001). We also examined whether a change in the UA level over seven years was a predictor for MetS and obtained supporting results (OR of 1.28 per 59 µmol/L increase in the UA levels between 1994 and 2001, 95% CI = 1.16-1.42, P < 0.001). There were no interactions between UA and sex or UA and an indictor variable of obesity (BMI < 30 kg/m$^2$ vs. BMI ≥ 30 kg/m$^2$) for any of these analyses.

## 5.2 Paper 2: Uric acid levels predict mortality and ischaemic stroke in subjects with diastolic dysfunction: The Tromsø Study 1994-2013

After the 19-year follow-up period, UA levels predicted all-cause mortality in subjects with an E/A ratio < 0.75 (hazard ratio [HR] of 1.12 per 59 µmol/L increase in the UA levels at baseline, 95% CI = 1.00-1.25) or E/A ratio > 1.5 (HR of 1.51 per 59 µmol/L increase in the UA levels at baseline, 95% CI = 1.09-2.09, P-value for the interaction between the E/A ratio category and UA = 0.02), as illustrated in Figure 5.

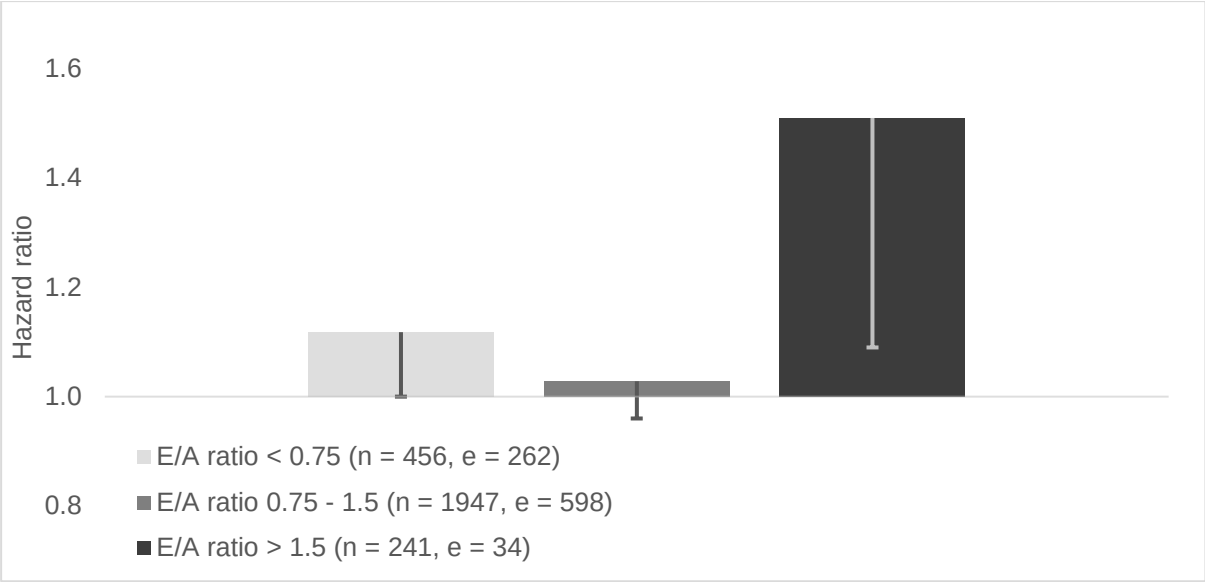


*Figure 5. Multivariate Cox proportional hazards model and hazard ratios for all-cause mortality in subjects with low, normal and high E/A ratios per 59 µmol/L increase in the uric acid levels. Whiskers represent the 95% confidence intervals. Covariates: Sex, age, body mass index, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, eGFR, HbA1c, smoking, physical activity, and use of antihypertensive medication. Abbreviations: e, events; eGFR, estimated glomerular flitration rate; HbA1c, haemoglobin A1c.*

UA levels also predicted all-cause mortality in individuals with an EDT < 140 ms or > 220 ms (HR of 1.46 per 59 µmol/L increase in the UA levels at baseline, 95% CI = 1.01-2.12 and HR = 1.13, 95% CI = 1.02-1.26; P-value for the interaction with the EDT category = 0.04). In participants with an isovolumetric relaxation time (IVRT) ≤ 60 ms, the all-cause mortality risk was higher as the UA levels increased (HR of 4.98 per 59 µmol/L increase in the UA levels at baseline, 95% CI = 2.02-12.26, P-value for the interaction with the IVRT category = 0.004). Finally, the UA levels predicted ischaemic stroke in subjects with severely enlarged LA (HR of 1.62 per 59 µmol/L increase in the UA levels at baseline, 95% CI = 1.03-2.53, P-value for the interaction with the LA size category = 0.047). An interaction between the UA levels and any marker of DD was not observed for myocardial infarction, and interactions between sex and echocardiographic markers of DD or UA level were not observed in these analyses.

## 5.3 Paper 3: Low adiponectin levels are associated with diastolic dysfunction in women: The Tromsø Study

Each 1 µg/mL decrease in the adiponectin levels was associated with DD index average tissue Doppler e' < 9 and E/e' ratio ≥ 8 in women (OR of 1.17 per 1 µg/mL decrease in the adiponectin levels, 95% CI = 1.04-1.30, P = 0.01 and OR of 1.12 per 1 µg/mL decrease in the adiponectin levels, 95% CI = 1.02-1.24, P = 0.02). These associations were not observed in men (OR of 0.99 per 1 µg/mL decrease in the adiponectin levels, 95% CI = 0.85-1.16, P = 0.93 and OR of 0.90 per 1 µg/mL decrease in the adiponectin levels, 95% CI = 0.78-1.03, P = 0.13). These analyses are presented in Figure 6. The P-values for the interactions between the adiponectin levels and gender for these markers of DD were 0.048 and 0.04, respectively.

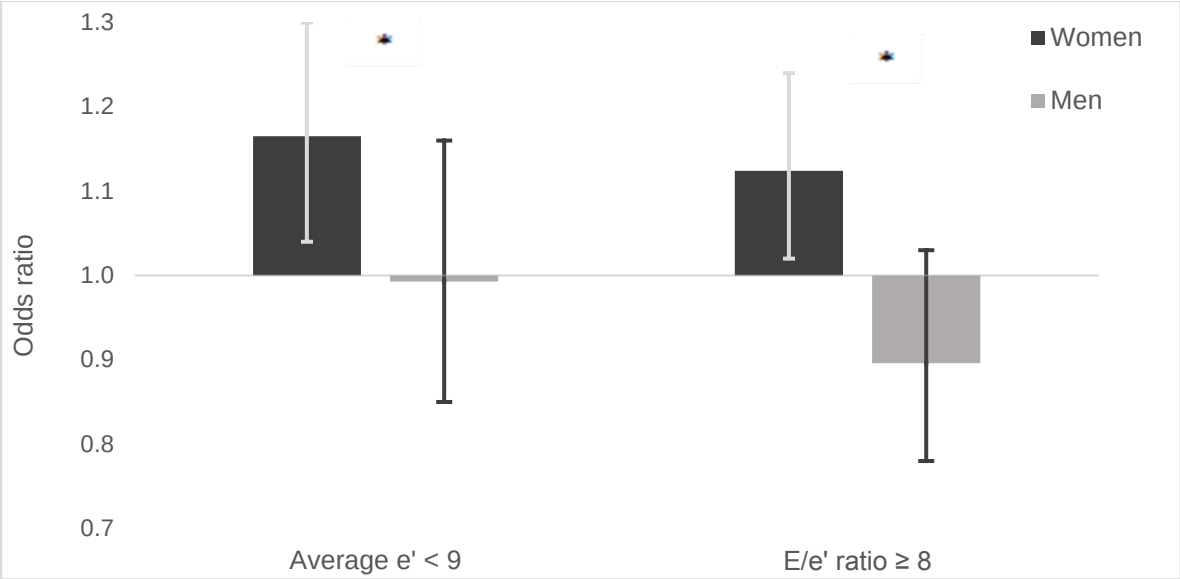


*Figure 6. Multivariate binary logistic regression models segregated by sex, with an average e' < 9 and E/e' ratio ≥ 8 as dependent variables. The odds ratios are presented per 1 µg/mL decrease in the adiponectin levels. Whiskers represent the 95% confidence intervals. *P-value for the interaction with sex < 0.05. Covariates: Age, sex, waist circumference, mean systolic blood pressure, mean diastolic blood pressure, blood pressure lowering drugs, total cholesterol, high-density lipoprotein, triglycerides, estimated glomerular filtration rate, physically active, daily smoker, albumin-creatinine ratio and uric acid.*

Adiponectin levels in the lower sex-specific tertile were also associated with DD in women and with an increased odds of concentric LV hypertrophy (OR = 2.44, 95% CI = 1.03-5.78, P = 0.04). In men, the odds were decreased for the same outcome (OR = 0.32, 95% CI = 0.11-0.89, P = 0.03, P-value for the interaction with sex = 0.002). Moreover, the adiponectin levels in the lower tertile were associated with a lower odds of eccentric LV hypertrophy in men (OR = 0.53, 95% CI = 0.33-0.88, P = 0.02), but not women (OR = 1.07, 95% CI = 0.71-1.62, P = 0.74, P-value for the interaction = 0.02). Additionally, the adiponectin levels in the lower tertile were associated with a moderately enlarged LA in women (OR = 1.43, 95% CI = 1.01-2.03, P = 0.04) but not in men (OR = 1.01, 95% CI = 0.64-1.58, P = 0.98, P-value for the interaction with sex = 0.04). Finally, according to the multivariate fractional polynomial regression analysis, lower adiponectin levels were associated with an increased LV mass in women (fractional power -2, P = 0.001) but not men (P = 0.66, P-value for the interaction with sex = 0.01). There was no interaction between adiponectin and UA levels for the association with indices of DD.

# 6 General discussion

## 6.1 Methodological considerations

### 6.1.1 Type I and Type II errors

When examining statistical associations, researchers usually employ a null hypothesis, which is a hypothesis that states that the variables in question have absolutely no relationship[99]. The object of the statistical analyses is to accept or reject the null hypothesis. A Type I error is an incorrect rejection of the null hypothesis, i.e., to declare an association between variables that does not exist[100]. Conversely, a Type II error is to wrongly accept a false null hypothesis, i.e., to state that there is no association when, in fact, an association is

present[100]. In the studies performed in this thesis, we have regarded $P < 0.05$ as statistically significant, which is also known as an alpha level of 5%, indicating that the maximal probability of committing a Type I error is 5%, provided that bias or incorrect test assumptions are not present. A low alpha level is set to minimize Type I errors. However, there is a trade-off between the probabilities of a Type I error and a Type II error, and the lower the alpha level is set, the higher the probability of committing a Type II error[100]. The convention is to set an alpha level of 5%, which in itself is an arbitrary value[100], but it seems to offer a compromise in the trade-off between the probability of Type I and Type II errors. The large study populations assessed in the papers in this study protect against Type II errors. However, our stratifications of the cohorts, which were performed in all three papers, increase the probability of Type II errors.

## 6.1.2 Study validity

The object of epidemiological research is to obtain a precise and valid estimation of the frequency of a disease or the effect of an exposure on the occurrence of a disease in the general population[100]. A further objective, which is also the objective of this thesis, is often to obtain an accurate estimate that is generalizable to relevant target populations. The notion of an accurate estimate implies an estimate with little error. Estimation errors may be classified as either random or systematic[100]. An estimate that has little random error may be described as precise[100]. Systematic errors in estimations are also known as biases[100]. An estimate with little systematic error may be described as valid[100]. The study validity is the degree to which the conclusions drawn from the study are reasonable when the study methods and study population are considered[99]. The two fundamental types of study validity are external validity and internal validity[99]. Internal validity is the validity of the conclusions drawn from the study as they apply to the source population from which the study population was derived[100]. External validity is the validity of the conclusions drawn from the study as they apply to subjects outside of the source population[100].

### 6.1.2.1 External validity

This concept is synonymous with generalizability and is an important point to discuss in articles that stem from The Tromsø Study. The population of The Tromsø Study is mostly comprised of Caucasian, middle-aged to elderly and healthy individuals, and the external validity of the study may be reduced because of this lack of demographic diversity.

## 6.1.3 Bias

Bias is the lack of internal validity, and there are three main categories of bias: selection bias, information bias and confounding bias[100,101].

### 6.1.3.1 Selection bias

Selection bias occurs when the study population is not representative of the target population[102]. Specifically, for The Tromsø Study, selection bias is present when the participants of the study have a different relationship between exposure and outcomes than the subjects who were eligible for the study, including individuals who did not participate. All individuals 25 years and older who were registered as living in the Tromsø municipality were invited to participate in Tromsø 4[92]. After excluding individuals who died or moved away from Tromsø, 23% of the eligible population did not participate in the survey[92]. These individuals were younger than the eligible population (mean age of 44.1 years vs. 47.2 years for women

and 40.9 years vs. 46.6 years for men)[92]. The non-participants also included a higher proportion of males (54% vs. 47%)[92]. Other researchers have also found lower participation rates for the younger age groups than for older age groups in population-based studies[103]. Legal restrictions hindered analyses of morbidity and mortality among the non-participants in the Tromsø Study; however, the following indicates that the consistent participants may have been healthier: Age- and sex-adjusted mortality for subjects who participated in all three Tromsø surveys 2-4 was 6.9/1,000 person-years; however, it was 11.1/1,000 person-years for individuals who were invited to participate in all three surveys but only participated in Tromsø 4[92]. Other researchers have also observed higher death rates in non-participants than in participants[104,105]. The study population in Paper 1 and the basis for the study population in Paper 2 were the subjects who attended the special study of Tromsø, in which all men aged 55–74 years and women aged 50–74 years, as well as smaller (5–8%) random samples of the other age groups aged < 85 years were invited to participate. Twenty-six percent of the eligible population did not participate in this special study. We may speculate that individuals who participated in both surveys of Tromsø 4 were even healthier than the individuals who only participated in the first survey. Thus, a risk of selection bias was present due to divergence of health, age and gender of the non-participating population and the participating population, as well as the age selection criteria used for the special study. The same concern applies to the subsequent Tromsø Studies. The study population in Paper 1 consists of subjects who participated in the special study of Tromsø 4 and returned for follow-up seven years later in Tromsø 5; 15% of the eligible population did not participate. The non-participating population also here tended to be younger and male[92]. Paper 3 examines the cross-sectional data from Tromsø 6, and with the exception of the recently completed Tromsø 7, this study was the Tromsø Study with the lowest participation rate of 34% for invited subjects who did not participate. Subjects were invited according to age, and with the exception of the age groups of 40-42 and 60-87 years, samples were available from the other age groups. The study populations for Paper 3 comprised subjects that participated in the special study of Tromsø 6, for which the invitation was based on age groups; 36% of the eligible population did not participate. If these losses to follow-up differ in exposure and outcomes from the rest of the cohort, they may introduce selection bias. Because both younger people, who are more likely to be healthy than older people, and unhealthier subjects tend to decline participation, the total effect of the biases is difficult to predict.

Some subjects have missing values, which will subsequently exclude them from the multivariate analyses. These missing data may constitute bias if the persons with complete data for the analyses do not represent the target population[102]. However, the distribution of missing values does not appear to differ for the groups compared in our models.

#### 6.1.3.2 Information bias

Information bias occurs during data collection and denotes a flaw in measuring exposure, covariate or outcome variables that results in different information accuracy between the groups of the study population being compared[99,102]. For categorical variables, information bias is called misclassification. Much of our data were derived from self-administered questionnaires. Some of the covariates in our models are based on subjects reporting potentially embarrassing or socially undesirable behaviours, such as smoking habits, alcohol

consumption and physical activity, and may be subject to so-called underreporting bias[102]. Questions may have been misunderstood, thus leading to possible misclassification.

Another possible scenario for misclassification occurs during the allocation of subjects to binary variables. In the papers, we attempted to minimize this bias by treating most covariates, except for the lifestyle categories and medication use, as continuous variables. However, some biological variables were treated as categorical variables. In Paper 1, for example, the diagnosis of MetS consists of five components, in which all biological variables were dichotomized. The practice of dichotomizing continuous variables for use in multiple regression analyses is controversial, and some researchers have argued that this practice should be avoided[106]. The main concern is a loss of statistical power[106]. However, the loss of statistical power is more of a concern in studies with smaller samples[106] than in studies with larger samples such as the samples assessed in this thesis. Furthermore, the process of dichotomizing continuous variables is widely performed in clinical research and clinical practice, and is sometimes unavoidable, as in the case of MetS, for which diagnosis of the syndrome relies on the simplistic yes/no answers to five component factors. This observation is also true for markers of DD, for which the cut-off values are designated according to guidelines. With the exception of the low adiponectin levels described in Paper 3, the dichotomization of continuous variables was not data-driven but rather was performed according to clinical guidelines.

In particular, the use of non-fasting blood samples raises the risk of misclassification regarding the elevated fasting glucose and triglyceride levels, as discussed further below. We used the mean of the second and third blood pressure measurements to reduce the risk of misclassification for the elevated blood pressure variable. Information bias may also occur as measurement error, as inaccuracy and biological variability may occur in laboratory values. This error may cause other dichotomized variables, such as the low HDL category in the diagnosis of MetS in Paper 1, the echocardiographic markers of DD in Papers 2 and 3, the low adiponectin levels in Paper 3 and Paper 3 and the albuminuria category in Paper 3, to be misclassified. However, there is no reason to believe that these measurement errors are related to exposure or are dissimilarly distributed between the comparison groups, and the concern about these errors as a source of bias are therefore reduced.

#### 6.1.3.3 Confounders

Confounding (also called confounding bias) occurs when all or part of the apparent relationship between exposure and outcomes is accounted for by other variables (also known as confounders) that affect the outcome but that are not affected by the exposure[99]. This effect may overestimate the effect of the exposure on the outcomes, known as positive confounding, or underestimate it, known as negative confounding[99]. Researchers must adjust for possible confounders in the statistical models to reduce the confounding bias. In our models, we included several covariates that are possible confounders, based on known risk factors for MetS and cardiovascular disease. However, we cannot completely exclude unmeasured confounders, particularly when we examine associations that have not been studied extensively, as performed in the papers presented in this thesis.

### 6.1.4 Causality

In this thesis, we have shown several associations between factors. However, the discovery of an association in epidemiological research is not sufficient to claim knowledge about cause and effect. Universal and objective criteria for causality have yet to be defined[100], but the most rigorous method for testing a hypothesis available in epidemiology and medicine is the randomized controlled trial (RCT)[99], which is the most appropriate method for assessing cause and effect. The cross-sectional design of Paper 3 has severe limitations regarding the assessment of causality. In this study design, we explored sex-specific associations between adiponectin levels and DD, but we could not generate inferences about causality. However, the prospective cohort study designs of Paper 1 and Paper 2 offer more information on possible cause and effect by allowing us to evaluate the temporal sequence. Namely, we established that elevated UA levels occurred before the outcome variable of interest, and temporality is a vital aspect when assessing causality[99].

### 6.1.5 The use of non-fasting blood sample values

Participants in the Tromsø Studies were not given any special instructions regarding fasting before blood sampling. Thus, some subjects had fasted for at least eight hours since their last meal, but most had not, and all participants provided the time since their last meals. For example, the population in Paper 1 had a baseline median time since their last meal of between two and three hours, and eight hours had elapsed since the last meal for only 6.1% of the cohort. The lack of fasting blood samples is a particular concern for Paper 1, which relies on the correct diagnosis of MetS. Overall, our ability to establish the presence of elevated fasting glucose and triglyceride levels is affected by this limitation. Overnight fasting, as utilized in a study of MetS from 2013, is by far the best approach[107]. However, logistical considerations prevented us from obtaining fasting blood samples from most of the participants in the Tromsø Studies in 1994-95, 2001-02 and 2007-08. We adjusted the elevated fasting glucose and elevated triglyceride components of the MetS diagnosis to compensate for this limitation, as shown in Table 1. We have maintained the cut-off of ≥ 5.6 mmol/L for elevated fasting glucose levels in the subjects for which at least four hours had elapsed since the last meal. We established a cut-off of ≥ 7.8 mmol/L for subjects for which less than four hours had elapsed since the last meal, which is the cut-off used for impaired glucose tolerance in oral glucose tolerance tests[24]. For the diagnosis of elevated triglycerides, we maintained a cut-off of ≥ 1.7 mmol/L if the time since the last meal was at least four hours, similar to the glucose levels. For subjects for which less than four hours had elapsed since the last meal, we set a cut-off for elevated triglyceride levels to ≥ 2.28 mmol/L, as non-fasting triglyceride levels are 20-30% higher than the fasting levels[108]. Using this method, we aimed to reduce the number of people misclassified in our study.

### 6.1.6 Old data

Both Papers 1 and 3 use the baseline data from Tromsø 4 in 1994-95, which may be a limitation of the articles. However, if our results can be reproduced in newer data, conceivably, our findings will be even more relevant to current trends, because risk factors such as overweight and obesity are even more prevalent now than in 1994-95. Moreover, the baseline data will be at least as old as the follow-up time in a long-term study.

### 6.1.7 The lack of tissue Doppler data for Tromsø 4

Papers 2 and 3 both utilize echocardiographic data on DD from the Tromsø Study. However, the data were acquired 14 years apart, and some technological and echocardiographic progress was achieved during that time. Foremost is the addition of tissue Doppler diagnostics in Tromsø 6, and a lack of this technology in Tromsø 4. Tissue Doppler data, particularly the acquisition of e'-wave data and calculation of the E/e' ratio, have become hallmarks of DD diagnostics[9], and the lack of those parameters is a limitation of Paper 2 and somewhat restricts the comparison of the data presented in Papers 2 and 3. However, the battery of DD parameters used in Paper 2 is still adequate, as all markers are listed in the current guidelines of The American Society of Echocardiography as ideal parameters for the classification of DD[38].

### 6.1.8 Diameter-based left atrial size estimation

The studies examining echocardiographic markers of DD, Papers 2 and 3, utilize an estimation of LA size based on M-mode measures. The best assessment is probably derived from 2D LA volumes, and the M-mode method may underestimate the LA size[109]. Although current guidelines state that estimations of LA size from M-mode measures may not always represent an accurate picture of the LA size, they also deem the measurement reproducible, based on a wealth of published data[98]. When echocardiography was performed for Paper 2 in 1994, a generally accepted method for assessing LA size was not available. Although the lack of LA volume is a limitation for Paper 2, its absence from the baseline data is not surprising. In Paper 3, the data were acquired in 2007-08 and the limitation is more serious. However, the same measurement for LA size was used in the two studies, enhancing the comparability between the papers.

## 6.2 Discussion of the results

### 6.2.1 The modulatory effect of overweight on the relationship between the uric acid levels and metabolic syndrome

The main finding of this paper was that the UA levels predicted the development of elevated blood pressure, according to the MetS criteria, in the overweight subjects but not in normal-weight individuals. This phenomenon has not been examined in many other studies. A small study (n = 69) from the United Arab Emirates examined the univariable relationship between UA levels and the components of MetS in healthy, young females who were stratified into normal-weight (BMI ≤ 25 kg/m$^2$), overweight (BMI > 25, < 30 kg/m$^2$), and obese (BMI ≥ 30 kg/m$^2$) categories[110]. This study identified statistically significant correlations between UA levels and the waist circumference and triglyceride components only, and the associations were confined to the obese group. The authors did not identify significant correlations between the UA level and elevated blood pressure or elevated fasting glucose levels in the strata. However, this study differed from Paper 1 in several features; the previous study was much smaller, only featured healthy, young females, and did not examine a multivariate relationship between the UA levels and MetS components. A recent study assessed the ability of UA levels to predict future hypertension among more than 26,000 normotensive Japanese males aged 18-60 years, with a mean follow-up time of 7.2 years[111], and did not find an interaction between the UA levels and BMI (< 25 kg/m$^2$ vs. ≥ 25 kg/m$^2$). This study was also different from ours in several aspects, which may explain the discrepancy between

the results and those in Paper 1. First, the Japanese study examined the relationship between UA levels and hypertension, which is defined as blood pressure ≥ 140/90 mm Hg, and not the MetS criterion for elevated blood pressure, which is defined as ≥ 130/85 mm Hg. Second, only males were included, the elderly were excluded, and, similar to the study from the United Arab Emirates, the ethnic profile was different. In the cohort assessed in Paper 1, an interaction between UA levels and a BMI-cut off for obesity (< 30 kg/m$^2$ vs. ≥ 30 kg/m$^2$) was not observed, which may be due to the small group of obese subjects in the cohort. As many as 57.9% of the subjects were overweight, but only 13.5% were obese, naturally reducing the power of the statistical analyses in the stratum of obese individuals.

As mentioned in the Introduction, the association between UA levels and the development of hypertension has been repeatedly reported in previous studies, but the concept that this association is only present in overweight persons has not been thoroughly investigated. There are two main theories regarding how UA is associated with the development of hypertension, both of which involve oxidative stress[112]. First, the degradation of hypoxanthine to xanthine and xanthine to UA, which is catalysed by XO, may produce ROS. Therefore, increased ROS production by XO may be detected as increased serum UA levels. Second, UA itself has been shown to stimulate NADPH oxidase (NOX) activity and ROS production in cultured mouse adipocytes, followed by reduced nitric oxide (NO) bioavailability, this was triggered by intracellular uptake of extracellular UA[113]. ROS has been proposed to cause hypertension[114]. Rats with induced mild hyperuricaemia developed intrarenal oxidative stress and hypertension, and ROS scavengers attenuated the elevated blood pressure[115]. Increased oxidative stress is particularly detrimental when the antioxidant capacity is reduced by accumulated fat[116], which may corroborate the findings presented in Paper 1.

There are a few clinical studies in humans to support a causative role for UA or XO activity in hypertension. A study of 125 children 6 to 18 years of age referred for evaluation of hypertension found that 89 % of the children with primary hypertension had UA levels > 327 µmol/L, but none of the children with white-coat hypertension or the controls had UA levels that high[117]. A randomized trial that enrolled 30 adolescents 11 to 17 years of age with newly diagnosed primary hypertension and UA ≥ 357 µmol/L, treated the subjects with allopurinol 200 mg twice daily for four weeks, and placebo twice daily for four weeks, with a two-week washout period in between, or the other way around[118]. The study found that allopurinol significantly reduced systolic and diastolic blood pressure, compared to placebo, and 20 of the participants were rendered normotensive during allopurinol treatment vs. one participant while taking placebo. The same investigators conducted a double-blinded RCT that enrolled 60 prehypertensive (blood pressure ≥ 120/80 mm Hg and < 140/90 mm Hg), obese (> 95$^{th}$ percentile for sex and age) adolescents 11 to 17 years of age with UA ≥ 297 µmol/L, and treated them with either allopurinol 200 mg twice daily, the uricosuric drug probenecid 500 mg twice daily or placebo twice daily for seven weeks[119]. The study found that both allopurinol and probenecid significantly and markedly reduced blood pressure compared to placebo (mean reduction in systolic blood pressure 10.2 mm Hg and mean reduction in diastolic blood pressure 9.0 mm Hg). There was no significant difference in blood pressure reduction between allopurinol and probenecid, and this points to a non-XO mediated mechanism, and implicates UA as the biochemical mediator of increased blood pressure in this study. A study that enrolled 59 hyperuricaemic adults with UA > 416 µmol/L that received

allopurinol 300 mg per day for three months found that allopurinol slightly but significantly reduced systolic and diastolic blood pressure[120]. That the effect of UA-lowering therapy on blood pressure seems to be greater in younger people, has led some investigators to theorize that early hyperuricaemic hypertension is UA dependent, but later becomes salt-sensitive as renal microvascular disease and interstitial inflammation develops, and this hypertension is less sensitive to UA-lowering therapy[112].

As shown in this study, hyperuricaemia occurred before the onset of elevated blood pressure and elevated fasting glucose levels in overweight subjects, but the prospective epidemiological design of the study restricts our ability to make inferences about causality. We do not know whether the onset of these MetS components occurs because of elevated UA levels or whether UA is a bystander in the process. However, UA is associated with the development of metabolic derangements, which poses a greatly enhanced risk of cardiovascular disease, particularly in overweight subjects. This finding requires further analysis.

### 6.2.2 Uric acid levels as a predictor of adverse cardiovascular events

After a 19-year follow-up period, Paper 2 showed that elevated serum UA levels were associated with increased mortality and the incidence of ischaemic stroke in persons with echocardiographic indices of DD. As the baseline UA levels increased, subjects with an increased or a decreased E/A ratio, increased or decreased EDT, or reduced IVRT all had a higher risk of death during the follow-up period. In persons with severely enlarged LA, the risk of ischaemic stroke increased with higher baseline UA levels. ROS are also implicated in the association between UA levels and DD. NO bioavailability may be limited by ROS, and this phenomenon has been proposed to eventually lead to cardiac remodelling and DD, as well as endothelial dysfunction[121]. Experimental studies have implicated XO-derived ROS in the pathology of HF, both by showing increased XO activity in the failing heart and by showing that XO inhibition improves survival in animal models of HF[122]. An RCT conducted in 405 subjects examined whether the XO inhibitor oxypurinol improved mortality, morbidity and quality of life in patients with HFrEF to a greater degree than the placebo after 24 weeks[123]. XO inhibition did not benefit unselected patients, but a subgroup with UA levels ≥ 565 μmol/L who were treated with oxypurinol experienced clinical improvement compared with the status of patients given the placebo. Building on this finding, another RCT of 253 patients with HFrEF and UA levels ≥ 565 μmol/L studied whether the XO inhibitor allopurinol improved survival or HF symptoms and signs after 24 weeks[124]. The study did not find a clinical benefit of allopurinol. Although XO inhibition was associated with improved survival in a large epidemiological study of patients with both HFpEF and HFrEF[125], no larger randomized trial has yet demonstrated the efficacy of XO inhibition, or UA-lowering drugs in general, on the clinical outcomes of patients with HF. However, UA itself, and not XO, may be the culprit in cardiovascular disease. In one study, the endothelial function of hyperuricaemic subjects (mean UA 553 μmol/L) was reduced relative to that of the controls, possibly due to reduced vascular NO activity, which was alleviated with allopurinol treatment[126]. The study hypothesized that reduced UA levels and not inhibition of ROS production by XO, mediated the effect, because allopurinol did not improve endothelial function in normouricaemic subjects.

Hypertension is a well-established risk factor for cardiovascular disease[127], and some researchers hypothesize that the possible link between UA levels and cardiovascular disease is mediated by the risk posed by hypertension[61]. This hypothesis could be true for the specific association between UA levels and DD because hypertension is closely associated with DD[11], and both hypertension and DD are implicated in the development of HFpEF[39]. However, the models in this study adjusted for both systolic and diastolic blood pressure, as well as the use of blood pressure-lowering drug, so any link between UA levels and DD mediated by hypertension is through other mechanisms not measured at baseline. Hyperuricaemia has been shown to downregulate the production of adiponectin[18], an anti-inflammatory and insulin-sensitizing agent produced by adipocytes, as described above. Low levels of adiponectin are associated with the development of hypertension[80] and insulin resistance[79] and may partially explain why UA levels are associated with the new onset of elevated blood pressure in Paper 1 and adverse outcomes in subjects with DD in Paper 2. Unfortunately, the serum adiponectin levels were not measured in the fourth wave of the Tromsø Study, and we were therefore unable to corroborate this theory.

This study showed a relationship between UA levels and the risk of mortality in subjects with echocardiographic markers of DD, but not in subjects without these markers. We do not know whether hyperuricaemia is the cause of the enhanced mortality risk in persons with indices of DD. However, UA levels are associated with worse outcomes in subjects with DD, which is closely associated with metabolic disorders such as obesity, diabetes mellitus and MetS, further supporting the hypothesis that UA levels are associated with cardiovascular disease, particularly in subjects with conditions associated with metabolic derangements.

Previous work by our research group did not identify UA as a risk factor for myocardial infarction[66], and this finding did not change when we tested for interactions between UA levels and indices of DD for myocardial infarction in Paper 2. Both studies rely on a thorough review of the above-described endpoints. Therefore, when there is adequate control for confounders and a solid endpoint registry, our research offers no reason to consider UA as a risk factor for myocardial infarction, in contrast to other publications[65,128]. This indicates that the higher all-cause mortality with increasing UA in subjects with DD discovered in Paper 2, is through other processes than myocardial infarctions.

### 6.2.3 Low adiponectin levels as a sex-specific predictor of DD

This article reported the novel concept that the association of low adiponectin levels and DD, including several echocardiographic markers of DD and LV mass, was generally confined to the female sex. In men, the opposite trend was observed; all markers of DD were associated with higher adiponectin levels in men. Traditionally, high adiponectin levels have been regarded as favourable in terms of cardiac health, but research has challenged this perspective, and the role and action of adiponectin in heart disease is not clear. In general, low levels of adiponectin have been associated with the development of coronary heart disease in healthy subjects[129], but high adiponectin levels are a risk factor for the severity of HF and mortality in patients with chronic HF[82]. One study following 3,263 relatively young persons for a mean time of 10.4 years found that higher adiponectin levels were associated with an increased risk of cardiovascular death and all-cause mortality (with no significant sex differences), although higher adiponectin levels were associated with a lower LV mass and a

lower prevalence of MetS[130]. Our findings demonstrating a relationship between adiponectin levels and some indices of DD in the cohort as a whole are supported by several epidemiological studies. One study examining 275 subjects with essential hypertension and normotensive controls found a negative association between adiponectin levels and LV mass and DD (defined as an E/A ratio > 1, IVRT > 100 ms and EDT > 200 ms)[131]. However, another study examining the adiponectin levels in 26 patients (20 of them male) with hypertrophic cardiomyopathy found that adiponectin was positively correlated with DD (with LV pressure half-time as a marker of myocardial relaxation)[132]. In a cross-sectional study involving participants of the Framingham Offspring study (n = 2,615), adiponectin levels were inversely correlated to LV mass but not LA enlargement[90]. In another cross-sectional, population-based study (n = 843), adiponectin did not mediate the association between visceral fat and DD[133]. A recent study (n = 100) reported low levels of adiponectin in patients with DD, and even lower levels in patients with DD and diabetes as a sign of early diabetic cardiomyopathy (DD was defined by the E/A ratio)[134]. One theory for this equivocal relationship between adiponectin and heart disease is that high levels are beneficial in healthy subjects, but adiponectin levels are upregulated as a compensatory mechanism during chronic HF[83] or increase simply due to reduced kidney function, which commonly coexists with heart failure[135]. However, one fairly recent small study examining 25 patients with mild or moderate symptoms of HF compared with 25 healthy controls found a significant and negative relationship between DD and adiponectin levels (DD was defined as an E/A ratio < 1 and EF > 50%)[136]. Moreover, as a further complication, one study observed a concomitant increase in the plasma brain natriuretic peptide (BNP) and adiponectin levels in healthy subjects, and the authors argue that adiponectin levels are also a positive indicator of reduced cardiac function in healthy persons[137]. The relationship between adiponectin levels, obesity, sex, and organ damage is a complex one, and further studies are clearly needed. Our results for the sex-specific association between the adiponectin levels and DD may shed some light on the biphasic relationship between the adiponectin levels and DD observed in studies with very unequal proportions of men and women and in studies that did not have sufficient power to examine the sex-specific differences. Few articles have studied the sex-specific differences in the relationship between adiponectin levels and DD. One paper examined a cohort consisting of 193 patients undergoing cardiac catheterization for coronary artery disease and specifically assessed sex-specific differences. A negative relationship between adiponectin levels and DD was observed, but a significant sex-specific difference in this association was not observed[138]. A population-based study of 556 individuals did not find any association between DD and adiponectin levels for either sex[139].

We did not identify any significant interaction between adiponectin and UA levels for either sex or in the cohort as a whole. Thus, we were unable to corroborate the hypothesis that the interaction between UA levels and markers of DD for the endpoints in Paper 2 was in any way mediated by adiponectin levels. However, only the total adiponectin levels were available in Tromsø 6. Quantification of the HMW fraction of adiponectin may have yielded more information than the total adiponectin levels alone, and we cannot exclude an association between the levels of UA and the HMW adiponectin fraction. Another point worth discussing is that adiponectin levels also increase simply due to reduced kidney function, which commonly coexists with HF, and as mentioned above, this could explain the possible link between the UA and adiponectin levels. However, the eGFR was mostly normal in our

study, and we controlled for the eGFR in all our models. Thus, as a confounder, reduced kidney function was probably less of a concern in our results. Moreover, an obvious limitation of Paper 3 was the cross-sectional design. The associations discovered in this study should be re-examined in a study with a prospective design to assess whether the low adiponectin levels occur before DD in women. In summary, we discovered a sex-specific association between low adiponectin levels and indices of DD and increased LV mass, perhaps representing a small step towards deciphering why HFpEF tend to occur disproportionately in women, in addition to obese, diabetic and hypertensive subjects.

# 7 Conclusions and perspectives

We have shown that UA levels predicted the development of MetS during a seven-year period, consistent with previous studies. The novel findings of our study are that the UA levels predicted the development of elevated blood pressure and elevated fasting glucose levels in overweight subjects but not in people with a normal weight. UA levels were associated with a higher risk of mortality and ischaemic stroke in subjects with indices of DD than that found in individuals without these markers. Low adiponectin levels were associated with DD in women but not in men. There was no interaction between adiponectin and UA levels in the association with markers of DD.

This thesis contributes to research linking UA levels with metabolic derangements and poorer prognosis in patients with cardiovascular disease. Although our prospective study of UA and MetS offers more information than a cross-sectional study – we now know that hyperuricaemia occurs before the onset of elevated blood pressure and elevated fasting glucose levels in overweight subjects – our findings cannot provide any information regarding the causality of the association. UA may be a causative factor for the development of MetS components and increased mortality and ischaemic stroke risk in subjects with DD, or it may be a marker of some other causative factor or factors. Based on previous publications, we proposed that one of these factors might be adiponectin, a hormone that was not measured in the Tromsø Study in 1994-95 and therefore was not included in Papers 1 and 2. However, we could not corroborate this theory when we examined the data from the Tromsø Study of 2007-08 for Paper 3, and further prospective studies are needed. The sex-specific difference in the association between adiponectin levels and DD discovered in Paper 3 requires further examination due to the lack of information about the biological basis of the female preponderance in HFpEF.

Based on the above, this thesis offers the following theories:

- Uric acid is associated with the deterioration of existing metabolic disturbances, as shown in the development of MetS features in overweight subjects and poor outcome in subjects with DD with increasing UA.
- Increased mortality risk with increasing UA levels in subjects with DD is not due to increased risk of myocardial infarction.
- Adipose tissue dysfunction may be part of the pathology of HFpEF in women, and some of the reason for the sex difference in HFpEF.
- There is no significant interaction between adiponectin and UA levels for the association with DD in the general population.

Our findings should spur further research on the topics described below.

- Studies assessing pressure overloaded animal models, with both male and female animals, to address the effects of UA and adiponectin levels on adipose tissue and the development of DD and HFpEF.
- A large-scale RCT examining UA-lowering therapy in subgroups of overweight subjects and subjects with DD or HFpEF.
- Further investigations, including prospective observational studies, of the preponderance of women with HFpEF should focus on adiponectin and other adipokines, as well as adipocyte function.

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# Paper 1

# Paper 2

# Paper 3

# Appendix

## Tromsø 4 questionnaire

## YOUR OWN HEALTH

What is your current state of health? *Tick one box only.*

| | | |
|---|---|---|
| Poor | 12 | 1 |
| Not so good | | 2 |
| Good | | 3 |
| Very good | | 4 |

Do you have, or have you had:

| | | Yes | No | Age first time |
|---|---|---|---|---|
| A heart attack | 13 | | | years |
| Angina pectoris (heart cramp) | 16 | | | years |
| A cerebral stroke/ brain haemorrhage | 19 | | | years |
| Asthma | 22 | | | years |
| Diabetes | 25 | | | years |

Do you use blood pressure lowering drugs?

| | | |
|---|---|---|
| Currently | 28 | 1 |
| Previously, but not now | | 2 |
| Never used | | 3 |

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months? 29 — Yes / No

Have you in the last two weeks felt:

| | | No | A little | A lot | Very much |
|---|---|---|---|---|---|
| Nervous or worried? | 30 | | | | |
| Anxious? | 31 | | | | |
| Confident and calm? | 32 | | | | |
| Irritable? | 33 | | | | |
| Happy and optimistic? | 34 | | | | |
| Down/depressed? | 35 | | | | |
| Lonely? | 36 | | | | |
| | | 1 | 2 | 3 | 4 |

## SMOKING

Did any of the adults at home smoke while you were growing up? 37 — Yes / No

Do you currently, or did you previously, live together with daily smokers after your 20th birthday? 38 — Yes / No

If "YES", for how many years in all? 39 — Years

How many hours a day do you normally spend in smoke-filled rooms? 41 — Hours

*Put 0 if you do not spend time in smoke-filled rooms.*

Do you yourself smoke:

| | | Yes | No |
|---|---|---|---|
| Cigarettes daily? | 43 | | |
| Cigars/ cigarillos daily? | 44 | | |
| A pipe daily? | 45 | | |

If you previously smoked daily, how long is it since you quit? 46 — Years

If you currently smoke, or have smoked previously:

How many cigarettes do you or did you usually smoke per day? 48 — cigarettes

How old were you when you began daily smoking? 52 — Age years

How many years in all have you smoked daily? 54 — Years

## EXERCISE

How has your physical activity in leisure time been during this last year? *Think of your weekly average for the year.*

*Time spent going to work counts as leisure time.*

| | | None | Less than 1 | 1-2 | 3 or more |
|---|---|---|---|---|---|
| | | Hours per week | | | |
| Light activity *(not sweating/out of breath)* | 56 | | | | |
| Hard activity *(sweating/ out of breath)* | 57 | | | | |
| | | 1 | 2 | 3 | 4 |

## COFFEE

How many cups of coffee do you drink daily?
*Put 0 if you do not drink coffee daily.*

| | | |
|---|---|---|
| Coarsely ground coffee for brewing | 58 | Cups |
| Other coffee | 60 | Cups |

## ALCOHOL

Are you a teetotaller? 62 — Yes / No

How many times a month do you normally drink alcohol? *Do not count low-alcohol beer.*
*Put 0 if less than once a month.* 63 — Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? 65
*Do not count low-alcohol beer.*
*Put 0 if less than once a month.*

| Beer | Wine | Spirits |
|---|---|---|
| Glasses | Glasses | Glasses |

## FAT

What type of margarine or butter do you usually use on bread? *Tick one box only.*

| | | |
|---|---|---|
| Don't use butter/margarine | 71 | 1 |
| Butter | | 2 |
| Hard margarine | | 3 |
| Soft margarine | | 4 |
| Butter/margarine mixtures | | 5 |
| Light margarine | | 6 |

## EDUCATION/WORK

What is the highest level of education you have completed?

| | | |
|---|---|---|
| 7-10 years primary/secondary school, modern secondary school | 72 | 1 |
| Technical school, middle school, vocational school, 1-2 years senior high school | | 2 |
| High school diploma (3-4 years) | | 3 |
| College/university, less than 4 years | | 4 |
| College/university, 4 or more years | | 5 |

What is your current work situation?

| | | |
|---|---|---|
| Paid work | 73 | |
| Full-time housework | 74 | |
| Education, military service | 75 | |
| Unemployed, on leave without payment | 76 | |

How many hours of paid work do you have per week? 77 — No. of hours

Do you receive any of the following benefits?

| | | |
|---|---|---|
| Sickness benefit (sick leave) | 79 | |
| Rehabilitation benefit | 80 | |
| Disability pension | 81 | |
| Old-age pension | 82 | |
| Social welfare benefit | 83 | |
| Unemployment benefit | 84 | |

## ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)? 85 — Yes / No / Don't know

# The Tromsø Health Survey

**The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.**

**This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.**

**If you are in doubt about what to answer, tick the box that you feel fits best.**

**The completed form should be sent to us in the enclosed pre-paid envelope.**

**Thank you in advance for helping us.**

*Yours sincerely,*

**Faculty of Medicine**
**University of Tromsø**

**National Health Screening Service**

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire ..... 17 ❑

Day Month Year

Date for filling in this form:..... 18 ...../...../.....

## CHILDHOOD/YOUTH

In which Norwegian municipality did you live at the age of 1 year?

.....24 - 28

*If you did not live in Norway, give country of residence instead of municipality.*

How was your family's financial situation during your childhood?

- Very good ..... 29 ❑
- Good ..... ❑
- Difficult ..... ❑
- Very difficult ..... ❑

How many of the first three years of your life

- did you live in a town/city? ..... 30 ____years
- did your family have a cat or dog in the home? ..... 31 ____years

How many of the first 15 years of your life

- did you live in a town/city? ..... 32 ____years
- did your family have a cat or dog in the home? ..... 34 ____years

## HOME

Who do you live with?

| *Tick once for each item and give the number.* | | Yes | No | Number |
|---|---|---|---|---|
| Spouse/partner | 36 | ❑ | ❑ | |
| Other people over 18 years | 37 | ❑ | ❑ | _____ |
| People under 18 years | 40 | ❑ | ❑ | _____ |

How many of the children attend day care/kindergarten? .... 43 _____

What type of house do you live in?

- Villa/detached house ..... 45 ❑ 1
- Farm ..... ❑ 2
- Flat /apartment ..... ❑ 3
- Terraced /semi-detached house ..... ❑ 4
- Other ..... ❑ 5

How big is your house? ..... 46 _____ $m^2$

Approximately what year was your house built? ..... 49 _____

| | | Yes | No |
|---|---|---|---|
| Has your house been insulated after 1970? | 53 | ❑ | ❑ |
| Do you live on the lower ground floor/basement? | 54 | ❑ | ❑ |
| If "Yes", is the floor laid on concrete? | 55 | ❑ | ❑ |

What is the main source of heat in your home?

- Electric heating ..... 56 ❑
- Wood-burning stove ..... ❑
- Central heating system using:
  - Paraffin ..... ❑
  - Electricity ..... ❑

| | | Yes | No |
|---|---|---|---|
| Do you have fitted carpets in the living room? | 60 | ❑ | ❑ |
| Is there a cat in your home? | 61 | ❑ | ❑ |
| Is there a dog in your home? | 62 | ❑ | ❑ |

## WORK

If you have paid or unpaid work, how would you describe your work?

- Mostly sedentary work? ..... 63 ❑ 1
  *(e.g. office work, mounting)*
- Work that requires a lot of walking? ..... ❑ 2
  *(e.g. shop assistant, light industrial work, teaching)*
- Work that requires a lot of walking and lifting? ..... ❑ 3
  *(e.g. postman, nursing, construction)*
- Heavy manual work? ..... ❑ 4
  *(e.g. forestry, heavy farm-work, heavy construction)*

Can you decide yourself how your work should be organised?

- No, not at all ..... 64 ❑ 1
- To a small extent ..... ❑ 2
- Yes, to a large extent ..... ❑ 3
- Yes, I decide myself ..... ❑ 4

| | | Yes | No |
|---|---|---|---|
| Are you on call, do you work shifts or nights? | 65 | ❑ | ❑ |

Do you do any of the following jobs (full- or part-time)?

| *Tick one box only for each item.* | | Yes | No |
|---|---|---|---|
| Driver | 66 | ❑ | ❑ |
| Farmer | | ❑ | ❑ |
| Fisherman | | ❑ | ❑ |

## YOUR OWN ILLNESSES

Have you ever had:
*Tick one box only for each item. Give your age at the time.*
*If you have had the condition several times, how old were you **last** time?*

| | Yes | No | Age |
|---|---|---|---|
| Hip fracture ..... 69 | ❑ | ❑ | _____ |
| Wrist/forearm fracture ..... 72 | ❑ | ❑ | _____ |
| Whiplash ..... 75 | ❑ | ❑ | _____ |
| Injury requiring hospital admission ..... 78 | ❑ | ❑ | _____ |
| Gastric ulcer ..... 81 | ❑ | ❑ | _____ |
| Duodenal ulcer ..... 84 | ❑ | ❑ | _____ |
| Gastric/duodenal ulcer surgery ..... 87 | ❑ | ❑ | _____ |
| Neck surgery ..... 90 | ❑ | ❑ | _____ |

Have you you ever had, or do you still have:
*Tick one box only for each item.*

| | Yes | No |
|---|---|---|
| Cancer ..... 93 | ❑ | ❑ |
| Epilepsy ..... | ❑ | ❑ |
| Migraine ..... | ❑ | ❑ |
| Chronic bronchitis ..... | ❑ | ❑ |
| Psoriasis ..... | ❑ | ❑ |
| Osteoporosis ..... 98 | ❑ | ❑ |
| Fibromyalgia/fibrositis/chronic pain syndrome ..... | ❑ | ❑ |
| Psychological problems for which you have sought help | ❑ | ❑ |
| Thyroid disease ..... | ❑ | ❑ |
| Liver disease ..... | ❑ | ❑ |
| Kidney disease ..... 103 | ❑ | ❑ |
| Appendectomy ..... | ❑ | ❑ |
| Allergy and hypersensitivity: | | |
| Atopic eczema (e.g. childhood eczema) ..... | ❑ | ❑ |
| Hand eczema ..... | ❑ | ❑ |
| Hay fever ..... | ❑ | ❑ |
| Food allergy ..... 108 | ❑ | ❑ |
| Other hypersensitivity (not allergy) ..... | ❑ | ❑ |

How many times have you had a cold, influenza (flu), vomiting/diarrhoea, or similar in the last six months? ____ times

| | Yes | No |
|---|---|---|
| Have you had this in the last 14 days? ..... 112 | ❑ | ❑ |

## ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
*Tick "None" if none of your relatives have had the disease.*

| | Mother | Father | Brother | Sister | Child | None |
|---|---|---|---|---|---|---|
| Cerebral stroke or brain haemorrhage 113 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Heart attack before age 60 ..... 119 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Cancer ..... 125 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Asthma ..... 131 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Gastric/duodenal ulcer ..... 137 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Osteoporosis ..... 143 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Psychological problems ..... 149 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Allergy ..... 155 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Diabetes ..... 161 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| – age when they got diabetes ..... 167 | ___ | ___ | ___ | ___ | ___ | |

## SYMPTOMS

| | Yes | No |
|---|---|---|
| Do you cough about daily for some periods of the year? ..... 177 | ❑ | ❑ |
| If "Yes": | | |
| Is your cough productive ? ..... 178 | ❑ | ❑ |
| Have you had this kind of cough for as long as 3 months in each of the last two years? ..... 179 | ❑ | ❑ |
| Have you had episodes of wheezing in your chest? ..... 180 | ❑ | ❑ |
| If "Yes", has this occurred: | | |
| *Tick one box only for each item.* | | |
| At night ..... 181 | ❑ | ❑ |
| In connection with respiratory infections ..... | ❑ | ❑ |
| In connection with physical exertion ..... | ❑ | ❑ |
| In connection with very cold weather ..... | ❑ | ❑ |
| Have you noticed sudden changes in your pulse or heart rhythm in the last year? ..... 185 | ❑ | ❑ |

How often do you suffer from sleeplessness?

| | |
|---|---|
| Never, or just a few times a year ..... 186 | ❑ 1 |
| 1-2 times a month ..... | ❑ 2 |
| Approximately once a week ..... | ❑ 3 |
| More than once a week ..... | ❑ 4 |

If you suffer from sleeplessness, what time of the year does it affect you most?

| | |
|---|---|
| No particular time of year ..... 187 | ❑ 1 |
| Especially during the polar night ..... | ❑ 2 |
| Especially during the midnight sun season ..... | ❑ 3 |
| Especially in spring and autumn ..... | ❑ 4 |

| | Yes | No |
|---|---|---|
| Have you in the last year suffered from sleeplessness to the extent that it has affected your ability to work? ..... 188 | ❑ | ❑ |

How often do you suffer from headaches?

| | |
|---|---|
| Rarely or never ..... 189 | ❑ 1 |
| Once or more a month ..... | ❑ 2 |
| Once or more a week ..... | ❑ 3 |
| Daily ..... | ❑ 4 |

Does the thought of getting a serious illness ever worry you?

| | |
|---|---|
| Not at all ..... 190 | ❑ 1 |
| Only a little ..... | ❑ 2 |
| Some ..... | ❑ 3 |
| Very much ..... | ❑ 4 |

## USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness:
*Tick **0** if you have **not** had such contact*

| | Number of times the past year |
|---|---|
| To a general practitioner (GP)/Emergency GP ..... 191 | _____ |
| To a psychologist or psychiatrist ..... | _____ |
| To an other medical specialist (not at a hospital) ..... | _____ |
| To a hospital out-patient clinic ..... 197 | _____ |
| Admitted to a hospital ..... | _____ |
| To a medical officer at work ..... | _____ |
| To a physiotherapist ..... 203 | _____ |
| To a chiropractor ..... | _____ |
| To an acupuncturist ..... | _____ |
| To a dentist ..... 209 | _____ |
| To an alternative practitioner (homoeopath, foot zone therapist, etc.) | _____ |
| To a healer, faith healer, clairvoyant ..... | _____ |

## MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
*Put **0** for items you have **not** used.*

Medicines
- Painkillers ..... 215 _____ months
- Sleeping pills ..... _____ months
- Tranquillizers ..... _____ months
- Antidepressants ..... 221 _____ months
- Allergy drugs ..... _____ months
- Asthma drugs ..... _____ months

Dietary supplements
- Iron tablets ..... 227 _____ months
- Calcium tablets or bonemeal ..... _____ months
- Vitamin D supplements ..... _____ months
- Other vitamin supplements ..... 233 _____ months
- Cod liver oil or fish oil capsules ..... _____ months

Have you in the last 14 days used the following medicines or dietary supplements?
*Tick **one** box only for **each** item.*

| | Yes | No |
|---|---|---|
| **Medicines** | | |
| Painkillers ..... 237 | ❑ | ❑ |
| Antipyretic drugs (to reduce fever) ..... | ❑ | ❑ |
| Migraine drugs ..... | ❑ | ❑ |
| Eczema cream/ointment ..... | ❑ | ❑ |
| Heart medicines (not blood pressure) ..... | ❑ | ❑ |
| Cholesterol lowering drugs ..... | ❑ | ❑ |
| Sleeping pills ..... | ❑ | ❑ |
| Tranquillizers ..... | ❑ | ❑ |
| Antidepressants ..... | ❑ | ❑ |
| Other drugs for nervous conditions ..... | ❑ | ❑ |
| Antacids ..... 247 | ❑ | ❑ |
| Gastric ulcer drugs ..... | ❑ | ❑ |
| Insulin ..... | ❑ | ❑ |
| Diabetes tablets ..... | ❑ | ❑ |
| Drugs for hypothyroidism (Thyroxine) ..... | ❑ | ❑ |
| Cortisone tablets ..... 252 | ❑ | ❑ |
| Other medicine(s) ..... | ❑ | ❑ |
| **Dietary supplements** | | |
| Iron tablets ..... | ❑ | ❑ |
| Calcium tablets or bonemeal ..... | ❑ | ❑ |
| Vitamin D supplements ..... | ❑ | ❑ |
| Other vitamin supplements ..... 257 | ❑ | ❑ |
| Cod liver oil or fish oil capsules ..... | ❑ | ❑ |

## FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? 259 _____ good friends
*Do not count people you live with, but do include other relatives!*

How many of these good friends do you have contact with at least once a month? ..... 261 _____

| | Yes | No |
|---|---|---|
| Do you feel you have enough good friends? ..... 263 | ❑ | ❑ |

How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?
- Never, or just a few times a year ..... 264 ❑ 1
- 1-2 times a month ..... ❑ 2
- Approximately once a week ..... ❑ 3
- More than once a week ..... ❑ 4

## FOOD HABITS

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (10-12g)

A catering portion is enough for about ..... 265 _____ slices

What kind of fat is normally used in **cooking** (not on the bread) in your home?
- Butter ..... 266 ❑
- Hard margarine ..... ❑
- Soft margarine ..... ❑
- Butter/margarine blend ..... ❑
- Oils ..... 270 ❑

What kind of bread (bought or home-made) do you usually eat?
*Tick one or two boxes!*

| | White bread | Light textured | Ordinary brown | Coarse brown | Crisp bread |
|---|---|---|---|---|---|
| The bread I eat is most similar to: | ❑ 271 | ❑ | ❑ | ❑ | ❑ 275 |

How much (in **number** of glasses, cups, potatoes or slices) do you usually eat or drink **daily** of the following foodstuffs?
*Tick one box for **each** foodstuff.*

| | 0 | Less than 1 | 1-2 | 3-4 | 5-6 | More than 6 |
|---|---|---|---|---|---|---|
| Full milk (ordinary or curdled) (glasses) 276 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Semi-skimmed milk (ordinary or curdled) (glasses) | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Skimmed milk (ordinary or curdled) (glasses) | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Tea (cups) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Orange juice (glasses) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Potatoes ..... 281 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Slices of bread in total (incl. crisp-bread) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Slices of bread with - fish (e.g. mackerel in tomato sauce) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - lean meat (e.g. ham) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - fat meat (e.g. salami) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - cheese *(e.g. Gouda/ Norvegia)* ..... 286 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - brown cheese ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - smoked cod caviare ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - jam and other sweet spreads ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| | 1 | 2 | 3 | 4 | 5 | 6 |

How many **times per week** do you normally eat the following foodstuffs?
*Tick a box for **all** foodstuffs listed.*

| | Never | Less than 1 | 1 | 2-3 | 4-5 | almost daily |
|---|---|---|---|---|---|---|
| Yoghurt ..... 290 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Boiled or fried egg ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Breakfast cereal/ oat meal, etc. ... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Dinner with - unprocessed meat..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - sausage/meatloaf/ meatballs ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - fatty fish (e.g. salmon/redfish) 295 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - lean fish (e.g. cod) ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - fishballs/fishpudding/fishcakes ... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| - vegetables ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Mayonnaise, remoulade ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Carrots ..... 300 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Cauliflower/cabbage/ broccoli ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Apples/pears ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Oranges, mandarins ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Sweetened soft drinks ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Sugar-free ("Light") soft drinks ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Chocolate ..... | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Waffles, cakes, etc. ..... 307 | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| | 1 | 2 | 3 | 4 | 5 | 6 |

## ALCOHOL

| How often do you usually drink | beer? | wine? | spirits? |
|---|---|---|---|
| Never, or just a few times a year | ❑ | ❑ | ❑ 1 |
| 1-2 times a month | ❑ | ❑ | ❑ 2 |
| About once a week | ❑ | ❑ | ❑ 3 |
| 2-3 times a week | ❑ | ❑ | ❑ 4 |
| More or less daily | ❑ | ❑ | ❑ 5 |
| | 308 | | 310 |

Approximately how often during the last year have you consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not at all the last year ❑ 1
- A few times ❑ 2
- 1-2 times a month ❑ 3
- 1-2 times a week ❑ 4
- 3 or more times a week ❑ 5

For approximately how many years has your alcohol consumption been as you described above? 312 ____years

## WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? Write **0** if you never have.

- before age 20 314 _____ times
- later 316 _____ times

If you have lost weight deliberately, about how many kilos have you ever lost at the most?

- before age 20 318 _____ kg
- later 320 _____ kg

What weight would you be satisfied with (your "ideal weight")? 322 _____ kg

## URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

- Never 325 ❑ 1
- Not more than once a month ❑ 2
- Two or more times a month ❑ 3
- Once a week or more ❑ 4

Your comments:

# TO BE ANSWERED BY WOMEN ONLY

## MENSTRUATION

How old were you when you started menstruating? 326 _____years

If you no longer menstruate, how old were you when you stopped menstruating? 328 _____years

| Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? 330 | Yes ❑ | No ❑ |
|---|---|---|

If "Yes", how many times? 331 _____ times

If you still menstruate or are pregnant: day/month/year

What date did your last menstruation period begin? 333 ___/___/___

| Do you usually use painkillers to relieve period pains? 339 | Yes ❑ | No ❑ |
|---|---|---|

## PREGNANCY

How many children have you given birth to? 340 _____ children

| Are you pregnant at the moment? 342 | Yes ❑ | No ❑ | Don't know ❑ |
|---|---|---|---|

| Have you during pregnancy had high blood pressure and/or proteinuria? 343 | Yes ❑ | No ❑ |
|---|---|---|

| If "Yes", during which pregnancy? | Pregnancy First | Later |
|---|---|---|
| High blood pressure 344 | ❑ | ❑ |
| Proteinuria 346 | ❑ | ❑ |

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child.

| Child | Year of birth: | Number of months breastfed: |
|---|---|---|
| 1 | 348 _____ | _____ |
| 2 | _____ | _____ |
| 3 | 356 _____ | _____ |
| 4 | _____ | _____ |
| 5 | 364 _____ | _____ |
| 6 | _____ | _____ |

## CONTRACEPTION AND ESTROGEN

| Do you use, or have you ever used: | Now | Before | Never |
|---|---|---|---|
| Oral contraceptive pills (incl. minipill) 372 | ❑ | ❑ | ❑ |
| Hormonal intrauterine device | ❑ | ❑ | ❑ |
| Estrogen (tablets or patches) 374 | ❑ | ❑ | ❑ |
| Estrogen (cream or suppositories) | ❑ | ❑ | ❑ |
| | 1 | 2 | 3 |

If you use oral contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?

376 .....

If you use or have ever used oral contraceptive pills:

- Age when you started to take the pill? 380 _____years
- How many years in total have you taken the pill? 382 _____years
- If you have given birth, how many years did you take the pill before your first delivery? 384 _____years
- If you have stopped taking the pill: Age when you stopped? 386 _____years

***Thank you for the help! Remember to mail the form today!***

*The Tromsø Health Survey*

## Tromsø 5 questionnaire

## 1. YOUR OWN HEALTH

**1.1 What is your current state of health?** *(Tick one only)*

Poor ☐ 1 | Not so good ☐ 2 | Good ☐ 3 | Very good ☐ 4

**1.2 Do you have, or have you had?:**

| | Yes | No | Age first time |
|---|---|---|---|
| Asthma | ☐ | ☐ | |
| Hay fever | ☐ | ☐ | |
| Chronic bronchitis/emphysema | ☐ | ☐ | |
| Diabetes | ☐ | ☐ | |
| Osteoporosis | ☐ | ☐ | |
| Fibromyalgia/chronic pain syndrome | ☐ | ☐ | |
| Psychological problems for which you have sought help | ☐ | ☐ | |
| A heart attack | ☐ | ☐ | |
| Angina pectoris (heart cramp) | ☐ | ☐ | |
| Cerebral stroke/brain haemorrhage | ☐ | ☐ | |

**1.3 Have you noticed attacks of sudden changes in your pulse or heart rhythm in the last year?** Yes ☐ No ☐

**1.4 Do you get pain or discomfort in the chest when:**
Walking up hills, stairs or walking fast on level ground? Yes ☐ No ☐

**1.5 If you get such pain, do you usually:**

Stop? ☐ 1 | Slow down? ☐ 2 | Carry on at the same pace? ☐ 3

**1.6 If you stop, does the pain disappear within 10 minutes?** Yes ☐ No ☐

**1.7 Can such pain occur even if you are at rest?** Yes ☐ No ☐

## 2. MUSCULAR AND SKELETAL COMPLAINTS

**2.1 Have you suffered from pain and/or stiffness in muscles and joints during the last 4 weeks?**
*(Give duration only if you have had problems)*

| | No complaint | Some complaint | Severe complaint | Duration: Up to 2 weeks | Duration: 2 weeks or more |
|---|---|---|---|---|---|
| Neck/shoulders | ☐ | ☐ | ☐ | ☐ | ☐ |
| Arms, hands | ☐ | ☐ | ☐ | ☐ | ☐ |
| Upper part of your back | ☐ | ☐ | ☐ | ☐ | ☐ |
| Lumbar region | ☐ | ☐ | ☐ | ☐ | ☐ |
| Hips, legs, feet | ☐ | ☐ | ☐ | ☐ | ☐ |
| Other places | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 1 | 2 | 3 | 1 | 2 |

**2.2 Have you ever had:**

| | Yes | No | Age last time |
|---|---|---|---|
| Fracture in the wrist/forearm | ☐ | ☐ | |
| Hip fracture? | ☐ | ☐ | |

## 3. OTHER COMPLAINTS

**3.1 Below is a list of various problems. Have you experienced any of this during the last week (including today)?**
*(Tick once for each complaint)*

| | No complaint | Little complaint | Pretty much | Very much |
|---|---|---|---|---|
| Sudden fear without reason | ☐ | ☐ | ☐ | ☐ |
| Felt afraid or anxious | ☐ | ☐ | ☐ | ☐ |
| Faintness or dizziness | ☐ | ☐ | ☐ | ☐ |
| Felt tense or upset | ☐ | ☐ | ☐ | ☐ |
| Tend to blame yourself | ☐ | ☐ | ☐ | ☐ |
| Sleeping problems | ☐ | ☐ | ☐ | ☐ |
| Depressed, sad | ☐ | ☐ | ☐ | ☐ |
| Feeling of being useless, worthless | ☐ | ☐ | ☐ | ☐ |
| Feeling that everything is a struggle | ☐ | ☐ | ☐ | ☐ |
| Feeling of hopelessness with regard to the future | ☐ | ☐ | ☐ | ☐ |
| | 1 | 2 | 3 | 4 |

## 4. USE OF HEALTH SERVICES

**4.1 How many times in the last 12 months have you been to/used:**
*(Tick once for each line)*

| | None | 1-3 times | 4 or more |
|---|---|---|---|
| General practitioner (GP) | ☐ | ☐ | ☐ |
| Medical officer at work | ☐ | ☐ | ☐ |
| Psychologist or psychiatrist *(private or out-patient clinic)* | ☐ | ☐ | ☐ |
| Other specialist *(private or out-patient clinic)* | ☐ | ☐ | ☐ |
| Emergency GP *(private or public)* | ☐ | ☐ | ☐ |
| Hospital admission | ☐ | ☐ | ☐ |
| Home nursing care | ☐ | ☐ | ☐ |
| Physiotherapist | ☐ | ☐ | ☐ |
| Chiropractor | ☐ | ☐ | ☐ |
| Dentist | ☐ | ☐ | ☐ |
| Alternative practitioner | ☐ | ☐ | ☐ |

## 5. CHILDHOOD/YOUTH AND AFFILIATION

**5.1 How long altogether have you lived in the county?** ☐☐ year
*(Put 0 if less than half a year)*

**5.2 How long altogether have you lived in the municipality?** ☐☐ year
*(Put 0 if less than half a year)*

**5.3 Where did you live most of the time before the age of 16?**
*(Tick one option and specify)*

Same municipality .... ☐1

Another municipality in the county ..... ☐2 Which one: _____

Another county in Norway ☐3 Which one: _____

Outside Norway ..... ☐4 Country:: _____

**5.4 Have you moved within the last five years?**

No ☐ 1 | Yes, one time ☐ 2 | Yes, more than once ☐ 3

## 6. BODY WEIGHT

**6.1 Estimate your body weight when you were 25 years old:** ☐☐☐ kg

## 7. FOOD AND BEVERAGES

**7.1 How often do you usually eat these foods?**
*(Tick once per line)*

| | Rarely /never | 1-3 times /month | 1-3 times /week | 4-6 times /week | 1-2 times /day | 3 times or more /day |
|---|---|---|---|---|---|---|
| Fruit, berries | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Cheese *(all types)* | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Potatoes | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Boiled vegetables | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Fresh vegetables/salad | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Fatty fish *(e.g. salmon, trout, mackerel, herring)* | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 1 | 2 | 3 | 4 | 5 | 6 |

**7.2 What type of fat do you usually use?** *(Tick once per line)*

| | Don't use | Butter | Hard margarine | Soft/light margarine | Oils | Other |
|---|---|---|---|---|---|---|
| On bread | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| For cooking | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 1 | 2 | 3 | 4 | 5 | 6 |

**7.3 Do you use the following dietary supplements:**

| | Yes, daily | Sometimes | No |
|---|---|---|---|
| Cod liver oil, fish oil capsules | ☐ | ☐ | ☐ |
| Vitamins and/or mineral supplements? | ☐ | ☐ | ☐ |

**7.4 How much of the following do you usually drink?**
*(Tick once per line)*

| | Rarely /never | 1-6 glasses /week | 1 glass /day | 2-3 glasses /day | 4 glasses or more /day |
|---|---|---|---|---|---|
| Full milk, full-fat curdled milk, yoghurt | ☐ | ☐ | ☐ | ☐ | ☐ |
| Semi-skimmed milk, semi-skimmed curdled milk,low-fat yoghurt | ☐ | ☐ | ☐ | ☐ | ☐ |
| Skimmed milk, skimmed curdled milk | ☐ | ☐ | ☐ | ☐ | ☐ |
| Extra semi-skimmed milk | ☐ | ☐ | ☐ | ☐ | ☐ |
| Juice | ☐ | ☐ | ☐ | ☐ | ☐ |
| Water | ☐ | ☐ | ☐ | ☐ | ☐ |
| Mineral water (e.g. Farris, Ramløsa etc) | ☐ | ☐ | ☐ | ☐ | ☐ |
| Cola-containing soft drink | ☐ | ☐ | ☐ | ☐ | ☐ |
| Other soda/soft drink | ☐ | ☐ | ☐ | ☐ | ☐ |
| | 1 | 2 | 3 | 4 | 5 |

**7.5 Do you usually drink soft drink:** with sugar ☐ 1 without sugar ☐ 2

**7.6 How many cups of coffee and tea do you drink daily?** *Number of cups*
*(Put 0 for the types you don't drink daily)*

Filtered coffee ..... ☐☐

Boiled coffee/coarsely ground coffee for brewing ..... ☐☐

Other type of coffee ..... ☐☐

Tea ..... ☐☐

**7.7 Approximately how often have you during the last year consumed alcohol?** *(Do not count low-alcohol and alcohol-free beer)*

| Never consumed alcohol | Have not consumed alcohol last year | A few times last year | About 1 time a month |
|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| **2-3 times per month** | **About1 time a week** | **2-3 times a week** | **4-7 times a week** |
| ☐ 5 | ☐ 6 | ☐ 7 | ☐ 8 |

To those who have consumed the last year:

**7.8 When you drink alcohol, how many glasses or drinks do you normally drink?** *number* ☐☐

**7.9 Approximately how many times during the last year have you consumed alcohol equivalent to 5 glasses or drinks within 24 hours?** *Number of times* ☐☐

**7.10 When you drink, do you normally drink:** *(Tick one or more)*

Beer ☐ Wine ☐ Spirits ☐

## 8. SMOKING

**8.1 How many hours a day do you normally spend in smoke-filled rooms?** *Number of total hours* ☐☐

| | Yes | No |
|---|---|---|
| **8.2 Did any of the adults smoke at home while you were growing up?** | ☐ | ☐ |
| **8.3 Do you currently, or did you previously live together with a daily smoker after your 20th birthday?** | ☐ | ☐ |

| | Yes, now | Yes, previously | Never |
|---|---|---|---|
| **8.4 Do you/did you smoke daily?** | ☐ | ☐ | ☐ |

**If NEVER: Go to question 9 :** (EDUCATION AND WORK)

| **8.5 If you smoke daily now, do you smoke:** | Yes | No |
|---|---|---|
| Cigarettes? | ☐ | ☐ |
| Cigars/cigarillos? | ☐ | ☐ |
| A pipe? | ☐ | ☐ |

**8.6 If you previously smoked daily, how long is it since you quit?** *Number of years* ☐☐

**8.7 If you currently smoke, or have smoked previously:**

How many cigarettes do you or did you normally smoke per day? *Number of cigarettes* ☐☐

How old were you when you began daily smoking? *Age in years* ☐☐

How many years in all have you smoked daily? *Number of years* ☐☐

## 9. EDUCATION AND WORK

**9.1 How many years of education have you completed?** *Number of years* ☐☐
*(Include all the years you have attended school or studied)*

**9.2 Do you currently have paid work?**

Yes, full-time ☐ 1 Yes, part-time ☐ 2 No ☐ 3

**9.3 Describe the activity at the workplace where you had paid work for the longest period in the last 12 months.** *(e.g. Accountancy firm, school, paediatric department, carpentry workshop, garage, bank, grocery store, etc.)*

**Business:** _____
*If retired, enter the former business and occupation. Also applies to 9.4*

**9.4 Which occupation/title have or had you at this workplace?**
*(e.g. Secretary, teacher, industrial worker, nurse, carpenter, manager, salesman, driver, etc.)*

**Occupation:** _____

**9.5 In your main occupation, do you work as self-employed, as an employee or family member without regular salary?**

Self-employed ☐ Employee ☐ Family member ☐

| | Yes | No |
|---|---|---|
| **9.6 Do you believe that you are in danger of losing your current work or income within the next two years?** | ☐ | ☐ |

| **9.7 Do you receive any of the following benefits?** | Yes | No |
|---|---|---|
| Sickness benefit (are on sick leave) | ☐ | ☐ |
| Old age pension, early retirement (AFP) or survivor pension | ☐ | ☐ |
| Rehabilitation/reintegration benefit | ☐ | ☐ |
| Disability pension (full or partial) | ☐ | ☐ |
| Unemployment benefits during unemployment | ☐ | ☐ |
| Social welfare benefits | ☐ | ☐ |
| Transition benefit for single parents | ☐ | ☐ |

## 10. EXERCISE AND PHYSICAL ACTIVITY

**10.1 How has your physical activity in leisure time been during this last year?**
*Think of a weekly average for the year.*
*Time spent going to work is count as leisure time. Answer both questions.*

| | Hours per week | | | |
|---|---|---|---|---|
| | None | Less than 1 | 1-2 | 3 or more |
| Light activity *(not sweating/out of breath)* | ☐ | ☐ | ☐ | ☐ |
| Hard physical activity *(sweating/out of breath)* | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |

**10.2 Describe exercise and physical exertion in your leisure time. If your activity varies much e.g. between summer and winter, then give an average. The question refers only to the last year.**
*(Tick the most appropriate box)*

- Reading, watching TV or other sedentary activity? ☐ 1
- Walking, cycling or other forms of exercise at least 4 hours a week? ☐ 2
  *(Include walking or cycling to work, Sunday walk/stroll,etc.)*
- Participation in recreational sports, heavy gardening, etc.? ☐ 3
  *(Note: duration of activity at least 4 hours a week)*
- Participation in hard training or sports competitions, regularly several times a week? ☐ 4

## 11. FAMILY AND FRIENDS

**11.1 Do you live with:**

| | Yes | No |
|---|---|---|
| Spouse/partner? | ☐ | ☐ |

**11.2 How many good friends do you have?** *Number of friends* ☐☐

*Count the ones you can talk confidentially with and who can give you help when you need it. Do not count people you live with, but do include other relatives.*

**11.3 How much interest do people show for what you do?**
*(Tick only once)*

| Great interest | Some interest | Little interest | No interest | Uncertain |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**11.4 How many associations, sport clubs,groups, religious communities or similar do you take part in?** *Number* ☐☐
*(Write 0 if none)*

**11.5 Do you feel that you can influence what happening in your local community where you live?** *(Tick only once)*

| Yes, a lot | Yes, some | Yes, a little | No | Never tried |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

## 12. ILLNESS IN THE FAMILY

**12.1 Have one or more of your parents or siblings had a heart attack (heart wound) or angina pectoris (heart cramp)?**

| | Yes | No | Don't know |
|---|---|---|---|
| | ☐ | ☐ | ☐ |

**12.2 Tick for the relatives who have or have had any of the illnesses:** *(Tick for each line)*

| | Mother | Father | Brother | Sister | Child | None of these |
|---|---|---|---|---|---|---|
| Cerebral stroke or brain haemorrhage | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Heart attack before age of 60 years | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Asthma | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Cancer | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Diabetes | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**12.3 If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who got it earliest in life):**

| Don't know, not applicable | Mother's age | Father's age | Brother's age | Sister's age | Child's age |
|---|---|---|---|---|---|
| ☐ | ☐☐ | ☐☐ | ☐☐ | ☐☐ | ☐☐ |

## 13. USE OF MEDICINES

*With medicines, we mean drugs purchased at pharmacies. Supplements and vitamins are not considered here.*

**13.1 Do you use:**

| | Now | Previously, but not now | Never used |
|---|---|---|---|
| Blood pressure lowering drugs | ☐ | ☐ | ☐ |
| Cholesterol-lowering drugs | ☐ | ☐ | ☐ |

**13.2 How often have you during the last 4 weeks used the following medicines?**
*(Tick once for each line)*

| | Not used in the last 4 weeks | Less than every week | Every week but not daily | Daily |
|---|---|---|---|---|
| Painkillers non-prescription | ☐ | ☐ | ☐ | ☐ |
| Painkillers on prescription | ☐ | ☐ | ☐ | ☐ |
| Sleeping pills | ☐ | ☐ | ☐ | ☐ |
| Tranquillizers | ☐ | ☐ | ☐ | ☐ |
| Antidepressants | ☐ | ☐ | ☐ | ☐ |
| Other prescription medicines | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |

**13.3 For those medicines you have checked in points 13.1 and 13.2, and that you've used during the last 4 weeks:**

State the name and the reason that you are taking/have taken these (disease or symptom):
*(Tick for each duration you have used the medicine)*

| Name of the medicine: *(one name per line)* | Reason for use of the medicine | How long have you used the medicine: Up to 1 year | How long have you used the medicine: 1 year or more |
|---|---|---|---|
| | | ☐ | ☐ |
| | | ☐ | ☐ |
| | | ☐ | ☐ |
| | | ☐ | ☐ |
| | | ☐ | ☐ |
| | | ☐ | ☐ |
| | | ☐ | ☐ |

*If there is not enough space here, you may continue on a separate sheet that you attach*

## 14. THE REST OF THE FORM IS TO BE ANSWERED BY WOMEN ONLY

**14.1 How old were you when you started menstruating?** *Age in years* ☐☐

**14.2 If you no longer menstruating, how old were you when you stopped menstruating?** *Age in years* ☐☐

**14.3 Are you pregnant at the moment?**

| Yes | No | Uncertain | Above fertile age |
|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |

**14.4 How many children have you given birth to?** *Number of children* ☐☐

**14.5 Do you use, or have you ever used?**
*(Tick once for each line)*

| | Now | Before, but not now | Never |
|---|---|---|---|
| Oral contraceptive pills/mini pill/ contraceptive injection | ☐ | ☐ | ☐ |
| Hormonal intrauterine device (IUD) *(not ordinary IUD)* | ☐ | ☐ | ☐ |
| Estrogen *(tablets or patches)* | ☐ | ☐ | ☐ |
| Estrogen *(cream or suppositories)* | ☐ | ☐ | ☐ |

**14.6 If you use/have used prescription estrogen:**
How long have you used it? *Number of years* ☐☐

**14.7 If you use contraceptive pills, mini pill, contraceptive injection, hormonal IUD or estrogen, what brand do you use?**

_____

IE 050000 - 1042-1 - 24.000 - Beyer Hecos 02.01

## Tromsø 6 questionnaire

# Tromsø-undersøkelsen

The form will be read electronically. Please use a blue or black pen
You can not use comas, use upper-case letters.

**2007 - 2008 Confidential**

## HEALTH AND DISEASES

1 **How do you in general consider your own health to be?**

- ☐ Very good
- ☐ Good
- ☐ Neither good nor bad
- ☐ Bad
- ☐ Very bad

2 **How is your health compared to others in your age?**

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

3 **Do you have, or have you had?**

| | Yes | No | Age first time |
|---|---|---|---|
| Heart attack | ☐ | ☐ | |
| Angina pectoris | ☐ | ☐ | |
| Stroke/brain hemorrhage | ☐ | ☐ | |
| Atrial fibrillation | ☐ | ☐ | |
| High blood pressure | ☐ | ☐ | |
| Osteoporosis | ☐ | ☐ | |
| Asthma | ☐ | ☐ | |
| Chronic bronchitis/Emphysyma/COPD | ☐ | ☐ | |
| Diabetes mellitus | ☐ | ☐ | |
| Psychological problems *(for which you have sought help )* | ☐ | ☐ | |
| Low metabolism | ☐ | ☐ | |
| Kidney disease, *not including urinary tract infection (UTI)* | ☐ | ☐ | |
| Migraine | ☐ | ☐ | |

4 **Do you have persistent or constantly recurring pain that has lasted for 3 months or more?**

☐ Yes ☐ No

5 **How often have you suffered from sleeplessness during the last 12 months?**

- ☐ Never, or just a few times
- ☐ 1-3 times a month
- ☐ Approximately once a week
- ☐ More that once a week

6 **Below you find a list of different situations. Have you experienced some of them in the last week (including today)?** (Tick once for each complaint)

| | No complaint | Little complaint | Pretty much | Very much |
|---|---|---|---|---|
| Sudden fear without reason | ☐ | ☐ | ☐ | ☐ |
| You felt afraid or worried | ☐ | ☐ | ☐ | ☐ |
| Faintness or dizziness | ☐ | ☐ | ☐ | ☐ |
| You felt tense or upset | ☐ | ☐ | ☐ | ☐ |
| Easily blamed yourself | ☐ | ☐ | ☐ | ☐ |
| Sleeping problems | ☐ | ☐ | ☐ | ☐ |
| Depressed, sad | ☐ | ☐ | ☐ | ☐ |
| You felt useless, worthless | ☐ | ☐ | ☐ | ☐ |
| Feeling that life is a struggle | ☐ | ☐ | ☐ | ☐ |
| Feeling of hopelessness with regard to the future | ☐ | ☐ | ☐ | ☐ |

## USE OF HEALTH SERVICES

7 **Have you during the past year visited:** If YES; how many times?

| | Yes | No | No. of times |
|---|---|---|---|
| General practitioner (GP) | ☐ | ☐ | |
| Psychiatrist/psychologist | ☐ | ☐ | |
| Medical specialist outside hospital *(other than general practitioner /psychiatrist)* | ☐ | ☐ | |
| Physiotherapist | ☐ | ☐ | |
| Chiropractor | ☐ | ☐ | |
| Alternative medical practitioner *(homeopath, acupuncturist, foot zone therapist, herbal medical practitioner, laying on hands practitioner, healer, clairvoyant, etc.)* | ☐ | ☐ | |
| Dentist/dental service | ☐ | ☐ | |

8 **Have you during the last 12 months been to a hospital?**

| | Yes | No | No. of times |
|---|---|---|---|
| Admitted to a hospital | ☐ | ☐ | |
| Had consultation in a hospital without admission; | | | |
| At psychiatric out-patient clinic | ☐ | ☐ | |
| At another out-patient clinic | ☐ | ☐ | |

9 **Have you undergone any surgery during the last 3 years?**

☐ Yes ☐ No

## USE OF MEDICINE

10 **Do you take, or have you taken some of the following medications?** (Tick once for each line)

| | Never used | Now | Earlier | Age first time |
|---|---|---|---|---|
| Drugs for high blood pressure | ☐ | ☐ | ☐ | |
| Lipid lowering drugs | ☐ | ☐ | ☐ | |
| Drugs for heart disease | ☐ | ☐ | ☐ | |
| Diuretics | ☐ | ☐ | ☐ | |
| Medications for osteoporosis | ☐ | ☐ | ☐ | |
| Insulin | ☐ | ☐ | ☐ | |
| Tablets for diabetes | ☐ | ☐ | ☐ | |
| Drugs for metabolism Thyroxine/levaxin | ☐ | ☐ | ☐ | |

11 **How often have you during the last 4 weeks used the following medications?**(Tick once for each line)

| | Not used the last 4 weeks | Less than every week | Every week, but not daily | Daily |
|---|---|---|---|---|
| Painkillers on prescription | ☐ | ☐ | ☐ | ☐ |
| Painkillers non-prescription | ☐ | ☐ | ☐ | ☐ |
| Sleeping pills | ☐ | ☐ | ☐ | ☐ |
| Tranquillizers | ☐ | ☐ | ☐ | ☐ |
| Antidepressants | ☐ | ☐ | ☐ | ☐ |

12 **State the names of all medications -both those on prescription and non-prescription drugs- you have used regularly during the last 4 weeks.** Do not include vitamins, minerals, herbs, natural remedies, other nutritional supplements, etc.

If the space is not enough for all medications, use an additional paper of your own.

**When attending** the survey centre you will be asked whether you have used antibiotics or painkillers the last 24 hours. If you have, you will be asked to provide the name of the drug, strength, dose and time of use.

## FAMILY AND FRIENDS

13 **Who do you live with?** (Tick for each question and give the number)

| | Yes | No | Number |
|---|---|---|---|
| Spouse/cohabitant | ☐ | ☐ | |
| Other persons older than 18 years | ☐ | ☐ | |
| Persons younger than 18 years | ☐ | ☐ | |

14 **Tick for relatives who have or have had**

| | Parents | Children | Siblings |
|---|---|---|---|
| Myocardial infarction | ☐ | ☐ | ☐ |
| Myocardial infarction before 60 years | ☐ | ☐ | ☐ |
| Angina pectoris | ☐ | ☐ | ☐ |
| Stroke/brain haemorrhage | ☐ | ☐ | ☐ |
| Osteoporosis | ☐ | ☐ | ☐ |
| Stomach/duodenal ulcer | ☐ | ☐ | ☐ |
| Asthma | ☐ | ☐ | ☐ |
| Diabetes mellitus | ☐ | ☐ | ☐ |
| Dementia | ☐ | ☐ | ☐ |
| Psychological problems | ☐ | ☐ | ☐ |
| Drugs/substance abuse | ☐ | ☐ | ☐ |

15 **Do you have enough friends who can give you help when you need it?**

☐ Yes ☐ No

16 **Do you have enough friends whom you can talk confidentially with?**

☐ Yes ☐ No

17 **How often do you normally take part in organised gatherings, e.g. sports clubs, political meetings, religious or other associations?**

☐ Never, or just a few times a year
☐ 1-2 times a month
☐ Approximately once a week
☐ More than once a week

## WORK, SOCIAL SECURITY AND INCOME

18 **What is the highest level of education you have completed?** (Tick one)

☐ Primary, 1-2 years secondary school
☐ Vocational school
☐ High secondary school (A-level)
☐ College/university less than 4 years
☐ College/university 4 years or more

19 **What is your main occupation/activity?** (Tick one)

☐ Full time work ☐ Housekeeping
☐ Part time work ☐ Retired/benefit recipient
☐ Unemployed ☐ Student/military service

20 **Do you receive any of the following benefits?**

- ☐ Old-age, early retirement or survivor pension
- ☐ Sickness benefit (are in a sick leave)
- ☐ Rehabilitation benefit
- ☐ Full disability pension
- ☐ Partial disability pension
- ☐ Unemployment benefits
- ☐ Transition benefit for single parents
- ☐ Social welfare benefits

21 **What was the households total taxable income last year?** Include income from work, social benefits and similar

- ☐ Less than 125 000 NOK
- ☐ 125 000-200 000 NOK
- ☐ 201 000-300 000 NOK
- ☐ 301 000-400 000 NOK
- ☐ 401 000-550 000 NOK
- ☐ 551 000-700 000 NOK
- ☐ 701 000 -850 000 NOK
- ☐ More than 850 000 NOK

22 **Do you work outdoors at least 25% of the time, or in cold buildings (e.g. storehouse/industry buildings)?**

- ☐ Yes
- ☐ No

## PHYSICAL ACTIVITY

23 **If you have paid or unpaid work, which statement describes your work best?**

- ☐ Mostly sedentary work
  *(e.g. office work, mounting)*
- ☐ Work that requires a lot of walking
  *(e.g. shop assistant, light industrial work, teaching)*
- ☐ Work that requires a lot of walking and lifting
  *(e.g. postman, nursing, construction)*
- ☐ Heavy manual labour

24 **Describe your exercise and physical exertion in leisure time. If you activity varies much, for example between summer and winter, then give an average. The question refers only to the last year.** (Tick the one that fits best)

- ☐ Reading, watching TV, or other sedentary activity.
- ☐ Walking, cycling, or other forms of exercise at least 4 hours a week *(here including walking or cycling to place of work, Sunday-walking, etc.)*
- ☐ Participation in recreational sports, heavy gardening, etc. *(note:duration of activity at least 4 hours a week)*
- ☐ Participation in hard training or sports competitions, regularly several times a week.

25 **How often do you exercise?** (With exercise we mean for example walking, skiing, swimming or training/sports)

- ☐ Never
- ☐ Less than once a week
- ☐ Once a week
- ☐ 2-3 times a week
- ☐ Approximately every day

26 **How hard do you exercise on average?**

- ☐ Easy- do not become short-winded or sweaty
- ☐ You become short-winded and sweaty
- ☐ Hard- you become exhausted

27 **For how long time do you exercise every time on average?**

- ☐ Less than 15 minutes
- ☐ 15-29 minutes
- ☐ 30-60 minutes
- ☐ More than 1 hour

## ALCOHOL AND TOBACCO

28 **How often do you drink alcohol?**

- ☐ Never
- ☐ Monthly or more infrequently
- ☐ 2-4 times a month
- ☐ 2-3 times a week
- ☐ 4 or more times a week

29 **How many units of alcohol** (a beer, a glass of wine or a drink) **do you usually drink when you drink alcohol?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 or more

30 **How often do you drink 6 units of alcohol or more in one occasion?**

- ☐ Never
- ☐ Less frequently than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

31 **Do you smoke sometimes, but not daily?**

- ☐ Yes
- ☐ No

32 **Do you/did you smoke daily?**

- ☐ Yes, now
- ☐ Yes, previously
- ☐ Never

33 **If you previously smoked daily, how long is it since you stopped?**

Number of years ☐☐

34 **If you currently smoke, or have smoked before: How many cigarettes do you or did you usually smoke per day?**

Number of cigarettes ☐☐

35 **How old were you when you began smoking daily?**

Number of years ☐☐

36 **How many years in all have you smoked daily?**

Number of years ☐☐

37 **Do you use or have you used snuff or chewing tobacco?**

- ☐ No, never
- ☐ Yes, previously
- ☐ Yes, sometimes
- ☐ Yes, daily

## DIET

38 **Do you usually eat breakfast every day?**

☐ Yes ☐ No

39 **How many units of fruits or vegetables do you eat on average per day?** (units means for example a fruit, a cup of juice, potatoes, vegetables)

Number of units ☐☐

40 **How many times per week do you eat hot dinner?**

Number ☐☐

41 **How often do you usually eat these products?** (Tick once for each line)

| | 0-1 times/ mth | 2-3 times/ mth | 1-3 times/ week | 4-6 times/ week | 1-2 times/ day |
|---|---|---|---|---|---|
| Potatoes | ☐ | ☐ | ☐ | ☐ | ☐ |
| Pasta/rice | ☐ | ☐ | ☐ | ☐ | ☐ |
| Meat *(not processed)* | ☐ | ☐ | ☐ | ☐ | ☐ |
| Processed meat *(sausages/meatloaf/meatballs)* | ☐ | ☐ | ☐ | ☐ | ☐ |
| Fruits, vegetables, berries | ☐ | ☐ | ☐ | ☐ | ☐ |
| Lean fish | ☐ | ☐ | ☐ | ☐ | ☐ |
| Fat fish *(e.g. salmon, trout, mackerel, herring, halibut, redfish)* | ☐ | ☐ | ☐ | ☐ | ☐ |

42 **How much do you normally drink the following?** (Tick once for each line)

| | Rarely/ never | 1-6 glasses /week | 1 glass /day | 2-3 glasses /day | 4 or more glasses /day |
|---|---|---|---|---|---|
| Milk, curdled milk, yoghurt | ☐ | ☐ | ☐ | ☐ | ☐ |
| Juice | ☐ | ☐ | ☐ | ☐ | ☐ |
| Soft drinks with sugar | ☐ | ☐ | ☐ | ☐ | ☐ |

43 **How many cups of coffee and tea do you drink daily?** (Put 0 for the types you do not drink daily)

| | Number of cups |
|---|---|
| Filtered coffee | ☐☐ |
| Boiled coffee (coarsely ground coffee for brewing) | ☐☐ |
| Other types of coffee | ☐☐ |
| Tea | ☐☐ |

44 **How often do you usually eat cod liver and roe?** (i.e. "mølje")

☐ Rarely/never ☐ 1-3 times/year ☐ 4-6 times/year

☐ 7-12 times/year ☐ More than 12 times/year

45 **Do you use the following supplements?**

| | Daily | Sometimes | No |
|---|---|---|---|
| Cod liver oil or fish oil capsules | ☐ | ☐ | ☐ |
| Omega 3 capsules *(fish oil, seal oil)* | ☐ | ☐ | ☐ |
| Vitamins and/or mineral supplements | ☐ | ☐ | ☐ |

## QUESTONS FOR WOMEN

46 **Are you currently pregnant?**

☐ Yes ☐ No ☐ Uncertain

47 **How many children have you given birth to?**

Number ☐☐

48 **If you have given birth, fill in for each child: birth year, birth weight and months of breastfeeding** (Fill in the best you can)

| Child | Birth year | Birth weight in grams | Months of breastfeeding |
|---|---|---|---|
| 1 | ☐☐☐☐ | ☐☐☐☐ | ☐☐ |
| 2 | ☐☐☐☐ | ☐☐☐☐ | ☐☐ |
| 3 | ☐☐☐☐ | ☐☐☐☐ | ☐☐ |
| 4 | ☐☐☐☐ | ☐☐☐☐ | ☐☐ |
| 5 | ☐☐☐☐ | ☐☐☐☐ | ☐☐ |
| 6 | ☐☐☐☐ | ☐☐☐☐ | ☐☐ |

49 **During pregnancy, have you had high blood pressure?**

☐ Yes ☐ No

50 **If yes, which pregnancy?**

☐ The first ☐ Second or later

51 **During pregnancy, have you had proteinuria?**

☐ Yes ☐ No

52 **If yes, which pregnancy?**

☐ The first ☐ Second or later

53 **Were any of your children delivered prematurely (a month or more before the due date) because of preeclampsia?**

☐ Yes ☐ No

54 **If yes, which child?**

| 1st child | 2nd child | 3rd child | 4th child | 5th child | 6th child |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

55 **How old were you when you started menstruating?**

Age ☐☐

56 **Do you currently use any prescribed drug influencing the menstruation?**

Oral contraceptives, hormonal IUD or similar ☐ Yes ☐ No

Hormone treatment for menopausal problems ☐ Yes ☐ No

**When attending** the survey centre you will get a questionnaire about menstruation and possible use of hormones. Write down on a paper the names of all the hormones you have used and bring the paper with you. You will also be asked whether your menstruation have ceased and possibly when and why.