UiT The Arctic University of Norway

Faculty of Health Science, UiT – The Arctic University of Norway

Association of metabolic syndrome with hyperfiltration in a general non-diabetic population – The Renal Iohexol Clearance Survey

Erikka Wikan Bystad

Master's thesis in medicine, MED-3950, May 2021

Preface

During my medical studies I have developed a special interest for kidney medicine. I therefore contacted Professor Toralf Melsom, to ask if he had any ideas for a master thesis project within kidney medicine. He proposed to investigate the association between metabolic syndrome and renal hyperfiltration using data from The Renal Iohexol Clearance Survey (RENIS).

Toralf Melsom has been my main supervisor and Bjørn Odvar Eriksen and Vidar Stefansson has been my co-supervisors. I am very grateful to Toralf for his dedication to this master thesis and all the time he has spent helping me with statistics, finding relevant theory and proposing corrections. Also, I would like to thank my co-supervisors for their feedback on the thesis.

Eirikka W. Bystad

Trondheim, 11.05.21

Table of contents

Abstract

Background: Metabolic syndrome (MS) affects approximately one quarter of the world, making it a global epidemic (1). Although MS has been associated with increased risk of rapid decline in the glomerular filtration rate (GFR) (2), only a few studies have investigated the association of MS with abnormally elevated GFR, known as renal hyperfiltration (RHF). Previous studies of MS and RHF were limited by the use of estimated GFR (eGFR) and the results were divergent. Establishing the relationship between MS and RHF is of clinical importance as there are promising treatment options for RHF.

Methods: In the Renal Iohexol Clearance Survey (RENIS) we included 1551 subjects from the population based Tromsø survey (2007-2009). The participants were 50-62 years old without known diabetes, cardiovascular disease or kidney disease. The GFR was measured (mGFR) using iohexol clearance. The aim was to investigate the relationship between MS and RHF. The dichotomous variable for RHF was defined as an absolute GFR (ml/min) above the 90^{th} percentile adjusted for gender, age and height (3).

Results: MS was associated with increased absolute GFR (ml/min) and RHF (yes/no) independent of age, sex and height (OR 2.44 95% CI; 1.71 – 3.46, p<0.001). All risk factors except for hypertension were independently associated with RHF and increased absolute GFR. The risk of RHF was highest in subjects fulfilling 5 out of 5 criteria (OR 4.06, 95% CI; 1.54-10.67, p=0.005) compared to those fulfilling 0 or 1 criteria. Conversely, MS was not associated with higher estimated GFR based on creatinine, cystatin C or both together.

Conclusions: Subjects with MS have a higher absolute GFR and increased risk of RHF compared to subjects without MS. RCTs are needed to explore whether treatment of RHF can prevent accelerated GFR decline and CKD in persons with MS.

Abbreviations

RENIS-T6: Renal Iohexol Clearance Survey in Tromsø 6

CKD: Chronic kidney disease

MS: Metabolic syndrome

GFR: Glomerular filtration rate

eGFR: Estimated GFR

mGFR: Measured GFR

RHF: Renal hyperfiltration

BMI: Body mass index

ESRD: End stage renal disease

CVD: Cardiovascular disease

GBD: The Global Burden of Disease, Injuries and Risk Factors Study

DKD: Diabetic kidney disease

BSA: Body surface area

WC: Waist circumference

WHR: Waist hip ratio

ACEi: Angiotensin converting enzyme inhibitors

ARB: Angiotensin reseptor blockers

RAAS: Renin angiotensin aldosteron system

SGLT2: sodium-glucose cotransporter 2

1 Introduction

1.1 Background

Kidney function and GFR

The kidneys serve a number of crucial functions for the human body, including regulation of blood pressure, excretion of waste products, hormone production, acid/base regulation and electrolyte concentration. The functional unit which serves these functions through filtration, reabsorption and secretion is the nephron. The number of nephrons varies greatly between individuals ranging from 500.000 to 1.5 million in each kidney (4).

Kidney function is usually assessed as the glomerular filtration rate. GFR is the volume of filtered fluid from the glomerular capillaries into Bowmans capsule per unit time (ml/min). It's a product of average filtration rate in each nephron and the total number of nephrons. The GFR varies substantially between individuals, and it's related to age, sex and body size (5). As shown in figure 1, women have a lower GFR compared to men, with normal values approximately 130 ml/min/1.73 in young men and 120 ml/min/1.73 in young women (5). The figure also shows how mean values declines as a person age, as normal ageing includes loss of nephrons.

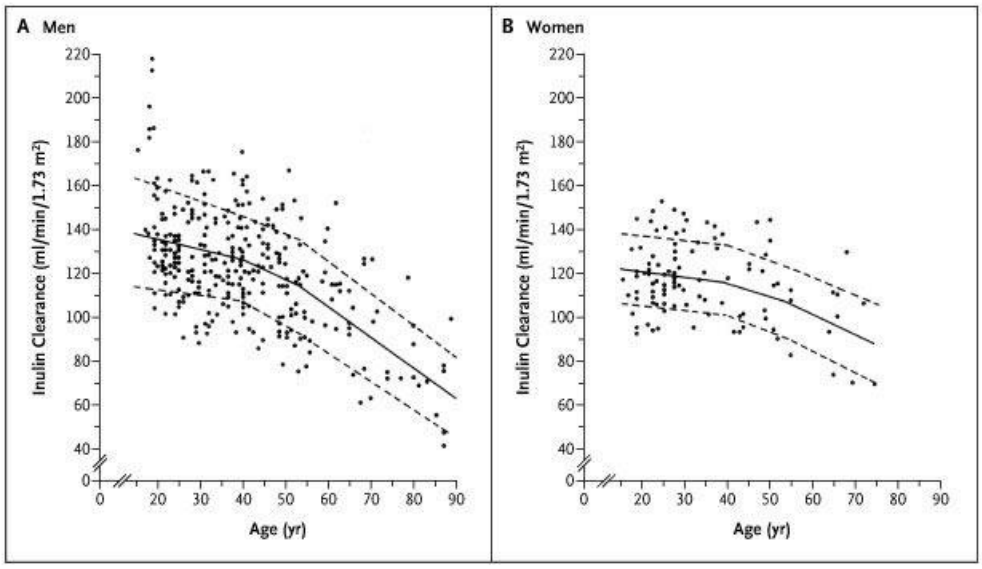

Figure 1: Normal values for GFR in men (A) and women (B) according to age (adapted from Wesson (6)).

Measurement of GFR

GFR can be measured precisely using exogenous filtration markers or estimated using endogenous filtration markers. The clearance of an ideal filtration marker equals the true GFR. An ideal filtration marker is freely filtered across the glomerular filtration barrier and not metabolized, secreted or reabsorbed in the tubules (7). Measured GFR by the use of exogenous filtration markers such as inulin, iothalamate and iohexol, is considered the gold standard approach. However, measuring GFR is expensive and inconvenient to do in clinical practice (5). Therefore, endogenous filtration markers are used to estimate GFR, and creatinine is the most widely used filtration marker. The generation of creatinine is determined primarily by muscle mass and diet, and therefore varies with age, gender, ethnicity, and body size (5). Equations that incorporate these non-GFR related factors are therefore made to improve GFR estimation. However, all estimating equations are prone to bias in individuals with atypical muscle mass (e.g. low BMI, body builders, muscle diseases), low or high intake of meat, intake of creatine or use of medications that alter the secretion of creatinine (8).

Chronic kidney disease – definition

Chronic kidney disease (CKD) is commonly defined by indicators of kidney damage e.g. albuminuria and/or decreased glomerular filtration rate below 60 ml/min/1.73 m^2 lasting for at least three months (9). CKD is divided into five stages (Table 1), where the majority is classified to stage 3 (9). Stage 5 is called end stage renal disease (ESRD), but only a small fraction progress to this stage where dialysis or renal transplantation is necessary. The CKD staging system, however, does not take into account factors that influence GFR, such as age and gender, and it also lacks classification of GFR in the upper range. These are just some of the reasons the CKD staging system has been criticized (10).

Table 1: Stages of chronic kidney disease according to KDOQI-guidelines

Stage	Description	GFR (ml/min/1,73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

CKD epidemiology

CKD is a global health burden. A meta-analysis from 2016 estimated the global CKD prevalence to be approximately 11-13% (9), and the prevalence in Norway is estimated to be on the same level (11). CKD is associated with increased risk of end stage renal disease, cardiovascular disease (CVD) and premature mortality, as well as high economic costs to the health system (9). In 2017 CKD resulted in 2.1 million deaths globally, plus an additional 1.4 million deaths from CVD attributable to impaired kidney function (12).

The change in age-standardized mortality from CKD has not followed the declining rate of many other non-communicable diseases. The Global Burden of Disease, Injuries and Risk Factors Study (GBD) reveals that "from 1990 to 2017, the global age-standardized mortality rate declined by 30.4% for cardiovascular disease, 14.9% for cancer, and 41.3% for COPD". Conversely, regarding CKD, there was no significant change in age-standardized mortality during the same period (12).

To prevent CKD at population level it is crucial to gain knowledge about the mechanisms and the risk factors associated with the early stages of CKD. Detection and treatment of known risk factors can reduce the incidence of CKD, improve morbidity and slow progression to ESRD (12).

Hyperfiltration theory

The term renal hyperfiltration refers to an abnormally elevated glomerular filtration rate. It can occur as a physiological phenomenon during pregnancy and after eating a high protein meal, but also as a pathological state that over time leads to kidney damage (13). The hyperfiltration theory was first proposed in 1981 by Brenner et al. They hypothesized that nephron loss would lead to compensatory glomerular hemodynamic changes and subsequent kidney damage (14). Their study showed that renal mass reduction in rats lead to hypertrophy of the remaining nephrons and increased glomerular filtration rate at a single nephron level. Afferent arteriolar resistance decreased more than the efferent arteriolar resistance, and as a consequence the glomerular pressure increased and hyperfiltration occurred (13). The compensatory hyperfiltration contributed to preserve GFR initially but ultimately led to glomerulosclerosis, albuminuria and reduced GFR in animal models, likely because of the increased glomerular capillary pressure found in hyperfiltration (illustrated in figure 2). Brenner et al. therefore hypothesized that glomerular hyperfiltration and/or increased

glomerular pressure were maladaptive responses that represented a common pathway for renal injury after a variety of initial injuries have reduced renal mass below a critical level (14).

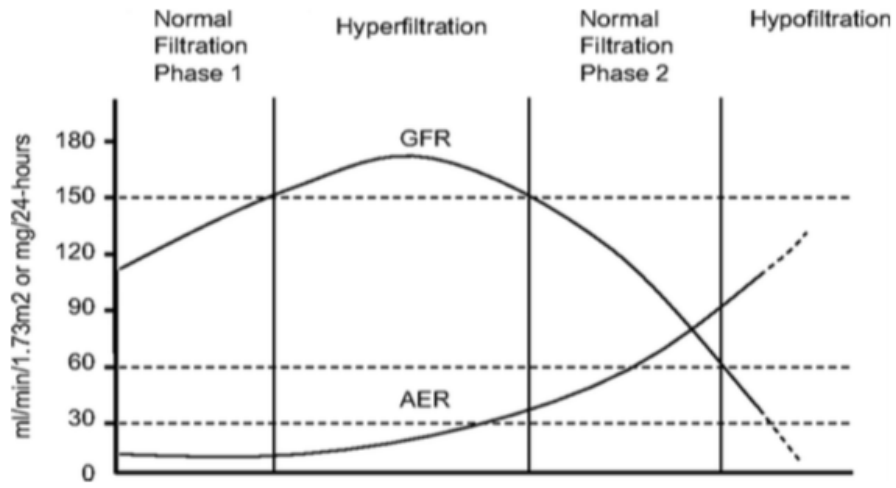

Figure 2: The stages of hyperfiltration-induced kidney damage (15)

The pathological role of renal hyperfiltration on renal and cardiovascular outcomes have been debated for almost 4 decades. Recent evidence indicates that long-term RHF may be maladaptive similarly to what have been found with single-nephron hyperfiltration in animal models. RHF is commonly observed at the early stage of diabetic kidney disease (DKD) and in obese individuals (16, 17). Reported prevalence of RHF in diabetic individuals vary from 10%–67% in DM1 and 6%–73% in DM2, and the presence of RHF has been associated with a more rapid GFR decline in DM1 (18). However, the risk factors for RHF and the underlying pathophysiology in the general non-diabetic population is still largely unknown.

How to define hyperfiltration

Whole-kidney GFR is used to reflect hyperfiltration at single-nephron level, as single nephron GFR cannot be measured in humans. An elevation in whole-kidney GFR within the same subject is considered closely correlated with hyperfiltration at single nephron level (7). However, whole-kidney GFR is a product of single-nephron GFR and the total number of nephrons, meaning there have to be made corrections for factors assumed to influence the number of nephrons. Nephron number decrease with age, are lower in women and in subjects with low stature (19). Thus, a non-corrected threshold for hyperfiltration would hide

hyperfiltration in these groups of subjects (20). The use of eGFR instead of mGFR can also contribute to misdiagnosis of hyperfiltration as the equations used to calculate GFR are imprecise in the high to normal range of GFR and are biased by non-GFR related factors (8). Estimated GFR is therefore poorly suited for studying hyperfiltration. The definition for high GFR that best reflects single-nephron hyperfiltration was recently investigated in a study by Chakkera et al (3). They found that mGFR adjusted for age, closely followed by age-height-gender based thresholds, were the definitions for high GFR that best reflected single-nephron hyperfiltration instead of increased GFR due to higher nephron number. Correction for body surface area and the use of eGFR were less correlated to single nephron hyperfiltration (3).

Metabolic syndrome and kidney dysfunction

In 1998 WHO defined the term metabolic syndrome. MS is a cluster of metabolic abnormalities, including impaired fasting glucose, obesity, dyslipidemia and hypertension (1). Different definitions of MS exist in the literature, but they all contain these general traits. MS is a global health problem affecting approximately one quarter of the world population, and the prevalence has increased over the last three decades (1). The components of MS share the same underlying mediators and mechanisms and identifies a group of patients with shared pathophysiology who have increased risk of type 2 diabetes and cardiovascular disease (21). In recent studies MS has also been linked to development of chronic kidney disease (2, 22). In a study by Stefansson et al. they found that MS was associated with an accelerated mean age-related mGFR decline of 0.30 ml/min per year (95% CI: 0.02–0.58) (2). Although studies suggest a relationship between MS and kidney damage, it is difficult to draw a causal association and discriminate which of the traits of MS gives rise to the detrimental renal effects because of the complexity of their interrelationship (22).

Metabolic syndrome and hyperfiltration

MS associated kidney damage and diabetic nephropathy is thought to share some common pathways, including renal hyperfiltration (23, 24). A few studies have investigated the association of MS with hyperfiltration, but with mixed results. In a study of 1572 apparently healthy young men (mean age= 18.4 years) MS was associated with a 6.9-fold increase in the odds of hyperfiltration (CI: 3.9 – 11.5 P<0,0001) compared to those without MS (25). On the contrary, Monami et al. did not find a significant association between MS and elevated GFR in a study of 2,694 nondiabetic subjects. However, these studies were limited by the use of estimated GFR based on creatinine (26).

The relationship between the individual traits of MS and RHF have also been studied, but the results are divergent, and most of them are also based on eGFR. E.g., hypertension has been linked to RHF in the early phase of hypertensive kidney disease in several studies (27, 28). Melsom et al. found that impaired fasting glucose was associated with an odds ratio of 1.56 for RHF (95% CI 1.07–2.25) using measured GFR (20). Low HDL, but not increased triglycerides, was associated with RHF assessed by eGFR in a study by Trantravahi et al (29). However, hypertriglyceridemia was associated with an OR of 1.62 (95% CI 1.10-2.40) for RHF using eGFR in a study with American adolescents (30). Finally, increased waist circumference (WC), and other obesity measures, have been linked to RHF in several studies using mGFR (17, 31).

1.2 Aim and justification for choice of issue

The aim of this study was to investigate the association of MS and its components with renal hyperfiltration in 1627 middle-aged inhabitants of Tromsø. The reason for my choice of issue was my general interest in kidney medicine. Chronic kidney disease is, as mentioned, an increasing problem worldwide, and knowledge about pathophysiology and risk factors for chronic kidney disease is crucial to reduce the incidence of CKD as well as reducing morbidity and mortality. Renal hyperfiltration is an important topic within kidney medicine that is not fully understood and thus needs to be explored further. As this is the first study on MS and RHF using precise measurements of GFR, it provides important knowledge on the topic.

2 Methods

2.1 Planning and execution of the study

The specific topic for the study was given from Toralf Melsom. The introduction was written during December 2020, analyzes of data was performed during January 2021 and from February to the end of May the master thesis was written.

2.2 Participants

RENIS-T6 was a sub-study of the sixth population-based Tromsø study (Tromsø 6) and was conducted from November 2007 to June 2009. Tromsø 6 included an age-stratified random sample of 12,984 inhabitants of the municipality of Tromsø in Northern Norway. 40% of all inhabitants aged 50–59 years and all inhabitants aged 60–62 years were invited to Tromsø 6. In these age groups, 3564 (65%) completed the main part of Tromsø 6, which included a physical examination, a self-administered questionnaire and standard blood samples. Of these, we excluded 739 who reported a previous myocardial infarction, angina pectoris, stroke, diabetes mellitus, or renal disease. The remaining 2825 persons were invited to participate in RENIS-T6, and 2107 (75%) responded positively. After excluding 77 persons because of possible allergic reactions to contrast-media, we included 1632 individuals to RENIS-T6 according to a predetermined target size. Five participants were excluded because the iohexol-clearance measurements were technical failures, leaving 1627 persons in the RENIS-T6 cohort. The cohort was representative of all persons in the Tromsø 6 survey who were eligible for inclusion.

2.3 Measurements

The data for this study was obtained for RENIS-T6 using standardized procedures and trained clinical staff at the Clinical Research Unit, University Hospital of North Norway.

Iohexol-clearance

GFR was measured using single-sample plasma clearance of iohexol as described in detail in a study by Eriksen et al (32). Briefly explained, 5 ml of iohexol was injected in an antecubital vein, and the venous catheter was flushed with 30 ml of isotonic saline. A blood sample for measurement of iohexol was drawn at a predetermined time-point based on an individual creatinine-based estimated GFR using Jacobsson's method.

Estimated GFR

Estimated GFR was based on the Chronic Kidney Disease Epidemiology research group (CKD-EPI) equations for creatinine, cystatin C, and both together. Creatinine analyzes were performed with an enzymatic method that was standardized against isotope dilution mass

spectroscopy (CREA Plus, Roche Diagnostics, GmbH, Mannheim, Germany). Cystatin C was measured using a particle-enhanced turbidimetric immunoassay method (Gentian, Moss, Norway).

Metabolic parameters, blood pressure and smoking

Serum samples for triglycerides, cholesterol and fasting glucose levels was measured on a Modular P800 (Roche Diagnostics, Mannheim, Germany). Waist circumference and height was measured as a part of the Tromsø 6 study and body weight in the RENIS-T6 study. Further description of body measurements is described in Stefansson et al.'s study (31).

Blood pressure was measured three times using an automated device, and the last two readings was averaged. Smoking status was obtained as a part of a detailed questionnaire in the main Tromsø 6 study. The study population was divided into smokers and non-smokers, whereas previous smokers were grouped with non-smokers for the purposes of this study (31).

Definition of hyperfiltration and other variables

The dichotomous variable for renal hyperfiltration was defined as an absolute mGFR (mL/min) above the 90^{th} percentile after adjusting for gender, age and height. We adjusted for these variables because they are shown to be associated with nephron number (5, 6). Accordingly, we selected all subjects above the 90^{th} percentile in the distribution of residuals from a multiple linear regression analysis where we used the logarithm of absolute GFR as the dependent variable and gender, the logarithm of age and height as independent variables (7, 31). This implies that the GFR cut-off for RHF for each individual depends on gender, age and height.

Metabolic syndrome was defined as fulfilling at least three out of five criteria, and MS was categorized as a dichotomous variable (yes/no). The MS definition used in this study is based on the International Diabetes Foundation (IDF) definition from 2006, and is shown in table 2 (1). However, we chose to exclude subjects with diabetes because of the known association to hyperfiltration, and increased waist circumference was not a definite criterion as IDF proposes it. The waist circumference limit was set to > 94 cm in men and > 80 cm in women. Impaired fasting glucose (IFG) was defined as a fasting plasma glucose ≥ 5.6 mmol/l, but subjects using antidiabetic drugs or having diabetes at baseline were excluded. Subjects with systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or the use of antihypertensive drugs, or a combination of these, were categorized as having hypertension.

High serum triglyceride level was defined as serum level ≥1,7 mmol/L or the use of triglyceride altering drugs. The criteria for low HDL-cholesterol level was a serum level < 1,03 mmol/L in men and < 1.29 in women, or the use of HDL-altering drugs.

Table 2: Definition of metabolic syndrome

Waist circumference	> 94 cm in men, > 80 cm in women
Fasting plasma glucose	≥ 5.6 mmol/L
Blood pressure	Systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or use of antihypertensive medication, or a combination of these
Triglycerides	≥ 1,7 mmol/L or use of triglyceride-altering drugs
HDL-cholesterol	< 1,03 mmol/L in men or < 1,29 in women or use of HDL-altering drugs

3 Statistics

We used Stata software version 15 (Stata Corp., College Station, Texas) for the statistical analyzes. Pearsons X^2 test, Welch's t-test and the Mann-Whitney U test were used to calculate p-values for differences between the group with and without MS. The cross-sectional association between MS, its individual components and RHF was investigated with absolute GFR (ml/min) as a continuous dependent variable using linear regression and as a dichotomized dependent variable (hyperfiltration: yes/no) using logistic regression. The linear regression analysis was repeated using GFR adjusted for BSA. Adjustments were made for the following known or possible determinants of GFR: age, sex, height, current smoking and weight, creating 4 different models including a crude model.

We tested for interactions between all independent variables and gender in both the linear and logistic regression analyses. Statistical significance was set at $P<0.05$.

4 Results

4.1 Study population

Thirty-three out of the 1627 study subjects were excluded because of undiagnosed diabetes mellitus, thirty-nine due to missing waist circumference measurements, and four due to missing triglyceride levels, leaving 1551 participants eligible for our study. The characteristics of the study population is presented in Table 3 as the mean (standard deviation) for continuous variables with symmetric distributions, median (interquartile range) for continuous variables with skewed distributions, and percentage for categorical variables.

Table 3: Characteristics for subjects with and without the metabolic syndrome

Variable	No metabolic syndrome	Metabolic syndrome	P-value
Subjects	1065 (68.7%)	486 (31.3%)	
Male gender	451 (42.4%)	306 (63.0%)	<0.001
Age (years)	58.5 (51.5-63.1)	59.2 (51.6-63.2)	0.02
mGFR (ml/min/1.73m^2)	93.1 ±14.2	95.1 ±14.5	0.01
mGFR (ml/min)	100.3 ±19.0	111.1 ±19.9	<0.001
eGFR (kreatinin)	95.1 ±9.3	94.0 ±10.2	0.05
eGFR (cystatin)	106.1 ±12.0	103.6 ±13.0	<0.001
eGFR (krea+cys)	103.6 ±11.1	101.3 ± 12.0	<0.001
Hyperfiltration (yes)	76 (7.1%)	73 (15.0%)	<0.001
Weight (kg)	75.45 ±13.0	88.5 ±12.9	<0.001
Height (cm)	169.7 ±8.7	172.7 ±8.5	<0.001
BMI (kg/m^2)	26.1 ±3.6	29.6 ±3.6	<0.001
Current smoking	226 (21.2%)	87 (17.9%)	0.1
Waist-hip-ratio	0.89 ±0.10	0.95 ±.060	<0.001
HbA1c (%)	5.5 ±0.3	5.6 ±0.3	<0.001
Office diastolic BP (mmHg)	81.4 ±9.5	87.7 ±8.9	<0.001
Office systolic BP (mmHg)	125.9 ±16.8	137.0 ±16.6	<0.001
ACEi	13 (1.2%)	15 (3.1%)	0.01
ARB	50 (4.7%)	78 (16.1%)	<0.001
Calsium-blocker use	38 (3.5%)	40 (8.2%)	<0.001
Beta-blocker use	32 (3.0%)	35 (7.2%)	<0.001
Diuretica use	67 (6.3%)	69 (14.2%)	<0.001

Use of other anti-hypertensive medicine	0 (0.0%)	1 (0.2%)	0.1
Waist circumference (cm)	91.5 ±10.8	102.5 ±9.5	<0.001
HDL (mmol/L)	1.7 ±0.4	1.3 ±0.3	<0.001
Triglycerides (mmol/L)	0.9 (0.5-1.6)	1.6 (0.7 – 3.1)	<0.001
Fasting glucose (mmol/L)	5.2 ±0.4	5.7 ±0.4	<0.001
Fullfilled metabolic syndrome criterion			
Blood pressure criterion	492 (46.2%)	425 (87.5%)	<0.001
Triglyceride criterion	35 (3.3%)	232 (47.7%)	<0.001
HDL criterion	56 (5.3%)	183 (37.7%)	<0.001
Glucose criterion	122 (11.5%)	326 (67.1%)	<0.001
Waist circ. criterion	753 (70.8%)	479 (98.6%)	<0.001

Values are expressed as means ± SD, percentages, or medians (interquartile range).

Out of 1551 participants, 486 (31.3%) fulfilled the criteria for metabolic syndrome. A higher percentage of males than females had MS, and subjects with MS were, on average, older, heavier, had a higher BMI and higher mGFR (Table 3). On the contrary, estimated GFR using different markers (creatinine, cystatin and a combination), was higher in the group *without* MS.

4.2 Association of MS, its components and GFR as a continuous variable

Table 4 shows the linear relationship between absolute GFR (ml/min) and MS, including the individual components of MS expressed as continuous and dichotomized variables.

There was a significant positive linear relationship between absolute GFR and MS in unadjusted analyzes and after adjusting for age, sex, height and current smoking (model 1-3). Individuals with MS had 6.37 ml/min higher mean absolute GFR compared to subjects without MS, adjusted for age, sex and height (CI: 4.66-8.08, p <0.001). The positive relationship between absolute GFR and MS was attenuated and no longer significant after additional adjustment for bodyweight (model 4). When GFR adjusted for BSA was used

instead of absolute GFR as the dependent variable, the association with MS was much weaker and only significant in the crude model (2.01, CI: 0.47-3.55, p=0.010) (supplemental table 8).

Of the individual components of MS, 4 out of 5 were associated with a significant higher absolute GFR in model 1-3 (Table 4). This was evident both when we expressed the MS components as continuous and dichotomized variables. The MS criterion with greatest impact on absolute GFR was waist circumference, followed by high triglycerides, impaired fasting glucose, and low HDL (model 2). The continuous variable with greatest impact on absolute GFR was glucose (7.41, CI: 5.69-9.13, p<0.001). Systolic blood pressure and hypertension, however, differed from the other variables with varying association with absolute GFR in different models. When using GFR adjusted for BSA, only glucose and the glucose criterion was associated with a higher GFR in the adjusted models, while hypertension was significantly associated with a lower GFR (supplemental table 8).

Table 4: Linear regression analyzes of the association between absolute GFR (mL/min) and the metabolic syndrome and its components

	Model 1			**Model 2**			**Model 3**			**Model 4**		
	Coef.	CI	P	Coef.	CI	P	Coef	CI	P	Coef.	CI	P
Metabolic syndrome	10.58	(8.52-12.64)	<0.001	6.37	(4.66-8.08)	<0.001	6.32	(4.61-8.03)	<0.001	1.68	(-0.09-3.46)	0.063
Waist circ., per SD	9.02	(8.15-9.90)	<0.001	5.69	(4.86-6.51)	<0.001	5.71	(4.89-6.54)	<0.001	1.73	(0.18-3.29)	0.029
Waist-criterion[a]	5.05	(2.62-7.48)	<0.001	8.39	(6.45-10.33)	<0.001	8.49	(6.54-10.43)	<0.001	1.82	(-0.34-3.98)	0.099
Triglycerides, per SD	3.73	(2.76-4.70)	<0.001	1.82	(1.02-2.62)	<0.001	1.71	(0.91-2.52)	<0.001	-0.49	(-1.31-0.33)	0.242
TG-criterion[a]	9.12	(6.55-11.69)	<0.001	4.54	(2.44-6.64)	<0.001	4.39	(2.29-6.50)	<0.001	0.61	(-1.44-2.66)	0.561
HDL, per SD	6.01	(5.07-6.94)	<0.001	2.29	(1.45-3.12)	<0.001	2.21	(1.38-3.05)	<0.001	-0.07	(-0.93-0.79)	0.873
HDL-criterion[a]	6.17	(3.46-8.88)	<0.001	3.94	(1.76-6.13)	<0.001	3.73	(1.54-5.92)	0.001	0.40	(-1.71-2.51)	0.711
Fasting glucose, per SD	7.30	(6.22-8.37)	<0.001	4.01	(3.07-4.94)	<0.001	4.03	(3.09-4.97)	<0.001	2.12	(1.18-3.06)	<0.001
Glucose-citerion[a]	10.23	(8.12-12.34)	<0.001	5.19	(3.41-6.97)	<0.001	5.20	(3.42-6.98)	<0.001	2.63	(0.92-4.36)	0.003
Systolic blood pressure, per SD	2.76	(1.78-3.74)	<0.001	0.80	(-0.04-1.63)	0.061	0.89	(0.05-1.73)	0.038	-0.55	(-1.36-0.26)	0.184

BT-criterion[a]	3.61	(1.61-5.60)	<0.001	0.44	(-1.22-2.10)	0.604	0.59	(-1.08-2.26)	0.491	-2.31	(-3.91--0.71)	0.005

Model 1: crude
Model 2 adjusted for age, sex and height
Model 3: model 2 +current smoking
Model 4: model 3+ weight

All variables were analyzed in separate regression models

[a] Dichotomized variables: waist circumference > 94 cm in men and > 80 for women, glucose > 5.6 mmol/L, SBT > 130 mmHg, DBT > 85mmHg or use of antihypertensive medication, or a combination of these, triglycerides > 1,7 mmol/L or use of TG-altering drugs, HDL < 1,03 in men or <1.29 in women or use of HDL-altering drugs

4.3 Association of MS, its components and renal hyperfiltration

Table 5 shows the relationship between renal hyperfiltration as the dichotomous dependent variable (hyperfiltration yes/no), and MS and the individual components of MS as independent variables, using multiple logistic regression analysis. The components of MS were expressed both as continuous and dichotomized variables.

A total of 149 subjects were classified with renal hyperfiltration, of whom 54% were women. The absolute and BSA-adjusted GFR cut-off points for hyperfiltration with average age and height was 104.7 ml/min/1.73m^2 and 108.4 ml/min in women and 114.7 ml/min/1.73m^2 and 135.2 ml/min for men (31). There was a higher percentage of subjects with hyperfiltration in the MS-group compared to the non-MS group (15.02% vs 7.14% ($p<0.001$) (Table 1)).

MS was significantly associated with an increased odds ratio of hyperfiltration in unadjusted analyzes and after adjusting for age, sex height and current smoking (model 1-3). This relationship was not significant after additional adjustment for bodyweight (model 4).

The same four individual components that were associated with an increase in absolute GFR in the linear regression analyzes, were also significantly associated with increased risk of hyperfiltration in model 1-3. The WC-criterion was associated with the highest odds of hyperfiltration, with an OR of 3.94 of renal hyperfiltration (CI: 2.04-7.60, $p<0.001$) in model 2, followed by the triglyceride-, glucose- and HDL-criterion, respectively. However, none of the criteria were significantly associated with increased risk of hyperfiltration independently

of bodyweight (model 4). When using continuous MS variables as the independent variables, the tendency was the same as for the dichotomized variables.

Table 5: Logistic regression analyzes of the association between renal hyperfiltration and the metabolic syndrome and its components

	Model 1			Model 2			Model 3			Model 4		
	OR	CI	P	OR	CI	P	OR	CI	P	OR	CI	P
Metabolic syndrome	2.30	(1.64-3.24)	<0.001	2.44	(1.71-3.46)	<0.001	2.42	(1.71-3.45)	<0.001	1.37	(0.93-2.02)	0.108
Waist circumference, per SD	1.99	(1.67-2.38)	<0.001	2.24	(1.86-2.69)	<0.001	2.24	(1.86-2.69)	<0.001	1.42	(0.99-2.03)	0.056
Waist-criterion[a]	3.93	(2.04-7.56)	<0.001	3.94	(2.04-7.60)	<0.001	4.00	(2.07-7.75)	<0.001	1.55	(0.76-3.16)	0.233
Triglycerides, per SD	1.40	(1.19-1.64)	<0.001	1.43	(1.21-1.69)	<0.001	1.41	(1.19-1.67)	<0.001	1.08	(0.89-1.30)	0.440
TG-criterion[a]	2.05	(1.40-3.02)	<0.001	2.15	(1.45-3.19)	<0.001	2.12	(1.43-3.13)	<0.001	1.32	(0.87-2.02)	0.186
HDL, per SD	1.52	(1.25-1.84)	<0.001	1.67	(1.36-2.06)	<0.001	1.65	(1.34-2.03)	<0.001	1.24	(0.99-1.55)	0.066
HDL-criterion[a]	1.58	(1.04-2.40)	0.032	1.61	(1.06-2.46)	0.025	1.57	(1.03-2.39)	0.038	1.03	(0.66-1.61)	0.901
Glucose, per SD	1.57	(1.30-1.90)	<0.001	1.67	(1.37-2.03)	<0.001	1.67	(1.38-2.04)	<0.001	1.31	(1.06-1.63)	0.013
Glucose-citerion[a]	1.76	(1.24-2.49)	0.001	1.87	(1.30-2.69)	0.001	1.89	(1.32-2.71)	0.001	1.35	(0.92-1.97)	0.127
Systolic blood pressure, per SD	1.09	(0.92-1.29)	0.320	1.10	(0.92-1.31)	0.297	1.12	(0.94-1.33)	0.224	0.92	(0.75-1.12)	0.388
BT-criterion[a]	1.06	(0.75-1.50)	0.738	1.06	(0.74-1.52)	0.738	1.09	(0.76-1.56)	0.637	0.71	(0.49-1.05)	0.086

Model 1: crude

Model 2 adjusted for age, sex and height

Model 3: model 2 +current smoking

Model 4: model 3+ weight

All variables were analyzed in separate regression models

[a] Dichotomized variables: waist circumference > 94 cm in men and > 80 for women, glucose > 5.6 mmol/L, SBT > 130 mmHg, DBT > 85mmHg or use of antihypertensive medication, or a combination of these, triglycerides > 1,7 mmol/L or use of TG-altering drugs, HDL < 1,03 in men or <1.29 in women or use of HDL-altering drugs

4.4 Risk of RHF according to number of MS risk factors

The study population was divided into 6 subgroups according to the number of MS criteria they fulfilled (0 to 5). The relative prevalence of hyperfiltration increased with the number of criteria met, except from group 3 which had a higher prevalence of hyperfiltration than group 4 (Table 6), $p < 0.001$ for trend across groups. The relationship between absolute GFR and number of MS criteria is visualized in Figure 3.

Table 6: Percentage of hyperfiltrators according to the number of risk factors for MS

Number of risk factors for MS	**0**	**1**	**2**	**3**	**4**	**5**
Percentage of hyperfiltrators	2.9%	7.0%	8.3%	15.4%	13.0%	18.8%

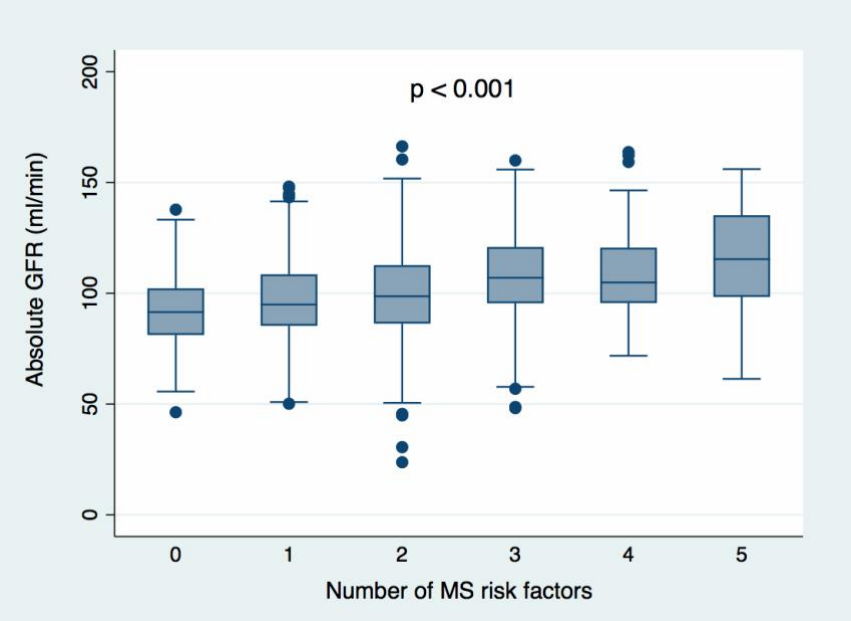

Figure 3: Absolute GFR according to the number of metabolic risk factors (adjusted for age and gender), P-value: <0.001.

It was a significant increase in odds ratio for RHF with increasing numbers of MS risk factors (Model 1-3, table 7a).

Table 7a: OR for RHF according to number of MS risk factors as continuous variable

	Model 1			Model 2			Model 3			Model 4		
	OR	CI	P	OR	CI	P	OR	CI	P	OR	CI	P
MS risk factors*	1.42	(1.23-1.64)	<0.001	1.46	(1.26-1.70)	<0.001	1.46	(1.25-1.69)	<0.001	1.07	(0.90-1.29)	0.399

*MS as a continuous variable, 0 to 5 criteria

Model 1: crude

Model 2: age, sex, height

Model 3: age, sex, height, current smoking

Model 4: age, sex, height, weight, current smoking

The risk of hyperfiltration in each of the subgroups was also examined. Because the number of participants with hyperfiltration in the group with only one MS risk factor (group 0) was low (4 subjects), we merged group 0 and 1. The results are shown in Table 7b. The highest odds of RHF were in the group fulfilling 5 out of 5 criteria adjusted for age, sex and height (OR: 4.06, CI: 1.54-10.67, p = 0.005).

Table 7b: OR for RHF according to number of MS risk factors in each subgroup

	Model 1			Model 2			Model 3			Model 4		
Number of risk factors	OR	CI	P	OR	CI	P	OR	CI	P	OR	CI	P
2	1.41	(0.89-2.28)	0.143	1.45	(0.09-2.34)	0.125	1.48	(0.92-2.38)	0.108	0.88	(0.52-1.46)	0.602
3	2.86	(1.80-4.56)	<0.001	3.05	(1.89-4.93)	<0.001	3.09	(1.92-5.00)	<0.001	1.40	(0.82-2.37)	0.215
4	2.35	(1.25-4.44)	0.008	2.56	(1.34-4.88)	0.004	2.51	(1.31-4.80)	0.005	0.90	(0.44-1.85)	0.769
5	2.63	(1.39-9.44)	0.008	4.06	(1.54-10.67)	0.005	4.16	(1.58-10.99)	0.004	1.28	(0.45-3.66)	0.645

Model 1: crude

Model 2: age, sex, height

Model 3: age, sex, height, current smoking

Model 4: age, sex, height, weight, current smoking

5 Discussion

5.1 Discussion of results

Main results

In this study of middle-aged subjects from the general non-diabetic population of Tromsø, MS was associated with renal hyperfiltration and increased absolute GFR independent of age, sex and height. This result was mainly driven by the waist circumference criterion and the glucose criterion of MS. Moreover, the triglyceride and HDL criteria were significantly associated with renal hyperfiltration and increased absolute GFR, whereas hypertension was not a statistically significant risk factor. The risk of hyperfiltration increased with the number of metabolic risk factors met. These findings suggest that MS and 4 out of 5 individual components of MS are risk factors for renal hyperfiltration.

mGFR vs eGFR

To the best of our knowledge, this is the first study of MS and RHF using actual measurements of GFR instead of estimations of GFR. Equations to calculate GFR are known to be imprecise in the high to normal range of GFR, and are biased by non-GFR related factors, such as diet, atypical muscle mass, medications, glucose levels, insulin resistance and low-grade inflammation (8). Accordingly, estimated GFR may lead to biased results when studying RHF, particularly in subjects with metabolic risk factors. This was recently confirmed in a study which found that the 95th percentile thresholds for eGFR were considerably lower than that for mGFR (134 ml/min/1.73m2 vs 118 ml/min/1.73m2), and high mGFR was a much better marker of single-nephron hyperfiltration than eGFR (3). The weakness of using eGFR to study RHF is also illustrated in our study as we found that the MS group had a higher mean mGFR, but a *lower* mean eGFR, compared to the non-MS group (Table 2). Thus, the use of eGFR implied a total opposite association between GFR and MS than the use of mGFR, and the results of this study would probably be different with the use of eGFR. This calls into question the results of studies on RHF based on eGFR (25, 26, 30).

Defining renal hyperfiltration

There is no consensus on how to define renal hyperfiltration. Variations include the use of eGFR vs mGFR, absolute GFR vs GFR adjusted for BSA and different adjustments for

independent variables though to influence nephron number such as age, sex, height and weight. Hence the best method to determine hyperfiltration is not settled. Chakkera et al studied this issue and found that a high age-height-gender-based absolute GFR definition was one of the best suited methods to differentiate between biopsy verified markers of hyperfiltration (nephron number and glomerular volume), and high GFR due to higher nephron number (3). This definition makes sense because age, sex and height all associate with nephron number (19). To correct for individual variations in nephron number, we therefore adjusted our definition of renal hyperfiltration for age, sex and height and used these covariates as our main model (model 2) with absolute GFR as dependent variable.

GFR adjusted for bodyweight or BSA

We found that using GFR adjusted for body surface area (supplemental table 8) or adjusting for bodyweight (model 4) diluted the positive association of MS with increased GFR and RHF. It is known that absolute GFR increases with increasing body weight, but the number of nephrons, however, does not increase. Increasing obesity must therefore result in an increase in single nephron GFR (33). Adjustment for weight or BSA in obese individuals will therefore mask the pathological state of hyperfiltration and possibly even misdiagnose these subjects to have impaired renal perfusion (34). Most previous hyperfiltration studies with mGFR have found a positive relationship between BMI and RHF that disappears upon the adjustment of GFR to BSA, confirming the unsuitability of BSA correction in obese individuals (31). Therefore, it has been suggested that GFR should be adjusted for height rather than BSA in obese individuals (35).

Definition of MS

WHO was the first to define MS in 1998, and over the last two decades, several definitions has been made (21).The definition of MS used in this study is the International Diabetes Federation criteria (IDF). This definition has been criticized for having too low cut-off for waist circumference (> 94 cm in men and > 80 cm in women), and other definitions therefore use a higher threshold for WC, accordingly > 102 cm in men and > 88 cm in women (36). The two different cut offs for WC were compared in a study on MS and eGFR decline: the use of higher cut-off value diluted the negative association between MS and GFR which was significant when using the IDF-criteria (2). This emphasizes that the choice of MS definition can influence the results of a study and may therefore only be representative for the current

definition. Accordingly, the results of this study may not be transferrable for other definitions of MS. Which definition of MS is the best is still not settled.

Individual factors of MS

The same four components of MS were significantly associated with increased absolute GFR and increased odds ratio of RHF in model 1-3 (Table 4 and 5): waist circumference, triglycerides, HDL and glucose.

The positive association between waist circumference and RHF is consistent with previous studies, as different measures of obesity have been associated with hyperfiltration (17, 31, 37). The degree of association between obesity measures and RHF varies between the different indicators of obesity. A study by Stefansson et al. found that waist hip ratio (WHR) was a better obesity measure than BMI or waist circumference to uncover hyperfiltration independently of body weight (31).

Increased triglyceride- and lower HDL-levels have been associated with both lower and higher eGFR and with hyperfiltration in previous studies (25, 30). However, these studies were limited by the use of eGFR and the study population differed from our population, including young men (mean age 18.4 years) and adolescents respectively. Similarly, impaired fasting glucose or prediabetes has been associated with both higher and lower eGFR (30, 38). A previous report from the RENIS-T6 study using mGFR found that impaired fasting glucose was associated with higher mGFR and hyperfiltration (20).

Hypertension, however, was not significantly associated with renal hyperfiltration in either model. This finding differs from some other studies that have found hypertension to be a risk factor for hyperfiltration (25, 27, 39). This may be explained by the fact that hyperfiltration is thought to be a transient state in the early phase of hypertensive kidney disease, followed by reduction in GFR (15). Accordingly, the hypertensive subjects of this study may have passed the hyperfiltration state, thus affecting the association between hypertension and RHF seen in this study. Moreover, we included subjects using antihypertensive medications, of which some are known to reduce the intraglomerular pressure and thus prevent RHF. For example, the use of RAAS (renin-angiotensin-aldosterone system) inhibitors have shown to protect against deterioration in renal function in patients with diabetic nephropathy by reducing the

intraglomerular pressure (40, 41). Excluding patients using antihypertensiva could possibly have influenced the association between hypertension and RHF seen in this study.

The clinical relevance of RHF

Renal hyperfiltration and its associated risk factors are of clinical importance if treatment has an impact on clinically relevant end points. The renoprotective effect of reducing hyperfiltration has been confirmed in several studies including animals and humans with diabetes (14, 40, 41). In addition to the mentioned RAAS inhibitors, the antidiabetic drug SGLT-2 inhibitor is a new and a promising treatment option. By inhibiting the sodium-glucose cotransporter 2 (SGLT2) in the proximal tubule of the nephron they reduce hyperfiltration through several mechanisms: 1) restoring the sodium-chloride concentration at the macula densa causing a subsequent TGF-mediated afferent arteriolar vasoconstriction thus reducing the glomerular pressure, 2) increasing the intratubular volume causing a retrograde increase in hydraulic pressure in Bowmans space, which reduces net filtration pressure (42). In addition, also non-drug treatment such as low-protein diet and physical exercise may possibly reduce RHF (43, 44).

5.2 Strengths and limitations

Compared to previous epidemiological studies on MS and hyperfiltration, the strength of this study is the use of mGFR instead of eGFR. Also, we used a definition of RHF that may be more closely correlated to single-nephron HF and that does not mask RHF in obese patients, compared to other definitions. Lastly, we excluded persons with self-reported CVD and diabetes to prevent confounding as previous studies have shown an association between these diseases and RHF (27, 42). However, we cannot exclude confounding from other GFR-related factors, like for instance birth weight, diet and ethnicity (45, 46).

This study has some limitations. Although a cross-sectional design may be appropriate to analyze risk factors associated with RHF, this design may also be problematic because hyperfiltration is thought to be a transient state that is succeeded by a loss of nephrons and decline in GFR. This means that when measuring GFR at a one single point, we lose subjects that have *had* hyperfiltration or subjects that may develop hyperfiltration. This may be the

reason why we didn't find an association between hypertension and RHF when other studies have (39). Also, a cross-sectional study design cannot prove causation, only correlation.

Concerning external validity, our study population was composed of middle-aged Caucasians, which may limit the transferability of our findings to other ethnicities or age groups. Additionally, because the use of mGFR is more expensive than using eGFR, our study population was smaller than in other eGFR-based studies. A larger study group would have increased the power of the statistical tests.

Selection bias

It´s conceivable that the subjects attending the RENIS-T6 study differ from the subjects who declined the invitation. For example, participants who accepted the invitation may be more concerned about their own health than the ones not attending, thus affecting lifestyle related risk factors. However, the magnitude of selection bias is likely not large because there were only small differences between those included in the study and all subjects eligible for the RENIS-T6 study (32).

6 Conclusion

In summary, MS was associated with increased absolute GFR and renal hyperfiltration independent of age, sex and height. Increased waist circumference, impaired fasting glucose, high triglycerides and low HDL-cholesterol were also associated with RHF and increased absolute GFR. Additional adjustment for weight diluted the positive relationship between MS and GFR, however, doing so is known to mask hyperfiltration in obese persons. Also, we found that subjects with MS had higher mean mGFR but lower mean eGFR compared to those without MS, illustrating the limitations of using eGFR when studying renal hyperfiltration.

It is not established whether hyperfiltration is a risk factor for the development of CKD in persons without diabetes, and longitudinal studies are needed to explore whether RHF predicts future chronic kidney disease in persons with MS (29). Moreover, RCT targeting hyperfiltration are warranted to assess whether GFR decline and CKD can be prevented at an early stage in subjects with MS.

7 References

1. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Current hypertension reports. 2018;20(2):12-.
2. Stefansson VTN, Schei J, Solbu MD, Jenssen TG, Melsom T, Eriksen BO. Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population. Kidney International. 2018;93(5):1183-90.
3. Chakkera HA, Denic A, Kremers WK, Stegall MD, Larson JJ, Ravipati H, et al. Comparison of high glomerular filtration rate thresholds for identifying hyperfiltration. Nephrol Dial Transplant. 2020;35(6):1017-26.
4. Hughson MD, Douglas-Denton R, Bertram JF, Hoy WE. Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. Kidney Int. 2006;69(4):671-8.
5. Stevens LA, Coresh J, Greene T, Levey AS. Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. New England Journal of Medicine. 2006;354(23):2473-83.
6. Wesson LG. Physiology of the human kidney. New York: Grune & Stratton; 1969.
7. Melsom T. Renal hyperfiltration, impaired fasting glucose and physical exercise in the general population : a cross-sectional study [Philosophiae Doctor]. Tromsø: University of Tromsø, UIT; 2012.
8. Brun A, Gøransson L, Jensen G, Langsjøen EC, Salvador CL, Skadberg Ø, et al. NSMBs anbefaling for kreatininbasert estimering av GFR. 2016 12.12.16.
9. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765.
10. Delanaye P, Jager KJ, Bökenkamp A, Christensson A, Dubourg L, Eriksen BO, et al. CKD: A Call for an Age-Adapted Definition. J Am Soc Nephrol. 2019;30(10):1785-805.
11. Hallan SI, Øvrehus MA, Romundstad S, Rifkin D, Langhammer A, Stevens PE, et al. Long-term trends in the prevalence of chronic kidney disease and the influence of cardiovascular risk factors in Norway. Kidney Int. 2016;90(3):665-73.
12. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020;395(10225):709-33.
13. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nature Reviews Nephrology. 2012;8(5):293-300.
14. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol. 1981;241(1):F85-93.
15. Palatini P. Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. Nephrol Dial Transplant. 2012;27(5):1708-14.
16. Vallon V, Komers R. Pathophysiology of the diabetic kidney. Compr Physiol. 2011;1(3):1175-232.
17. Wuerzner G, Pruijm M, Maillard M, Bovet P, Renaud C, Burnier M, et al. Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. Am J Kidney Dis. 2010;56(2):303-12.

18. Thomson HJ, Ekinci EI, Radcliffe NJ, Seah JM, MacIsaac RJ, Jerums G, et al. Elevated baseline glomerular filtration rate (GFR) is independently associated with a more rapid decline in renal function of patients with type 1 diabetes. J Diabetes Complications. 2016;30(2):256-61.
19. Hoy WE, Douglas-Denton RN, Hughson MD, Cass A, Johnson K, Bertram JF. A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. Kidney Int Suppl. 2003(83):S31-7.
20. Melsom T, Mathisen UD, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, et al. Impaired fasting glucose is associated with renal hyperfiltration in the general population. Diabetes Care. 2011;34(7):1546-51.
21. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009;2(5-6):231-7.
22. Locatelli F, Pozzoni P, Del Vecchio L. Renal manifestations in the metabolic syndrome. J Am Soc Nephrol. 2006;17(4 Suppl 2):S81-5.
23. Zhang X, Lerman LO. The metabolic syndrome and chronic kidney disease. Transl Res. 2017;183:14-25.
24. Gornostaeva E, Novikova MS, Beloborodova AV, Akarachkova ES, Shilov EM, Shvarkov SB. [Autonomic imbalance in patients with metabolic syndrome: role in the development of hyperfiltration--an early marker of renal lesions]. Ter Arkh. 2010;82(6):49-53.
25. Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, et al. Glomerular hyperfiltration: A new marker of metabolic risk. Kidney International. 2007;71(8):816-21.
26. Monami M, Pala L, Bardini G, Francesconi P, Cresci B, Marchionni N, et al. Glomerular hyperfiltration and metabolic syndrome: results from the FIrenze-BAgno A Ripoli (FIBAR) Study. Acta Diabetol. 2009;46(3):191-6.
27. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. Glomerular hyperfiltration in prediabetes and prehypertension. Nephrology Dialysis Transplantation. 2012;27(5):1821-5.
28. Schmieder RE, Veelken R, Gatzka CD, Rüddel H, Schächinger H. Predictors for hypertensive nephropathy: results of a 6-year follow-up study in essential hypertension. J Hypertens. 1995;13(3):357-65.
29. Tantravahi J, Srinivas TR, Johnson RJ. Hyperfiltration: a sign of poor things to come in individuals with metabolic syndrome. Nature Clinical Practice Nephrology. 2007;3(9):474-5.
30. Lee AM, Charlton JR, Carmody JB, Gurka MJ, DeBoer MD. Metabolic risk factors in nondiabetic adolescents with glomerular hyperfiltration. Nephrol Dial Transplant. 2017;32(9):1517-24.
31. Stefansson VTN, Schei J, Jenssen TG, Melsom T, Eriksen BO. Central obesity associates with renal hyperfiltration in the non-diabetic general population: a cross-sectional study. BMC Nephrology. 2016;17(1):172.
32. Eriksen BO, Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, Njølstad I, et al. Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. Kidney International. 2010;78(12):1305-11.
33. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol. 2003;14(6):1480-6.
34. Delanaye P, Krzesinski JM. Indexing of Renal Function Parameters by Body Surface Area: Intelligence or Folly? Nephron Clinical Practice. 2011;119(4):c289-c92.

35. Schmieder RE, Beil AH, Weihprecht H, Messerli FH. How should renal hemodynamic data be indexed in obesity? Journal of the American Society of Nephrology. 1995;5(9):1709-13.
36. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome. Circulation. 2009;120(16):1640-5.
37. Turer CB, Baum M, Dubourg L, Selistre LS, Skinner AC. Prevalence of hyperfiltration among US youth/young adults with overweight and obesity: A population-based association study. Obes Sci Pract. 2019;5(6):570-80.
38. Markus MRP, Ittermann T, Baumeister SE, Huth C, Thorand B, Herder C, et al. Prediabetes is associated with microalbuminuria, reduced kidney function and chronic kidney disease in the general population: The KORA (Cooperative Health Research in the Augsburg Region) F4-Study. Nutrition, Metabolism and Cardiovascular Diseases. 2018;28(3):234-42.
39. Palatini P, Dorigatti F, Saladini F, Benetti E, Mos L, Mazzer A, et al. Factors Associated With Glomerular Hyperfiltration in the Early Stage of Hypertension. American Journal of Hypertension. 2012;25(9):1011-6.
40. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9.
41. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456-62.
42. Tonneijck L, Muskiet MHA, Smits MM, van Bommel EJ, Heerspink HJL, van Raalte DH, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. Journal of the American Society of Nephrology. 2017;28(4):1023-39.
43. Kitada M, Ogura Y, Monno I, Koya D. A Low-Protein Diet for Diabetic Kidney Disease: Its Effect and Molecular Mechanism, an Approach from Animal Studies. Nutrients. 2018;10(5):544.
44. Melsom T, Mathisen UD, Eilertsen B-AW, Ingebretsen OC, Jenssen T, Njølstad I, et al. Physical exercise, fasting glucose, and renal hyperfiltration in the general population: the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). Clin J Am Soc Nephrol. 2012;7(11):1801-10.
45. Juraschek SP, Appel LJ, Anderson CAM, Miller ER, 3rd. Effect of a high-protein diet on kidney function in healthy adults: results from the OmniHeart trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(4):547-54.
46. White SL, Perkovic V, Cass A, Chang CL, Poulter NR, Spector T, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. Am J Kidney Dis. 2009;54(2):248-61.

8 Supplemental tables

Table 8: Linear regression model analysis of metabolic syndrome, its components and GFR adjusted for BSA

	Model 1			Model 2			Model 3			Model 4		
	Coef.	CI	P	Coef.	CI	P	Coef.	CI	P	Coef.	CI	P
Metabolic syndrome	2.01	(0.47-3.55)	0.010	0.99	(-0.48-2.45)	0.187	0.94	(-0.52-2.40)	0.205	1.49	(-0.10-3.09)	0.066
Waist circumference, per SD	0.95	(0.23-1.66)	0.009	0.03	(-0.70-0.77)	0.934	0.05	(-0.68-0.79)	0.885	1.41	(0.01-2.80)	0.049
Waist-criterion[a]	-2.15	(-3.92--0.39)	0.017	0.15	(-1.53-1.82)	0.864	0.25	(-1.42-1.93)	0.765	0.96	(-0.99-2.90)	0.335
Triglycerides, per SD	0.35	(-0.37-1.06)	0.345	-0.36	(-1.03-0.32)	0.303	-0.54	(-1.2-0.14)	0.122	-0.47	(-1.2-0.27)	0.213
TG-criterion[a]	1.95	(0.06-3.84)	0.043	0.49	(-1.29-2.27)	0.589	0.31	(-1.47-2.09)	0.733	0.59	(-1.25-2.43)	0.529
HDL, per SD	1.49	(0.78-2.20)	<0.001	-0.08	(-0.79-0.63)	0.831	-0.18	(-0.89-0.53)	0.614	-0.04	(-0.81-0.72)	0.909
HDL-criterion[a]	1.36	(-0.62-3.34)	0.179	0.62	(-1.23-2.47)	0.514	0.33	(-1.52-2.18)	0.728	0.57	(-1.33-2.46)	0.557
Glucose, per SD	2.40	(1.58-3.21)	<0.001	1.49	(0.69-2.3)	<0.001	1.55	(0.74-2.35)	<0.001	1.87	(1.02-2.71)	<0.001
Glucose-citerion[a]	3.41	(1.84-5.00)	<0.001	2.03	(0.51-3.54)	<0.001	2.08	(0.57-3.59)	0.007	2.35	(0.81-3.90)	0.003
Systolic blood pressure, per SD	-0.09	(-0.80-0.63)	0.815	-0.66	(-1.37-0.04)	0.065	-0.56	(-1.26-0.15)	0.124	-0.49	(-1.22-0.24)	0.184
BT-criterion[a]	-1.47	(-2.93--0.02)	0.047	-2.39	(-3.79--0.99)	0.001	-2.20	(-3.60- -0.80)	0.002	-2.15	(-3.59--0.71)	0.004

Model 1: crude

Model 2 adjusted for age, sex and height

Model 3: model 2 + current smoking

Model 4: model 3+ weight

All variables were analyzed in separate regression models

[a] Dichotomized variables: waist circumference > 94 cm in men and > 80 for women, glucose > 5.6 mmol/L, SBT > 130 mmHg, DBT > 85mmHg or use of antihypertensive medication, or a combination of these, triglycerides > 1,7 mmol/L or use of TG-altering drugs, HDL < 1,03 in men or <1.29 in women or use of HDL-altering drugs

9 GRADE

<table>
<tr><td colspan="3">Referanse: Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. Glomerular hyperfiltration in prediabetes and prehypertension. Nephrology Dialysis Transplantation. 2012;27(5):1821-5.</td><td>Studiedesign: Tverrsnittstudie
Grade-kvalitet: Middels</td></tr>
<tr><td>Formål</td><td>Materiale og metode</td><td>Resultater</td><td>Diskusjon/kommentarer/sjekkliste</td></tr>
<tr><td>Undersøke sammenhengen mellom hyperfiltrasjon, hypofiltrasjon og prediabetes og prehypertensjon

Bestemme referanseverdier for hyperfiltrasjon og hypofiltrasjon hos individer uten prediabetes og prehypertensjon

Konklusjon

Prevalensen av hyperfiltrasjon økte med økende nivå av prediabetes og prehypertensjon. Hypofiltrasjon var ikke</td><td>Populasjon: 99 140 mennesker med alder mellom 20-89 år som gikk til helsesjekk ved Aichi Prefecture i Japan.

Hovedutfall: eGFR over 95 percentilen justert for alder og kjønn, eGFR under 5 percentilen justert for alder og kjønn. GFR ble estimert vha serum kreatinin og MDRD-formelen.

Klassifisering av prediabetes og diabetes ved fastende plasmaglukose (mg/dl):
- Ikke diabetes < 100
- Nivå 1 prediabetes: 100-109
- Nivå 2 prediabetes: 110-125
- Diabetes: > 126

Klassifisering av prehypertensjon og hypertensjon ved systolisk og diastolisk trykk (mmHg):
- Ikke hypertensjon < 120/80</td><td>Hovedfunn

- Prevalensen av hyperfiltrasjon økte med økende nivå av prediabetes (OR: 1.29, 1.58 og 2.47 for hhv nivå 1 prediabetes, nivå 2 prediabets og diabetes, p<0.001) og prehypertensjon (OR: 1.10, 1.33 og 1.52 for nivå 1 prehypertensjon, nivå 2 prehypertensjon og hypertensjon).
- Hypofiltrasjon var ikke assosiert med prediabetes eller prehypertensjon.

Bifunn

- 95 percentilen for hyperfiltrasjon varierte mellom 96 ml/min/1.73m^2 hos 70-89 åringer til 117 ml/min/1.73m^2 hos 20-29 åringer</td><td>Sjekkliste:

• Formålet klart formulert?
Ja.

• Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?
Ja. Det ble justert for kjente faktorer assosiert med hyper- og hypofiltrasjon

• Kan resultatene overføres til den generelle befolkningen?
Studien er stor da den inkluderer nesten 100 000 mennesker, men den inkluderte trolig nesten utelukkende japanske individer, hvilket gjør at resultatene ikke kan overføres til den generelle befolkningen.

• Annen litteratur som styrker/svekker resultatene?</td></tr>
</table>

assosiert med prediabetes eller prehypertensjon **Land** Japan **År data innsamling** 2006-2008	- Nivå 1 prehypertensjon: 120-129/80-84 - Nivå 2 prehypertensjon: 130-139/85-89 - Hypertensjon: > 140/90 **Viktige konfunderende faktorer** Hyperfiltrasjon og hypofiltrasjon-definisjonen ble justert for kjønn og alder De statistiske analysene ble justert for: 1) alder, kjønn, 2) alder, kjønn, BMI, HDL, kolesterolsenkende medisin, urinsyre og røyking. Analysene av prediabetes ble også justert for systolisk BT og antihypertensiv medisin, mens prehypertensjon ble justert for fastende plasmaglukose og glukosesenkende medisiner. **Statistiske metoder: STATA versjon 9** Odds ratio og 95% konfidensintervall ble estimert for hyper- og hypofiltrasjon vha logistisk regresjon. Statistisk signifikans var satt til $p<0.05$	- 5 percentilen for hypofiltrasjon varierte mellom 50 ml/min/1.73m^2 hos 70-89 åringer til 75 ml/min/1.73m^2 hos 20-29 åringer - Det var ingen klinisk viktige forskjeller i karakteristika mellom gruppen med hhv. normal filtrasjon, hyperfiltrasjon og hypofiltrasjon foruten høyere fastende blodglukose hos de med hyperfiltrasjon og at en høyere andel av de med hypofiltrasjon var eldre menn med høyere urinsyrenivå, dyslipidemi og proteinuri sammenliknet med subjekter med normal filtrasjon. - Hypofiltrasjon var svakt assosiert med diabets og hypertensjon - Det var høyere prevalens av hyperfiltrasjon hos yngre individer og høyere prevalens av hypofiltrasjon hos eldre individer med prediabetes	Hyperfiltrasjon er en velkjent tidlig forandring i nyrene ved diabetes og hypertensjon. Dette styrker/sannsynliggjør resultatene i studien. Ifølge forfatterne var det på tidspunktet artikkelen ble skrevet kun én annen studie som hadde funnet en sammenheng mellom hyperfiltrasjon og prediabetes, men studiepopulasjonen var svært liten (n=24). **Styrker:** - Stor studiepopulasjon **Svakheter:** - Bruk av eGFR - **I**nkluderte kun japanske individer. - Diabetiske individer med normal filtrasjon på undersøkelsestidspunktet kan ha gått gjennom hyperfiltrasjon på et tidligere tidspunkt. - Man manglet informasjon om mikroalbuminuri og glukosetoleranse. Man brukte altså kun fastende glukose som kriterium for prediabetes og ikke nedsatt glukosetoleranse - Ingen longitudinelle data på GFR

<table>
<tr><td colspan="3">Referanse: Monami M, Pala L, Bardini G, Francesconi P, Cresci B, Marchionni N, et al. Glomerular hyperfiltration and metabolic syndrome: results from the FIrenze-BAgno A Ripoli (FIBAR) Study. Acta Diabetol. 2009;46(3):191-6.</td><td>Studiedesign: Pasientserie
Grade-kvalitet: Svak</td></tr>
<tr><td>Formål</td><td>Materiale og metode</td><td>Resultater</td><td>Diskusjon/kommentarer/sjekkliste</td></tr>
<tr><td>Utforske forholdet mellom hyperfiltrasjon og metabolsk syndrom (MS).

Undersøke nytten av hyperfiltrasjon som prediktor for endepunkt assosiert med MS, slik som diabetes.

Konklusjon
Forhøyet GFR, estimert ved hjelp av metoder som ikke medfører systematisk overestimering hos overvektige mennesker, er ikke assosiert med MS.

Land
Italia

År data innsamling</td><td>Populasjon: 2 694 ikke-diabetiske individer, uten bakgrunn med nyresykdom eller serum-kreatinin > 1.5 g/dl ved baseline

Hovedutfall: forhøyet eGFR basert på tre ulike formler for estimering av GFR
- Cockroft-Gault formula med faktisk kroppsvekt (CAW)
- Cockroft-Gault formula med ideell kroppsvekt (CIW)
- Modification of Diet in Renal Disease formula (MDRD)
MS basert på to ulike definisjoner:
- IDF kriterier
- NCEP kriterier</td><td>Hovedfunn
- Forhøyet eGFR var assosiert med økt prevalens av de fleste enkeltkomponentene av MS: økt midjeomrkets, hyperglykemi, lavt HDL-kolesterol, hypertriglyseridemi
- Det var kun signifikant assosiasjon mellom hyperfiltrasjon og MS ved bruk av CAW-formelen – hvilket er en definisjon som overestimerer GFR hos overvektige mennesker
- Forhøyet GFR predikerte ikke utvikling av diabetes

Bifunn
- eGFR var signifikant høyere ved bruk av MDRD-formelen enn ved CIW og CAW</td><td>Sjekkliste:
• Formålet klart formulert?
• Ja
• Er det tatt hensyn til viktige konfunderende faktorer i design/gjennomføring/analyser?
• Det er justert for en del konfunderende variabler, men det kunne muligens vært inkludert flere uavhengige variabler
• Kan resultatene overføres til den generelle befolkningen?
• Studien inkluderte kun middelaldrende italienere hvilket gjør at det ikke kan overføres til den generelle befolkningen
• Var studien prospektiv?
• Ja
• Var oppfølgingstiden lang nok til å påvise positive eller negative utfall?
• Usikkert. Det var en ganske begrenset oppfølgingstid, som forfatterne diskuterer som en svakhet ved studien</td></tr>
</table>

2001-2003	**Viktige konfunderende faktorer**
	Individer med nyresykdom og/eller diabetes ble ekskludert. Det ble justert for alder, kjønn og BMI i analysene.
	
	Statistiske metoder: SPSS 12.0.1
	Karakteristika ved studiepopulasjonen: pearson kji-kvadrattest, unpaired student t-test og Mann-Whitney U-test.
	Sammenhengen mellom hyperfiltrasjon og MS ble undersøkt ved logistisk regresjon.
	Sammenhengen mellom GFR som kontinuerlig variabel og fedme ble undersøkt ved multippel lineær regresjon med absolutt GFR og GFR justert for BSA som avhengig variabel.
		- eGFR basert på CAW var signifikant høyere enn ved bruk av CIW	**Hva diskuterer forfatterne som:**
			• **Styrke:**
			  • Bruk av flere GFR formler
			• **Svakhet:**
			  • Bruk av estimert GFR
			  • Nye tilfeller av diabetes ble registrert ved hjelp av registre slik at det trolig var pasienter med som ikke ble diagnostisert med diabetes selv om de utviklet det under oppfølgingstiden
			  • Kort oppfølgingstid (27.8 +/- 11.5 mnd)

<table>
<tr><td colspan="3">Referanse: Chakkera HA, Denic A, Kremers WK, Stegall MD, Larson JJ, Ravipati H, et al. Comparison of high glomerular filtration rate thresholds for identifying hyperfiltration. Nephrol Dial Transplant. 2020;35(6):1017-26.</td><td>Studiedesign: Tverrsnittstudie
Grade-kvalitet Middels</td></tr>
<tr><td>Formål</td><td>Materiale og metode</td><td>Resultater</td><td>Diskusjon/kommentarer/sjekkliste</td></tr>
<tr><td>Avgjøre hvilken definisjon for høy GFR som best gjenspeiler de kliniske og strukturelle forandringer som ses ved hyperfiltrasjon

Konklusjon
Høy alders-basert absolutt mGFR korrelerte best med hyperfiltrasjon, og høy alder-kjønn-høyde basert aboslutt mGFR var nesten like bra.

Land
USA

År data innsamling</td><td>Populasjon: 3317 potensielle nyredonorer ved Mayo og Cleveland klinikk.

Hovedutfall:
- mGFR og eGFR over 95 percentilen
- Nyrestørrelse (radiologisk)
- Nefronantall og glomerulusvolum (biopsi)

Viktige konfunderende faktorer
mGFR og eGFR ble justert for ulike variabler:
- Korrigering for BSA
- Alder
- Alder-høyde-kjønn

Statistiske metoder: SAS 0.4, STATA 13 og JMP 13.
eGFR ble estimert ved CKD-EPI formelen.
Kji-kvadrat test ble brukt til å undersøke prevalensen av høy GFR mellom aldersgruppene.
Multivariabel analyse vurderte det uavhengige bidraget til de to strukturelle determinantene til GFR (glomerulært volum og</td><td>Hovedfunn
- mGFR var en mye bedre markør på hyperfiltrasjon på enkelt-nefron nivå enn eGFR
- Ukorrigert mGFR var bedre enn korrigert mGFR
- Høy aldersjustert ukorrigert mGFR var den beste definisjonen til å avdekke hyperfiltrasjon på enkeltnefron nivå, men det har klinisk liten relevans da det ikke skiller mellom hyperfiltrasjon og høyt nefrontall
- Høy alder-høyde-kjønn justert ukorrigert mGFR var nesten like bra som aldersjusert mGFR til å avdekke hyperfiltrasjon, og hadde sine fordeler sammenliknet med aldersjustert mGFR da det var mindre assosiert med nefronantall og det mannlige kjønn

Bifunn
- Aldersjustert eGFR var assosiert med kvinner og svart rase
- Tresholds for mGFR var høyere enn for eGFR
- Prevalensen av generelt forhøyet GFR var høyest hos de yngste donorene</td><td>Sjekkliste:
• Formålet klart formulert?
• Ja
• Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?
• Ja
• Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?
• Ikke diskutert
• Tror du på resultatene?
• Ja
• Kan resultatene overføres til den generelle befolkningen?
• Studien omfatter kun potensielle nyredonorer hvilket vil si at de er relativt friske, og hverken veldig unge eller gamle. Deltagerne var også hovedsakelig hvite (92%). Det gjør det vanskelig å overføre til den generelle befolkningen.
• Annen litteratur som styrker/svekker resultatene?</td></tr>
</table>

2000-2012	nefronnummer) til høyt mGFR og høyt eGFR. Multivariabel analyse ble utført for å bestemme gjensidig avhengighet mellom kliniske egenskaper og strukturelle funn med høy GFR (Tester med P-verdier <0,05 ble ansett som statistisk signifikante.	- Prevalensen av høy GFR ved bruk av aldersjustert grense var ca 5% på tvers av aldersgrupper - Generelt forhøyet GFR var assosiert med ung alder, mindre hypertensjon, større nyrestørrelse og høyere nefronantall - Aldersjustert korrigert mGFR var assosiert med ikke-hvit rase, høyere BMI, høyere fastende glukose, større nyrevolum, høyere 24 timers u-protein og u-albumin, høyere glomerulær tetthet og høyere antall nefroner - Aldersjustert ukorrigert mGFR var sterkere assosiert med mannlig kjønn, hypertensjon, høyere BMI, større nyrevolum, høyere 24 timer u-protein og u-albumin, større glomerulusvolum og tubules sammenliknet med aldersjustert korrigert mGFR - Alder-høyde-kjønn justert ukorrigert mGFR var generelt svakere assosiert med de faktorene som aldersjustert ukorrigert mGFR var assosiert med - Høy BMI og høy fastende glukose var assosiert med høy aldersjustert mGFR - U-albumin var assosiert med høy aldersjustert mGFR	• Litteraturen støtter funnene i denne studien da det er kjent at eGFR er dårlig til å vurdere normal til forhøyet GFR. Studier har også tidligere vist at korrigert GFR (justert for BSA) skjuler hyperfiltrasjon og at ukorrigert GFR dermed er bedre når man skal studere hyperfiltrasjon. **Hva diskuterer forfatterne som:** **Styrke:** - Nevnes ikke **Svakhet:** - Seleksjonsbias da utvalget er potensielle nyredonorer som er relativt friske individer. Kunne derfor ikke undersøke komorbiditeter som er kjent assosiert med hyperfiltrasjon (diabetes, CVD)

<table>
<tr><td colspan="3">Referanse: Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, et al. Glomerular hyperfiltration: A new marker of metabolic risk. Kidney International. 2007;71(8):816-21.</td><td colspan="2">Studiedesign: Tverrsnittstudie
Grade - kvalitet | Svak</td></tr>
<tr><td>Formål</td><td>Materiale og metode</td><td>Resultater</td><td colspan="2">Diskusjon/kommentarer/sjekkliste</td></tr>
<tr><td>Undersøke sammenhengen mellom nyrefunksjon og metabolsk syndrom i det tidlige stadiet

Konklusjon
Høy metabolsk risiko er assosiert med hyperfiltrasjon før åpenbare manifestasjoner på kardiovaskulær sykdom
Land
Polen
År data innsamling</td><td>Populasjon: 1572 unge, friske, hvite menn

Hovedutfall:
- Hyperfiltrasjon: estimert GFR basert på kreatinin og Cockcroft-Gault formelen. Hyperfiltrasjon ble definer som kreatinin-clearance over gjennomsnittet + 2 standarddeviasjoner
- Høy metabolsk risiko (≥ 3 kriterier)

Viktige konfunderende faktorer
Hyperfiltrasjon-definisjonen ble justert for: 1) kjønn, alder og høyde, 2) kjønn, alder, høyde og vekt
De statiskiske analysene ble justert for: 1) blodtrykk, glukose, HDL, triglyserider, BMI 2) model 1 + alder,</td><td>Hovedfunn
- Det var 6.9 ganger økt risiko for hyperfiltrasjon hos individer med MS sammenliknet med individer uten MS
- Det var en gradvis økning i absolutt estimert kreatinin clearance ved økende antall metabolske risikofaktorer
Bifunn
- Høyt blodtrykk og fedme var sterkest korrelert til hyperfiltrasjon av de metabolske risikofaktorene
- Hypefiltrasjon var ikke assosiert med hyperglykemi. Glukose-nivået var faktisk lavere hos de med hyperfiltrasjon kontra normofitratorerne
- Høy prevalens as store metabolske</td><td colspan="2">Sjekkliste:
• Formålet klart formulert?
• Ja
• Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?
• Ja.
• Kan resultatene overføres til den generelle befolkningen?
• Nei. Den inkluderer kun hvite, unge, friske menn.
• Annen litteratur som styrker/svekker resultatene?
• Det finnes andre studier som støtter funnet av assosiasjon mellom MS og hyperfiltrasjon, men samtidig finnes det studier som rapporterer om at det ikke er en signifikant assosiasjon.
• Hyperglykemi/diabetes har vært assosiert med hyperfiltrasjon i flere tidligere studier, hvilket er motsatt av det som ble observert i denne studien

Hva diskuterer forfatterne som:
• Styrke:
• Epidemiologisk representativt utvalg av individer
• Nøye klinisk fenotyping</td></tr>
</table>

Ikke oppgitt	alkoholinntak, røyking og log insulin serumkonsentrasjon
	Statistiske metoder:
	Ikke oppgitt statistisk program.
	Kji-kvadrattest ble brukt til å analysere assosiasjonen mellom to dikotome kvalitative parametre.
	Pearsons lineære korrelasjon ble brukt til å undersøke korrelasjon mellom to kvantitative variabler.
	Crude odds ratio for hyperfiltrasjon ble estimert vha binær logistisk regresjon. Justert odds ratio ble estimert ved multivariabel logistisk regresjon
	Faktoranalyse ble brukt for åidentifisere klynger av fenotyper som bidro til variasjonen.
	Statistisk signifikans var satt til P<0.05
		risikofaktorer blant tilsynelatende friske unge menn	• Grunnet at studiepopulasjonen er unge, friske menn er det ingen potensiell bias som skyldes komobiditeter eller medikamenter
			• **Svakhet:**
			  • Vekt var en del av formlene brukt til å estimere kreatinin-clearance og BMI, følgelig kan sammenhengen mellom estimert nyrefunksjon og overvekt, i det minste til en viss grad, forklares med de matematiske likhetene i ligningene.
			  • Indirekte mål på nyrefunksjon (eGFR)
			  • Brukte ikke midjeomkrets som mål på fedme, kun BMI
			  • Fordi det var en tverrsnittstudie kan den ikke brukes til å fastslå kausalitet

<table>
<tr><td colspan="3">Referanse: Stefansson VTN, Schei J, Solbu MD, Jenssen TG, Melsom T, Eriksen BO. Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population. Kidney International. 2018;93(5):1183-90.</td><td colspan="2">Studiedesign: Pasientserie
Grade-kvalitet: Middels</td></tr>
<tr><td>Formål</td><td>Materiale og metode</td><td>Resultater</td><td colspan="2">Diskusjon/kommentarer/sjekkliste</td></tr>
<tr><td>Er BMI, midjeomkrets, midje-hofte-ratio og metabolsk syndrom risikofaktorer for akselerert fall i GFR.
Konklusjon
Metabolsk syndrom, men ikke BMI, midje-hofte-ratio eller midjeomkrets, var en uavhengig risikofaktor for akselerert aldersrelatert GFR fall i den generelle befolkningen
Land
Norge
År data innsamling</td><td>Populasjon
1627 mennesker fra den generelle befolkningen i Tromsø med alder 50 til 62 år uten kjent hjerte-karsykdom, nyresykdom eller diabetes.

Hovedutfall
Årlig fall i mGFR og eGFR fra baseline til follow up (decline-rate)

Viktige konfunderende faktorer
Justering ble gjort for følgende uavhengige variabler i forskjellige modeller: alder, kjønn, høyde, røyking, systolisk og diastolisk blodtrykk, puls, spesifikke blodtrykksmedisiner, kolesterolsenkende medisiner, NSAIDs-bruk, fastende</td><td>Hovedfunn
- Gjennomsnittlig mGFR fall var 0.95 ml/min/år
- Metabolsk syndrom medførte 0.30 ml/min/år raskere fall i mGFR enn individer uten metabolsk syndrom (signifikant)
- BMI, midjeomkrets og midje-hofte-ratio predikerte ingen signifikant endring i aldersrelatert mGFR-fall
Bifunn
- Assosiasjonen mellom MS og raskere GFR fall var hovedsakelig drevet av triglyserid-kriteriet, hvilket var assosiert med et fall på 0,36 ml/min/år analysert separat
- Ingen andre av de individuelle komponenetene av MS enn triglyserider var</td><td colspan="2">Sjekkliste:
• Er formålet klart formulert?
  • Ja
• Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? (selesksjonsbias)
  • Ja
• Var inklusjonskriteriene klart definert?
  • Ja
• Var responseraten høy nok?
  • 19% ble tapt i observasjonstiden. Det var kun små forskjeller i karakteristika mellom deltakere som var inkludert og de 19% som falt av.
• Ble det brukt objektive kriterier for å vurdere/validere endepunktene? (Classfifc. Bias)
  • Ja
• Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design?
  • Ingen signifikant interaksjon mellom kjønn BMI, WC, WHR, MS eller komponentene av MS
• Var registreringen prospektiv?
  • Ja
• Var oppfølgningen lang nok?
  • Median observasjonstid var 5.6 år</td></tr>
</table>

RENIS-T6/Tromsø 6 2007-2009
 	
RENIS-FU 2013-2015
	glukose, triglyserider, HDL og LSL, albumin-kreatinin-ratio
	
	Statistiske metoder: STATA 14.2
	Analyse av studiepopulasjonens karakteristika:
	Pearson kji-kvadrat test
	Welch t-test
	Mann-Whitney U-test
	
	Assosiasjon mellom prediktorer og decline-rate:
	Multivariabel justert lineær regresjon
	Ikke lineære sammenhenger ble analysert vha generaliserte additive modeller
	
	Statistisk signifikans var satt til $P < 0.05$
		assosiert med økt fall i GFR når de ble uttrykt som dikotome variabler
		- Høyere HDL-kolesterol var lineært assosiert med 0.58 ml/min/år raskere gjennomsnittlig fall i mGFR
		- Når man økte cut-off for midjeomkrets i definisjonen av MS til > 102 hos menn og > 88 hos kvinner utvasket dette assosiasjonen mellom MS og GFR-fall som ikke lenger ble signifikant
		- MS var assosiert med økt fall i gjennomsnittlig eGFR basert på kreatinin, men ikke cystatin C
			• **Var oppfølgningen tilstrekkelig for å nå endepunktene? (attrition/follow-up bias)**
			  • Ja
			• **Stoler du på resultatene?**
			  • Ja
			• **Kan resultatene overføres til praksis?**
			  • Ja
			• **Annen litteratur som støtter resultatene?**
			  • 5 tidligere studier har funnet en assosiasjon mellom økt BMI eller WC og gjennomsnittlig eGFR-fall. Kun én av dem fant en assosiasjon i sin fulljusterte model
			  • Høye triglyseridnivåer er kjent assosiert med økt risiko for CKD
			  • Når studien ble skrevet fantes det ingen andre studier på MS og endring i aldersrelatert GFR
			  • HDL er kjent for å være inverst assosiert med CKD, hvilket går i mot funnene i denne studien. Men, en U-formet sammenheng mellom HDL og risiko for CKD har blitt beskrevet før hvilket kan forklare sammenhengen som ble sett i denne studien.
			  • Det er varierende funn ved undersøkelse av indivder som er «metabolsk usunne» og fall i GFR. Noen studier finner ingen økt risiko for fall i GFR, mens andre gjør det.
			
			Hva diskuterer forfatterne som:
			  • **Styrke:** bruk av mGFR som mål på nyrefunksjon, eksklusjon av individer med hjerte-karsykdom, diabetes og nyresykdom – hindrer konfundering, kohorten er en aldersgruppe som er utsatt for tidlige stadier av kroniske sykdommer
			  • **Svakhet:** studiedesignet er observasjonelt og kn ikke brukes til å fastsette kasualitet**.** Kun hvite

			mennesker. Bruk av BMI og WHR som antropometriske mål for kroppsfett i stedet for gullstandardmetoder som CT eller MR.

<table>
<tr><td colspan="3">Referanse: Stefansson VTN, Schei J, Jenssen TG, Melsom T, Eriksen BO. Central obesity associates with renal hyperfiltration in the non-diabetic general population: a cross-sectional study. BMC Nephrology. 2016;17(1):172.</td><td colspan="2">Studiedesign: Tverrsnittstudie
Grade-kvalitet Middels</td></tr>
<tr><td>Formål</td><td>Materiale og metode</td><td>Resultater</td><td colspan="2">Diskusjon/kommentarer/sjekkliste</td></tr>
<tr><td>Undersøke sammenhengen mellom fedme og hyperfiltrasjon (HF)

Konklusjon
Sentral fedme er assosiert med hyperfiltrasjon i den generelle befolkningen. Midje-hofte-ratio er muligens en bedre indikator på fedmerelatert nyreskade enn BMI og midjeomkrets.
Land
Norge
År data innsamling</td><td>Populasjon: 1555 middelaldrende innbyggere i Tromsø uten diabetes, hjerte/karsykdom eller nyresykdom.
Hovedutfall: mGFR over 90 percentilen justert for forskjellige uavhengige faktorer som ga to hyperfiltrasjon definisjoner
Viktige konfunderende faktorer
Hyperfiltrasjon-definisjonen ble justert for: 1) kjønn, alder og høyde, 2) kjønn, alder, høyde og vekt
De statiskiske analysene ble justert for: 1) alder, kjønn, røyking, systolisk og diastolisk blodtrykk, ulike antihypertensive medisiner, 2) model 1 + lav HDL-verdi, forhøyet triglyseridverdi g bruk av kolesterolsenkende medisin, 3) model 1 + fastende plasma-glukose, insulinnivå og HOMA-IR, 4) sammenfatning av alle variablene i modell 1-3
Statistiske metoder: STATA MP 14.0
Karakteristika ved studiepopulasjonen: pearson kji-kvadrattest, welchs t-test og Mann-Whitney U-test.
Sammenhengen mellom hyperfiltrasjon og fedme: Multippel logistisk regresjon</td><td>Hovedfunn
- Kun midje-hofte-ratio var assosiert med hyperfiltrasjon uavhengig av hvilken definisjon for HF som ble brukt
- Hypefiltrasjons-definisjonen justert for kjønn, alder og høyde var signifikant assosiert med alle fedme-variablene
- Hyperfiltrasjon justert for vekt i tillegg var kun signifikant assosiert med hofte-midje-ratio
Bifunn
- Det var en tydelig sammenheng mellom høyere midje-hofte-ratio og høyere GFR
- Lineær regresjon med absolutt GFR var signifikant assosiert</td><td colspan="2">Sjekkliste:
• Formålet klart formulert?
• Ja
• Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?
• Ja. Det var ingen signifikant interaksjon mellom fedme-målene og kjønn, usunn lipidprofil, RHF-variabler eller mGFR
• Kan resultatene overføres til den generelle befolkningen?
• Ikke nødvendigvis, da studien kun inkluderer middelaldrende kaukasiere
• Annen litteratur som styrker/svekker resultatene?
• Justering av GFR for BSA har vist i tidligere studier å maskere det positive forholdet mellom BMI og mGFR, det er å tråd med funnene i denne studien
• Hofte-midje-ratio er påvist også i andre studier å være like god som eller bedre enn BMI som prediktor for femde-relatert sykdom, inklusive kronisk nyresykdom

Hva diskuterer forfatterne som:
• Styrke: presise målinger av GFRi form av iohexol-målinger. Eksklusjon av</td></tr>
</table>

2007 til 2009	med RHF som avhengig dikotom variabel og ulike indikatorer for fedme som uavhengig variabel Sammenhengen mellom GFR som kontinuerlig variabel og fedme: Multippel lineær regresjon med absolutt GFR og GFR justert for BSA som avhengig variabel Interaksjonsnalayse Statistisk signifikans var satt til $P < 0.05$	med fedme-variablene, men ved bruk av GFR justert for BSA var det ingen signifikante sammenhenger	individer med kjent diabetes, hjerte/karsykdom og nyresykodm hindrer konfundering. • **Svakhet:** studiedesignet er tverrsnittstudie og kan derfor ikke påvise kausalitet. Studiepopulsjonen er middelaldrende kaukasiere, hvilket kan påvirke overføringsevnen til andre populasjoner. Fedme ble målt indirekte med antropometriske data i setdet for bruk av gullstandardmetoder som CT og MR.