

High-intensity exercise attenuates the association between fasting glucose and renal hyperfiltration. A sex-specific population study.

Short title: Renal hyperfiltration and physical exercise

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Abstract

Background: Physical exercise may reduce the risk of chronic kidney disease, but how it does so is unknown. Abnormally elevated glomerular filtration rate (GFR), or hyperfiltration, is a proposed mechanism for kidney injury in diabetes, prediabetes, and obesity. We investigated whether lack of physical exercise is associated with hyperfiltration, and if exercise influences the positive association between fasting glucose and measured GFR.

Study Design: Cross-sectional study

Setting & Participants: A representative sample ($n = 1506$; aged 50–62 years) of the general population who participated in the Renal Iohexol Clearance Survey, part of the sixth Tromsø Study (RENIS-T6). Participants were without diabetes, cardiovascular disease, or kidney disease.

Predictor: Fasting glucose and leisure-time physical exercise

Outcomes: Measured GFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$) and hyperfiltration defined as GFR above the 90th percentile after adjusting for sex, age, weight, height, and use of renin–angiotensin system inhibitors

Measurements GFR was measured as single-sample plasma iohexol-clearance. Leisure-time physical exercise was assessed by a self-administered questionnaire.

Results: High-intensity exercise reduced the adjusted odds ratio of hyperfiltration in men (0.5 ; $P < 0.01$) but not in women. In both sexes, high-intensity exercise eliminated the positive association between fasting glucose and GFR. One mmol/L ($18 \text{ mg}/\text{dL}$) increase in glucose was associated with 7.3 and $6.2 \text{ mL}/\text{min}/1.73 \text{ m}^2$ higher GFR in men and women respectively ($P < 0.001$), but only in individuals who never exercised or exercised with low intensity (interaction, $P < 0.001$).

Limitations: Only middle-aged Caucasian individuals were investigated.

Conclusions: Physical exercise reduced the odds ratio of hyperfiltration in men and modified the effect of glucose on GFR of both sexes in an adult population without diabetes. The effect of exercise was exercise-intensity dependent. Longitudinal studies are needed to address the long-term effect of exercise on renal function.

Index words: Physical exercise, glomerular filtration rate, hyperfiltration, hyperglycemia and epidemiology.

Introduction

Chronic kidney disease (CKD) is common worldwide, and the global burden of end-stage renal disease is growing.¹ Obesity, hypertension, and diabetes are major risk factors for CKD, but understanding is limited about how to prevent CKD at the population level.

Epidemiological studies strongly suggest that physical exercise reduces the risk of CKD,²⁻⁵ but the mechanisms of a possible protective effect of exercise on CKD risk are unknown.

Abnormally elevated glomerular filtration rate (GFR), or renal hyperfiltration, has been proposed as a mechanism that contributes to glomerular injury and albuminuria and subsequently to CKD.⁶ Renal hyperfiltration is common in early diabetes and in obesity and has been associated with generalized vascular dysfunction.⁷⁻⁹ Recently, we found that hyperfiltration was associated with impaired fasting glucose, a condition present in some 30% of adults in the United States.^{10;11} Physical exercise, as opposed to hyperglycemia, confers several benefits in terms of vascular function that also could influence GFR,^{12;13} however, the effect of physical exercise on renal function is difficult to study when GFR is estimated using creatinine or cystatin C. Estimated GFR (eGFR) is imprecise in the normal and upper range of GFR and could be biased by metabolic factors or creatinine production, which exercise also affects.¹⁴ To overcome these limitations, we measured GFR with single-sample iohexol clearance in a representative sample of a middle-aged, general population without diabetes. Our aims were to investigate whether physical exercise is associated with a reduced risk of hyperfiltration, and whether physical exercise modifies the effect of fasting glucose on measured GFR (mGFR).

Methods

Participants

The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) was conducted from November 2007 to June 2009 as a part of the population-based sixth Tromsø study (Tromsø 6).¹⁵ Tromsø 6 included an age-stratified random sample of 12,984 inhabitants of the municipality of Tromsø in Northern Norway (current population 65,000). Among those invited to participate were 40% of all inhabitants between the ages of 50–59 years and all inhabitants between 60–62 years. In these age groups, 3564 (65%) completed the main part of Tromsø 6, which included a physical examination and a self-administered questionnaire. Of these, we excluded 739 who reported a previous myocardial infarction, angina pectoris, stroke, diabetes mellitus, or renal disease (Figure 1). The remaining 2825 persons were invited to participate in RENIS-T6, and 2107 (75%) responded positively. Seventy-seven persons were excluded because of allergies to contrast media, iodine, or latex, or for other reasons, and forty-eight persons did not appear at their appointments. Among the remaining 1982 persons, we included 1632 individuals according to a predetermined target size and stratified by sex and age group. Five participants were excluded because the iohexol-clearance measurements were technical failures, leaving 1627 persons in the RENIS-T6 cohort. The characteristics of the cohort were comparable with the total group of eligible recruits ($n = 2825$), as previously reported.¹⁶

For the present investigation, we excluded persons with fasting plasma glucose ≥ 126 mg/dL or HbA_{1c} $\geq 6.5\%$, who were considered to have diabetes,¹⁷ and persons with iohexol clearance < 60 mL/min/1.73 m², who were considered to have CKD.¹⁸

The study was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee of Northern Norway. All participants provided informed written consent.

Assessment of physical exercise

The self-administered questionnaire included questions about physical exercise during leisure time. We used the three questions about frequency, intensity, and duration of leisure-time physical exercise (Table 1). These questions were recently validated and found to perform well in a study in which physical fitness was assessed by measurement of maximal oxygen consumption ($\text{VO}_{2\text{max}}$).¹⁹

Measurements

All study participants met between 8:00–10:00 at the Clinical Research Unit at the University Hospital of Northern Norway, after an overnight fast. Participants had been instructed to avoid large meals of meat and non-steroid anti-inflammatory drugs for 2 days before the investigation. They had also been asked to drink 2–3 glasses of water before their arrival. Smokers were instructed to abstain from smoking in the preceding 8 hours. After arrival, participants rested in an armchair for 2 minutes. Blood pressure was measured three times at one-minute intervals with an automatic device (A&D model UA-799). The average of the last two readings was used in the analyses. Body weight was measured and information on current medication obtained.

A Teflon catheter was placed in an antecubital vein and fasting serum samples were drawn for glucose, creatinine, triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol measurements, and analyzed the same day. Serum samples for fasting insulin were frozen at -80°C . Five milliliters of iohexol (Omnipaque, 300 mg I/ml, Amersham Health, London, UK) were injected and the syringe weighed before and after injection. The venous catheter was flushed with 30 ml of isotonic saline. The optimal time for measuring iohexol concentration after injection was calculated by Jacobsson's method based on the GFR estimated from creatinine.²⁰ The serum iohexol concentration was measured by high-

performance liquid chromatography as previously described by Nilsson-Ehle.²¹ The analytical coefficient of variation during the study period was 3.0%. GFR was calculated as described by Jacobsson.²⁰ Further details about the iohexol-clearance measurements have been published previously.¹⁶

Creatinine analyses were performed on the Hitachi Modular model P800 using an enzymatic method that was standardized against isotope dilution mass spectroscopy (CREA Plus, Roche Diagnostics, GmbH, Mannheim, Germany). Cystatin C was measured by particle-enhanced turbidimetric immunoassay using reagents from Gentian (Gentian, Moss, Norway) on a Modular E analyzer (Roche Diagnostics). GFR was estimated from creatinine or cystatin C using the recalibrated four-variable Modification of Diet in Renal Disease (eGFR_{MDRD}) equation, the Chronic Kidney Disease Epidemiology Collaboration (eGFR_{CKD-EPI}) equation, and Rule's cystatin C based equation of 2006 (Table 2).²²⁻²⁴

Serum glucose, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol concentrations were measured on a Modular P800 (Roche Diagnostics). HbA_{1c} was measured in the main part of Tromsø 6 with a liquid chromatographic method (Variant II instrument, Bio-Rad Laboratories, Hercules, CA, USA). The insulin concentration was measured with an ELISA kit (DRG Instruments, Marburg, Germany). The intra- and inter- assay coefficients of variation were 4.7% and 6.3%, respectively. Insulin resistance was expressed by the homeostasis model assessment (HOMA-IR), which was calculated by multiplying fasting glucose (mmol/l) by fasting insulin (mU/l), and dividing the result by 22.5.²⁵

Ambulatory blood pressure was measured from after the measurement of iohexol clearance to the next day. Blood pressure was measured using the appropriate cuff size by Spacelab 90207 (Spacelab.inc; Redmond, Wash., USA) at 20-minute intervals from 08:00 to 22:00 and at 45-minute intervals from 22:00 to 08:00. The registration was considered valid in accordance with criteria adopted from the International Database on Ambulatory Blood

Pressure in Relation to Cardiovascular Outcome (also known as IDACO) study.²⁶ Persons with invalid measurements had their measurements repeated as soon as possible.

Statistical methods

Characteristics of the participants are presented according to three groups of physical exercise; those who never exercised, those who exercised with low intensity and those who exercised with high intensity. Mean values, or geometric means in cases of skewed data, were adjusted for age and sex. Linear and quadratic trends across groups were tested by analysis of covariance for mean values and multiple logistic regression for dichotomous variables.

Renal hyperfiltration was defined as measured absolute GFR (in mL/min) above the 90th percentile after adjusting for sex, age, weight, height, and angiotensin-converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) use.¹⁰ This was done by selecting all participants above the 90th percentile in the distribution of residuals from a multiple linear regression analysis in which we used the logarithm of absolute GFR as a dependent variable and sex, ACE-i or ARB use, and the logarithms of age, weight, and height as independent variables. Physical exercise was categorized according to four groups of frequency, three groups of intensity, and three groups of duration. Spearman's rank correlation coefficient was used to test the correlations between frequency, duration, and intensity of exercise.

The association between hyperfiltration (yes/no) and categories of exercise was assessed by multiple logistic regression, stratified by sex, and adjusted for age, weight, height, current smoking, ambulatory diastolic blood pressure, and current ACE-i or ARB use.

To test whether physical exercise modified the effect of fasting glucose on GFR, we performed multiple linear regression analysis with GFR expressed in mL/min/1.73 m² as the dependent variable and fasting glucose as the independent variable, stratified by category of exercise and sex. We adjusted for the following known or possible determinants of GFR: age,

weight, height, current smoking, ambulatory diastolic blood pressure, and current ACE-i or ARB use. We also tested for a possible interaction between fasting glucose and category of exercise on GFR. Similarly, to test whether exercise modified the association between glucose and hyperfiltration, we performed logistic regression analysis, with hyperfiltration (yes/no) as the dependent variable and glucose as the independent variable, stratified by category of exercise and sex. We adjusted for age, weight, height, current smoking, ambulatory diastolic blood pressure, and current ACE-i or ARB use. A possible interaction between category of exercise and glucose on hyperfiltration was tested. To assess the independent effects of exercise frequency, intensity, and duration, we also repeated analyses in which all three variables were included in the same model.

Stata software version 11 (Stata Corp., College Station, TX, USA) was used for the statistical analyses. Statistical significance was set at $P < 0.05$.

Results

The RENIS-T6 cohort consisted of 1627 persons, aged 50 to 62 years, and without self-reported diabetes, cardiovascular disease, or kidney disease (Figure 1). Thirty-three participants who had diabetes according to their fasting serum glucose or HbA1c, 34 who had $mGFR < 60 \text{ mL/min/1.73 m}^2$, and 54 whose information was missing on the exercise questionnaire were excluded (Figure 1). Accordingly, 1506 were investigated in the present study.

Table 2 shows the reported frequency, intensity, and duration of exercise separately for women and men. Because few individuals reported the highest category of intensity (exhausted), we merged the two upper intensity categories into one high-intensity group. Frequency and intensity of exercise were correlated ($r = 0.30$, $P < 0.001$), as were exercise duration and intensity ($r = 0.33$, $P < 0.001$), and duration and frequency ($r = 0.15$, $P < 0.001$).

Those who reported high-intensity exercise had a median score for exercise frequency of “2–3 times per week.”

Table 3 shows the age- and sex-adjusted characteristics of the participants according to exercise intensity. More intensive exercise was associated with more frequent exercise ($P < 0.001$), a lower percentage of smoking ($P < 0.001$), lower HDL cholesterol ($P < 0.01$), lower ambulatory heart rate ($P < 0.001$), and lower GFR estimated from creatinine-based equations (eGFR_{cre}) ($P < 0.01$). Measured GFR or GFR estimated by cystatin C (eGFR_{cys}), however, did not differ between exercise levels.

Table 4 gives the sex-specific associations between hyperfiltration (yes/no) and physical exercise, adjusted for age, height, weight, current smoking, ambulatory diastolic blood pressure, and the use of ACE-i or ARB. High-intensity exercise reduced the odds ratio of hyperfiltration in men but not in women (Table 4). The effect of exercise intensity on hyperfiltration in men remained similar and significant after adjustment for exercise frequency and duration (not shown). The interaction between sex and intensity of exercise on hyperfiltration was statistically significant when both sexes were analyzed in the same model ($P = 0.02$). Exercise frequency tended to reduce the odds of hyperfiltration in women, but the linear trend was not statistically significant (Table 4).

Table 5 shows the association between fasting glucose and mGFR or eGFR, stratified by intensity of exercise and sex. Fasting glucose was associated with a markedly increased mGFR in participants who never exercised or exercised with low intensity ($P < 0.001$), but not in those who exercised with high intensity. The interaction between fasting glucose and category of exercise on mGFR was significant in both men and women ($P < 0.05$). Similar but attenuated results were found for eGFR_{cys}, while no associations were found between fasting glucose and eGFR_{cre} in either exercise group (only shown for eGFR_{CKD-EPI}). The estimates remained unchanged for mGFR and eGFR in both sexes after additional adjustment

for HOMA-IR, HDL cholesterol, triglycerides, body mass index and ambulatory resting heart rate (not shown). Exercise frequency or exercise duration did not modify the effect of glucose on mGFR (not shown).

A similar pattern of effect modification by exercise was found on the association between glucose and hyperfiltration (Table 6). For men and women, fasting glucose increased the odds ratio of hyperfiltration in the never- or low-intensity exercise groups, but not in the high-intensity group (Table 6). However, the interaction between category of exercise and glucose on hyperfiltration did not reach statistical significance when all participants were analyzed in the same model ($P = 0.25$).

We repeated all analyses when persons with $\text{mGFR} < 60 \text{ mL/min/1.73 m}^2$ and persons with diabetes according to their fasting glucose or HbA_{1c} were included. These analyses yielded similar results.

Discussion

In the present study, we found that performing high-intensity exercise during leisure time reduced the odds ratio for hyperfiltration in men but not in women. Furthermore, high-intensity exercise eliminated the effect of fasting glucose on mGFR in both sexes. An elevation in fasting glucose was associated with a markedly higher mGFR, but only in individuals who reported that they never exercised or exercised with low intensity. There was also a strong tendency towards an increased effect of glucose on hyperfiltration (yes/no) in both men and women who never exercised or exercised with low intensity.

To our knowledge, this work is the first population-based study on the cross-sectional relationship between physical exercise and mGFR. Previous studies have reported the association between physical activity and eGFR, but the results have been divergent. In the third National Health and Nutrition Examination Survey (NHANES III), frequency of

physical activity was associated with lower eGFR_{cre}, while physical activity calculated as metabolic equivalents was associated with increased eGFR_{cre}.²⁷ In that study, however, GFR was estimated using the Cockcroft-Gault equations and not adjusted to body surface area. Another study reported higher baseline eGFR_{cys} in physically active older adults but not higher eGFR_{cre}.⁴

In the present study, physical exercise was associated with lower eGFR_{cre} but not lower eGFR_{cys} or mGFR, after adjusting for age and sex. In multiple regression, the association between glucose and GFR, and the effect modification by exercise, was attenuated with eGFR_{cys} and not detected by eGFR_{cre}. These findings demonstrate the pitfalls of studying the association between physical exercise or hyperglycemia and eGFR_{cre}. Physical exercise is likely to increase muscle mass, which increases serum creatinine and thus lowers eGFR_{cre}. Cystatin C is also influenced by non-GFR determinants, particularly obesity, smoking and triglycerides.²⁸ However, cystatin C may be less influenced by physical exercise and may have better ability to detect changes in GFR provoked by hyperglycaemia.²⁹

In longitudinal studies, physical activity has been shown to protect against elevated urinary albumin excretion (UAE) or renal function decline in diabetes.^{30;31} Similar findings emerged from the following three studies of a general population: In a 12–16-year follow-up of 9082 US adults (NHANES II), inactive individuals had an increased risk of end-stage renal disease or CKD-related death, compared to very active individuals, also after adjusting for blood pressure, obesity, and diabetes.² In a previous Tromsø study, initiation of hard physical activity ≥ 1 hour per week reduced the risk of increased UAE in men but not in women.³ In the Cardiovascular Health Study, high-intensity exercise, but not moderate- or low-intensity exercise, reduced the hazard ratio for rapid kidney function decline (eGFR_{cys}) during 7 years of follow-up of older adults.⁴ In the latter study, no significant interaction with sex was found.

However, in the AusDiab study of 6318 adults followed for 5 years, physical activity was not associated with incident CKD, defined as de novo albuminuria, eGFR_{cre} decline >10%, or final eGFR_{cre} < 60 mL/min/1.73 m².³² This study did not report sex-specific analyses and did not differentiate between low- and high-intensity exercises.

In the present study, high-intensity exercise reduced the odds ratio of hyperfiltration in men, independent of possible confounders like body mass index and blood pressure. No association was found between exercise and hyperfiltration in women. Because hyperfiltration has been associated with the development of microalbuminuria,^{7;33} the current finding may suggest an explanation for why hard physical activity in a previous study predicted reduced UAE progression in men but not in women.³ Possible mechanisms for this sex disparity are unknown. Subjective interpretation of exercise questions, which causes misclassification, could differ between men and women. However, it is unlikely that such misclassification could be large because intensive exercise tends to be better reported than less-intensive exercise.^{34;35} Sex-specific risk factors for early kidney dysfunction have been reported previously. In a study of the general Dutch population, increasing age, blood pressure, and plasma glucose were stronger predictors of increased UAE in men than in women.³⁶

The second main finding of the present study was that high-intensity exercise annulled the positive association between fasting glucose and GFR and possibly between glucose and hyperfiltration in men and women. Animal experiments support that hyperfiltration combined with hyperglycemia may induce podocyte stress, podocyte injury, and cell apoptosis.³⁷ Whether hyperfiltration or elevated GFR caused by borderline hyperglycemia is associated with renal injury in humans has not been investigated in longitudinal studies. However, increasing levels of fasting glucose, within the non-diabetic range, have been associated with the progression of albuminuria and decline in renal function in both sexes in the general population.^{38;39} Also, in the general population, an inverse U-shaped association was found

between plasma glucose and eGFR, possibly indicating a phase of hyperfiltration that precedes GFR decline.⁴⁰

The present study suggests that elevated fasting glucose could convey different renal risk in individuals who never exercise or exercise with low intensity compared to those who exercise with high intensity. By analogy, a previous study suggested differential risk of obesity relative to CKD between physically inactive persons versus moderately or very active persons.⁵ The modifying effect of exercise on the relationship between borderline hyperglycemia and GFR in the present study was not mediated by obesity or ambulatory blood pressure, as we adjusted for both. We are not aware of any longitudinal reports on the effect of exercise on renal injury caused by hyperglycemia.

In the current work, the modifying effect of exercise on the association between glucose and mGFR and the reduced odds of hyperfiltration in men clearly depended on exercise intensity. Physical exercise improves endothelial function, decreases inflammation, and reduces activation of the renin–angiotensin–aldosterone system and renal sympathetic activity,^{12;13;41} all factors that could potentially influence vascular tone and thus affect GFR. Moreover, emerging evidence indicates that the intensity of exercise is important for obtaining benefits for the vasculature and cardiovascular disease.^{12;41-43} Randomized controlled trials, one involving participants with impaired glucose tolerance and one involving patients with type 2 diabetes, have shown that high-intensity exercise but not low-intensity exercise decreased levels of inflammatory biomarkers^{30;44} and albuminuria.³⁰

In accordance with previous studies, we found lower heart rate and higher HDL cholesterol in the high-intensity exercise group. However, these metabolic factors, insulin resistance (HOMA-IR), and triglyceride levels had no influence on the exercise effect on the association between glucose and mGFR. We did not measure markers of inflammation or oxidative stress. Kidney disease in general, and particularly in diabetes, is clearly related to

increased inflammation and oxidative stress; however, whether inflammation or oxidative stress, which increases in hyperglycemia and is reduced by exercise, initiates hyperfiltration or renal damage remains controversial⁴⁵⁻⁴⁹.

The most important limitation of the present study was the cross-sectional design, which precludes conclusions about causality. Also, the study population consisted of middle-aged Caucasians only, and generalizations to other age groups or ethnicities should be made with caution. The data on physical exercise were based on questionnaires and not on objective measures of physical activity or fitness. However, the physical activity questionnaire in the present study was recently validated in a study of men in whom physical activity and fitness were assessed by accelerometer and $\text{VO}_{2\text{max}}$ ($\text{mL kg}^{-1} \text{min}^{-1}$).¹⁹ The questionnaire was found to be reliable and had validity equal to or better than the International Physical Activity Questionnaire.¹⁹ In contrast with many previous observational studies and in accordance with the updated recommendation of the American Heart Association, the present study included details on frequency, intensity, and duration of exercise.⁴² The main strength of our study is that GFR was measured with an exact method in a large population-based study.

Physical exercise reduced the odds ratio of hyperfiltration in men and modified the effect of glucose on mGFR in both sexes of a middle-aged general population without diabetes. The effect of exercise was intensity dependent and not mediated through body mass index, blood pressure, ambulatory resting heart rate, HDL cholesterol, triglycerides, or insulin resistance. Longitudinal studies are needed to investigate the effect of exercise on the risk of chronic kidney disease.

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Table 1. Response to questions about exercise in the sixth Tromsø Study.

EXERCISE	Women n = 748	Men n = 758	All n = 1506
EXERCISE FREQUENCY			
<i>How frequently do you exercise?</i>			
<input type="checkbox"/> Never, n (%)	20 (2.7)	36 (4.8)	56 (3.7)
<input type="checkbox"/> Less than once a week	88 (11.8)	151 (19.9)	239 (15.9)
<input type="checkbox"/> Once a week	137 (18.3)	197 (26.0)	334 (22.2)
<input type="checkbox"/> 2-3 times per week	332 (44.4)	282 (37.2)	614 (40.8)
<input type="checkbox"/> Almost every day	171 (22.8)	92 (12.1)	263 (17.5)
EXERCISE INTENSITY			
<i>If you exercise; how hard do you exercise?</i>			
<input type="checkbox"/> I take it easy without becoming breathless or sweaty	n = 730 336 (46.0)	n = 728 290 (39.8)	n = 1450 618 (42.6)
<input type="checkbox"/> I push myself so hard that I become breathless and sweaty	374 (51.2)	412 (56.6)	786 (53.9)
<input type="checkbox"/> I push myself to near-exhaustion	20 (2.7)	26 (3.6)	46 (3.16)
EXERCISE DURATION			
<i>If you exercise, for how long do you exercise?</i>			
<input type="checkbox"/> Less than 15 minutes	n = 700 16 (2.3)	n = 706 25 (3.5)	n = 1406 ^a 41 (2.9)
<input type="checkbox"/> 15-29 minutes	97 (13.9)	82 (11.6)	179 (12.7)
<input type="checkbox"/> 30-60 minutes	442 (63.1)	410 (58.1)	852 (60.6)
<input type="checkbox"/> More than 1 hour	145 (20.7)	189 (26.8)	334 (23.8)

Data are numbers and (%)

^a44 missing (did not answer the question)**Table 2.** Equations for estimating GFR

eGFR _{cys} ^a	$66.8 \times \text{cystatin C}^{-1.30}$
eGFR _{MDRD} ^b	$175 \times S_{cr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ [if female] $\times 1.272$ [if black]
eGFR _{CKD-EPI} ^c	$141 \times \min(S_{cr}/k, 1)^\alpha \times \max(S_{cr}/k, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ [if female] $\times 1.159$ [if black]

^a GFR estimated with Rules equation of 2006.^b GFR estimated by the Modification of Diet in Renal Disease equation^c GFR estimated by the Chronic Kidney Disease Epidemiology equationS_{cr} is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k, and max indicates the maximum of Scr/k

Table 3. General characteristics of the study population by category of leisure-time exercise intensity.

	Never exercise (n = 56)	Low-intensity exercise ^a (n = 618)	High-intensity exercise ^b (n = 832)	P value for trend
Age (years)	58.3 (57.3 - 59.3)	58.3 (58.0 - 58.6)	57.8 (57.5 - 58.1)	0.4
Male sex (%)	64	46	53	0.09 ^h
Current daily smoking (%)	57	28	13	< 0.001
Body mass index (kg/m ²)	26.9 (25.9 - 27.9)	27.5 (27.2 - 27.8)	27.0 (26.7 - 27.2)	0.9
Conventional SBP (mmHg)	127.8 (123.4 - 132.1)	129.6 (128.3 - 130.9)	129.5 (128.3 - 130.6)	0.5
Conventional DBP (mmHg)	83.3 (80.8 - 85.7)	83.1 (82.4 - 83.9)	83.7 (83.1 - 84.3)	0.7
Ambulatory SBP (mmHg)	123.9 (120.9 - 127.0)	123.5 (122.5 - 124.4)	122.9 (122.1 - 123.7)	0.5
Ambulatory DBP (mmHg)	76.3 (74.3 - 78.3)	76.5 (75.9 - 77.1)	76.6 (76.1 - 77.1)	0.8
Ambulatory heart rate (beats/min)	74.4 (72.1 - 76.6)	71.6 (70.9 - 72.2)	68.6 (68.0 - 69.2)	< 0.001
Total cholesterol (mg/dL)	212 (202 - 221)	219 (216 - 222)	218 (215 - 220)	0.2
LDL cholesterol (mg/dL)	136 (127 - 145)	143 (140 - 145)	141 (139 - 143)	0.3
HDL cholesterol (mg/dL)	54.5 (50.3 - 58.4)	58.0 (56.8 - 59.6)	60.3 (59.6 - 61.5)	< 0.01
Triglyceride level ^c (mg/dL)	102.7 (91.2 - 116.0)	97.4 (93.9 - 101.0)	91.2 (88.6 - 93.9)	0.06
Fasting glucose (mg/dL)	95.3 (93.3 - 97.5)	96.6 (96.0 - 97.3)	95.3 (94.8 - 95.8)	0.9
Fasting insulin level ^c (μU/mL)	8.5 (7.2 - 10.0)	8.6 (8.1 - 9.0)	7.7 (7.4 - 8.1)	0.3
HOMA-IR ^c (index)	2.0 (1.7 - 2.4)	2.0 (1.9 - 2.1)	1.8 (1.7 - 1.9)	0.3
Measured GFR ^d (ml/min/1.73 m ²)	93.8 (90.6 - 97.1)	92.7 (91.8 - 93.7)	91.9 (91.1 - 92.7)	0.3
eGFR _{MDRD} ^e (ml/min/1.73 m ²)	99.1 (95.0 - 103.3)	96.3 (95.0 - 93.4)	92.3 (91.3 - 93.4)	< 0.01
eGFR _{CKD-EPI} ^f (ml/min/1.73 m ²)	97.3 (95.0 - 99.5)	96 (95.4 - 96.7)	94.1 (93.5 - 94.7)	< 0.01
eGFR _{cys} ^g (ml/min/1.73 m ²)	91.6 (87.3 - 95.8)	91.6 (90.3 - 92.9)	93.3 (92.2 - 94.4)	0.4
Exercise > once/week (%)	0	42	75	< 0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostatic model assessment of insulin resistance.

Values are mean (95% confidence intervals), or geometric means in case of skewed data, or percentages, and adjusted by age and sex.

Differences between groups were tested by ANCOVA for mean values and logistic regression for proportions.

^aEasy exercise; without becoming breathless or sweaty. ^bHard exercise; becoming breathless and sweaty, or exhausted.

^cValues calculated as geometric means. ^dGFR measured by single-sample iohexol clearance and adjusted for body surface area.

^eGFR estimated by the Modification of Diet in Renal Disease equation. ^fGFR estimated by the Chronic Kidney Disease Epidemiology

Collaboration equation. ^gGFR estimated by Rules Cystatin C-based equation of 2006. ^h 0.002 for quadratic trend.

Note: Conversion factors for units: Cholesterol in mg/dL to mmol/L, × 0.02586; Triglyceride in mg/dL to mmol/L, × 0.01129; glucose in mg/dL to mmol/L, × 0.05551.

Table 4. Multivariable adjusted odds ratio for hyperfiltration

	Women			Men		
	Odds Ratio ^a	<i>P</i> value for trend	(95% CI)	Odds Ratio ^a	<i>P</i> value for trend	(95% CI)
Exercise frequency						
Never or less than once/week	Ref			Ref		
Once/week	0.8		(0.4 - 1.7)	0.9		(0.5 - 1.7)
2-3 times/week	0.4		(0.2 - 0.9)	0.9		(0.5 - 1.7)
Almost every day	0.7	0.2	(0.3 - 1.5)	0.7	0.4	(0.3 - 1.7)
Exercise intensity						
Low intensity ^b	Ref			Ref		
High intensity ^c	1.0	0.9 ^d	(0.6 - 1.7)	0.5	<0.01 ^d	(0.3 - 0.8)
Exercise duration						
< 30 min	Ref			Ref		
30-60 min	1.0		(0.5 - 2.2)	1.2		(0.6 - 2.5)
> 60 min	1.1	0.8	(0.5 - 2.7)	0.8	0.9	(0.4 - 2.0)

^aAdjusted for age, height, weight, current smoking, ambulatory diastolic blood pressure and ACE-i or ARB use.

^bEasy exercise; without becoming breathless or sweaty.

^cHard exercise; becoming breathless and sweaty or exhausted.

^d*P*=0.02 for the interaction between sex and exercise intensity on hyperfiltration when men and women were analyzed in the same model.

Table 5. Multiple linear regression analyses with measured GFR or estimated GFR as dependent variable and fasting glucose as independent variable, stratified by intensity of physical exercise.

Independent variable	Never exercise or low-intensity ^a exercise (n = 674)			High-intensity ^b exercise (n = 832)		
	Unadjusted estimate (95% CI) (mL/min/1.73 m ²)	P value	Adjusted ^c estimate (95% CI) (mL/min/1.73 m ²)	Unadjusted estimate (95% CI) (mL/min/1.73 m ²)	P value	Adjusted ^c estimate (95% CI) (mL/min/1.73 m ²)
Measured GFR						
<i>Women</i>						
Glucose (per 18 mg/dL)	3.0 (0.2, 5.8)	0.03	6.2 (3.4, 9.0)	-0.4 (-3.1, 2.3)	0.8	0.1 (-2.7, 2.9)
<i>Men</i>						
Glucose (per 18 mg/dL)	5.2 (2.0, 8.5)	0.002	7.3 (4.0, 10.6)	0.6 (-1.9, 3.1)	0.6	0.5 (-2.1, 3.1)
eGFR_{cys}						
<i>Women</i>						
Glucose (per 18 mg/dL)	-0.1 (-4.1, 3.9)	0.9	4.0 (0.1, 8.1)	-2.6 (-6.4, 1.2)	0.2	-0.02 (-4.0, 4.0)
<i>Men</i>						
Glucose (per 18 mg/dL)	3.2 (-0.5, 7.0)	0.09	4.7 (1.0, 8.4)	-0.6 (-3.8, 2.5)	0.7	1.0 (-2.2, 4.2)
eGFR_{CKD-EPI}						
<i>Women</i>						
Glucose (per 18 mg/dL)	-1.2 (-3.3, 1.0)	0.3	0.2 (-1.9, 2.4)	-1.2 (-3.3, 1.1)	0.3	-0.4 (-2.7, 1.8)
<i>Men</i>						
Glucose (per 18 mg/dL)	0.6 (-1.4, 2.5)	0.6	2.3 (0.4, 4.2)	-0.9 (-2.8, 0.9)	0.3	-0.1 (-1.9, 1.7)

Abbreviations: eGFR_{cys}, GFR estimated by Rule's cystatin C-based equation of 2006; eGFR_{CKD-EPI}, GFR estimated by the CKD-EPI equation.

^aEasy exercise; without becoming breathless or sweaty.

^bHard exercise; becoming breathless and sweaty or exhausted.

^cAdjusted for age, height, weight, current smoking, ambulatory diastolic blood pressure and ACE-i or ARB use.

^dP < 0.001 for interaction between fasting glucose and intensity of exercise on GFR when men and women were analyzed in the same model.

^eP = 0.034 for interaction between fasting glucose and intensity of exercise on GFR when men and women were analyzed in the same model.

Table 6. Multivariable adjusted odds ratio for hyperfiltration, stratified by intensity of physical exercise.

Independent variable	Never exercise or		High-intensity ^b	
	low-intensity ^a exercise (n = 674)	P value	Odds Ratio ^c (95% CI)	P value
Women				
Fasting glucose (per 18 mg/dL)	3.4	0.003	1.7 (0.7 to 4.0)	0.2 ^d
Men				
Fasting glucose (per 18 mg/dL)	2.1	0.04	1.2 (0.5 to 3.0)	0.7 ^d

^aEasy exercise; without becoming breathless or sweaty.

^bHard exercise; becoming breathless and sweaty or exhausted.

^cAdjusted for age, height, weight, current smoking, ambulatory diastolic blood pressure and ACE-i or ARB use.

^dP = 0.31 for interaction between fasting glucose and intensity of exercise on hyperfiltration when men and women were analyzed in the same model.

Figure 1. Inclusion of subjects in the Renal Iohexol-clearance Survey in Tromsø 6 (RENIS-T6) from the main part of the sixth Tromsø Study (Tromsø 6).

