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ORIGINAL ARTICLE

# The association of glucose metabolism and kidney function in middle-aged adults

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## ABSTRACT

**Background.** Previous clinical studies have shown that various measures of glucose metabolism are associated with a risk of chronic kidney disease in different populations, but results were not consistent. In this study we assessed measures of glucose metabolism and their association with kidney function in a population-based study.

**Methods.** The Netherlands Epidemiology of Obesity study is a population-based cohort study of middle-aged men and women. We categorized the study population according to glycaemic levels into normoglycaemia (reference group), pre-diabetes mellitus (pre-DM), known DM and newly diagnosed DM. Outcome variables were serum creatinine, estimated glomerular filtration rate (eGFR), glomerular hyperfiltration (defined as an eGFR >90th percentile; >102 mL/min/1.73 $m^2$) and micro-albuminuria. We examined the association between measures of glucose metabolism [fasting glucose, haemoglobin A1c (HbA1c), fasting insulin, glucose area under the curve (AUC), insulin AUC, Homoeostatic Model Assessment of Insulin Resistance (HOMA-IR), HOMA of $\beta$-cell function (HOMA-B) and disposition index] and measures of kidney function.

**Results.** Of the total population ($N = 6338$), 55% of participants were classified as normoglycaemic (reference), 35% as pre-DM, 7% as DM and 4% as newly diagnosed DM. Compared with the reference group, diagnosed and newly diagnosed DMs were associated with a slightly higher trend in eGFR {+2.1 mL/min/1.73 $m^2$ [95% confidence interval (CI) −0.2–4.4] and +2.7 mL/min/1.73 $m^2$ [95% CI −0.3–5.7], respectively}. A 1% higher HbA1c was associated with increased odds of hyperfiltration [odds ratio (OR) 1.41 (95% CI 1.06–1.88)]. Higher levels of fasting plasma glucose, AUC glucose and HOMA-B were associated with hyperfiltration. Fasting insulin, AUC insulin and HOMA-IR were not associated with hyperfiltration. The OR of microalbuminuria was 1.21 (95% CI 1.04–1.42) per mmol/L higher fasting glucose concentrations.

**Conclusions.** Both fasting and post-prandial glucose and HOMA-B, but not measures of insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with microalbuminuria.

**Keywords:** chronic renal failure, diabetes mellitus, diabetic kidney disease, diabetic nephropathy, type 2DM

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## INTRODUCTION

The global increase in obesity is a leading cause of the increased prevalence of pre-diabetes mellitus (DM) and type 2DM. A total of 40% of the patients with obesity had accompanying pre-DM [1], defined as a fasting glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or 2-h plasma glucose of 140–199 mg/dL (7.8–11.0 mmol/L) after a 75 mg oral glucose tolerance test or a haemoglobin A1c (HbA1c) level of 5.7–6.4% (39–47 mmol/mol), according to the American Diabetes Association (ADA) criteria [2]. Pre-DM is a clinically relevant condition, as ~45–50% of patients will develop type 2 DM within 10 years [3, 4] and pre-DM is associated with a higher risk of macrovascular and microvascular complications, such as nephropathy [5–8]. Importantly, the risk of chronic kidney disease (CKD) is directly related to glucose levels: in US patients with normoglycaemia, the prevalence of CKD is 3%, in patients with pre-DM it is 9% and in patients with (un)diagnosed DM it is 14% [9].

Postulated mechanisms by which pre-DM results in CKD are an increase in glomerular hyperfiltration, vascular permeability and/or endothelial dysfunction and inflammation [10]. Previous studies have shown that different measures of glucose metabolism [fasting glucose, HbA1c, fasting insulin, area under blood concentration curve (AUC), insulin AUC, Homoeostatic Model Assessment of Insulin Resistance (HOMA-IR), HOMA of $\beta$-cell function (HOMA-B) and disposition index] are associated with a risk of CKD. However, these studies were not consistent in all aspects. Some studies have shown that elevated post-prandial measures of glucose metabolism might contribute more to CKD than elevated fasting measures of glucose metabolism [11–16], while other studies have shown the opposite [17–19]. However, none of the studies assessed so many different measures of glucose metabolism and their association with kidney function in a single large cohort. Moreover, these studies did not assess glomerular hyperfiltration as well as microalbuminuria, although this is considered the earliest appearance of impaired kidney function in DM and has been linked with an increased risk of diabetic nephropathy [17, 20]. To date, it is unknown which measures of glucose metabolism are associated with both glomerular hyperfiltration and microalbuminuria.

In this study we examined the association between normoglycaemia, pre-DM, DM and newly diagnosed DM with CKD and markers thereof among a Dutch cohort of middle-aged adults. Furthermore, we examined the association between measures of glucose metabolism and the earliest appearance of impaired kidney function, microalbuminuria and glomerular hyperfiltration.

## MATERIALS AND METHODS

### Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based, prospective cohort study designed to investigate pathways that lead to obesity-related diseases. The NEO study includes 6671 individuals ages 45–65 years, with an oversampling of individuals with overweight or obesity. The study design and population are described in detail elsewhere [21]. This study is a cross-sectional analysis of the baseline measurements of the NEO study.

In short, men and women living in the greater area of Leiden (in the west of the Netherlands) were invited by letters sent by general practitioners and municipalities and by local advertisements. They were invited to respond if they were between 45 and 65 years of age and had a self-reported body mass index (BMI) of $\geq$27 kg/m$^2$. In addition, all inhabitants between 45 and 65 years of age from one municipality (Leiderdorp) were invited to participate, irrespective of their BMI, allowing for a reference distribution of BMI in the general population.

After consecutive exclusion of participants with missing data on diabetes medication ($n = 64$), fasting or post-prandial glucose ($n = 245$), fasting or post-prandial insulin ($n = 13$) and HbA1c concentrations ($n = 11$), 6338 participants were included in the present analyses.

The Medical Ethical Committee of the Leiden University Medical Centre (LUMC) approved the design of the study. All participants gave their written informed consent.

### Data collection

Participants were invited to a baseline visit at the NEO study centre of the LUMC after an overnight fast. Prior to this study visit, participants collected urine (morning spot) and completed a general questionnaire at home to report demographic, lifestyle and clinical information. On the questionnaire, participants reported ethnicity by self-identification in eight categories that we grouped into Caucasian (reference) and other. Tobacco smoking was reported in the three categories: currently, formerly and never smoked (reference). The highest level of education was reported in 10 categories according to the Dutch education system and grouped into high (including higher vocational school, university and post-graduate education) versus low education (reference). Participants reported their medical history of DM and cardiovascular diseases. Pre-existing cardiovascular disease was defined as myocardial infarction, angina, congestive heart failure, stroke or peripheral vascular disease. In addition, all use of medication in the month preceding the study visit was recorded. Family history of DM was reported as having any parent or sibling with or without DM (reference). Body weight was measured without shoes and 1 kg was subtracted from the body weight. BMI was calculated by dividing the weight in kilograms by the height in metres squared. Brachial blood pressure (BP) was measured in a seated position on the right arm using a validated automatic oscillometric device (Model M10-IT, Omron Health Care, Lake Forest, IL, USA). BP was measured three times with a 5 min rest between consecutive measurements. The mean systolic, diastolic and arterial [(2 $\times$ diastolic BP + systolic BP)/3] BPs were calculated.

### Fasting glucose, insulin measurements and mixed meal test

Fasting blood samples were drawn from the antecubital vein after the participant had rested for 5 min. Within 5 min after the first blood sample, participants drank a liquid mixed meal. This meal (total 400 mL) contained 600 kcal, with 16% of energy (En%) derived from protein, 50% from carbohydrates and 34% from fat. Subsequent blood samples were drawn 30 and 150 min after ingestion of the mixed meal. Fasting and post-prandial glucose and insulin concentrations were measured and from these HOMA-IR, HOMA-B and the disposition index were calculated. In Supplementary Information S1, a detailed overview of laboratory methods and calculations is given.

We categorized the study population in four different groups, according to glycaemic levels at baseline: normoglycaemia (reference), defined as a fasting glucose level <5.6 mmol/L and HbA1c <5.7% (39 mmol/mol); pre-DM, defined as a fasting

glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c of 5.7–6.4% (39–47 mmol/mol); diagnosed DM, defined as self-reported DM or the use of glucose-lowering medication; and newly diagnosed DM, defined as no self-reported DM and no use of glucose-lowering medication, but DM according to the ADA criteria, with a fasting glucose level ≥126 mg/dL (≥7.0 mmol/L) or plasma glucose level ≥200 mg/dL (≥11.1 mmol/L) after a mixed meal test or HbA1c ≥6.5% (48 mmol/mol) [2].

### Renal function and albuminuria

Serum creatinine (mg/dL) was used to calculate estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [22].

We defined glomerular hyperfiltration as an eGFR >90th percentile [17] (>102 mL/min/1.73 $m^2$). Urinary albumin was measured in an early-morning single urine void using an immunoturbidimetric assay and creatinine using a Jaffe kinetic compensated method between 1 September 2008 and 30 November 2010 and an enzymatic assay (isotope dilution mass spectrometry calibrated against Standard Reference Material 967) from 1 December 2010 until the end of the inclusion period. Because urinary creatinine concentrations are not affected by pseudochromogens they are exchangeable using either a Jaffe or an enzymatic method [23]. Microalbuminuria was defined as a urinary albumin:creatinine ratio (UACR) ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women [22].

### Statistical analyses

In the NEO study, individuals with a BMI >27 kg/$m^2$ are overrepresented due to the sampling frame applied. To correctly represent baseline associations in the general population [24], adjustments for the oversampling of individuals with a BMI ≥27 kg/$m^2$ were made by weighting all participants towards the BMI distribution of participants from the Leiderdorp municipality [25], whose BMI distribution was similar to the BMI distribution of the general Dutch population [26]. All results were based on weighted analyses. As a consequence, all results apply to a population-based study without oversampling of individuals with a BMI ≥27 kg/$m^2$. Because of the weighted analyses, percentages and proportions are given instead of absolute numbers of participants. Baseline characteristics are therefore expressed as mean [standard deviation (SD)] or percentage, stratified by groups of glucose metabolism.

Our first study aim was to examine the association between categorized glucose levels (normoglycaemia, pre-DM, DM and newly diagnosed DM) and CKD, and markers thereof. Outcome variables studied were serum creatinine, eGFR (CKD-EPI), glomerular hyperfiltration and UACR. A linear regression analysis was performed to calculate age- and sex-adjusted mean differences with 95% confidence intervals (CIs) in levels of serum creatinine, eGFR and albuminuria for the defined categories of glucose metabolism. The second study aim was to examine the associations between different measures of glucose metabolism (fasting glucose, HbA1c, fasting insulin, glucose AUC, insulin AUC, HOMA-IR, HOMA-B and disposition index) and measures of kidney function. For this analysis, we excluded 444 participants because of protocol violation during a mixed meal test. We performed linear regression for continuous outcomes and logistic regression analyses for binary outcomes (hyperfiltration or microalbuminuria). Participants who used oral glucose-lowering medication and/or insulin ($n = 335$) were excluded from the analyses where measures of glucose metabolism were used as independent variables. Analyses were adjusted for potential confounding due to age, sex, BMI, BP and smoking. In a sensitivity analysis, we additionally adjusted for antihypertensive agents, heart failure, cerebrovascular accident and myocardial infarction, though for these variables it may difficult to judge whether they act as a confounding factor or whether they are mediators for the glucose kidney function association. Analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA).

## RESULTS

### Characteristics according to different glycaemic categories

Of the total participants ($n = 6338$), 54.6% were classified as normoglycaemic (reference), 34.8% as pre-DM, 6.9% as DM and 3.8% as newly diagnosed DM, shown in Table 1. From the patients with known DM, 58.9% used oral glucose-lowering medication, 4.6% used insulin therapy, 13.6% patients used a combination of insulin and oral glucose-lowering medication and 23.0% used no glucose-lowering medication. Mean age was highest in participants with diagnosed DM (59 years). BMI was lowest in participants with normoglycaemia (25.4 kg/$m^2$) and highest in participants with diagnosed DM (30.8 kg/$m^2$). The presence of clinically relevant CKD, defined as eGFR ≤60 mL/min/1.73 $m^2$, was higher in participants with pre-DM (3.5%), DM (6.2%) and newly diagnosed DM (7.0%) than in the reference group (1.2%). Also, the presence of microalbuminuria was higher in participants with pre-DM (3.3%), DM (6.3%) and newly diagnosed DM (8.6%) than in the reference group (1.6%). More participants with pre-DM used angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) and statins compared with participants with normoglycaemia. Fasting and post-prandial measures of glucose metabolism according to glycaemic categories are provided in Table 2.

### Associations between different glycaemic categories and measures of kidney function

Table 3 shows the adjusted mean difference in eGFR between the four glycaemic categories. eGFR was similar in participants with normoglycaemia and pre-DM. Diagnosed and newly diagnosed DMs were associated with a higher eGFR [+ 2.1 mL/min/1.73 $m^2$ (95% CI −0.2–4.4) and +2.7 mL/min/1.73 $m^2$ (95% CI −0.3–5.7), respectively]. Pre-DM and (newly) diagnosed DM were associated with increased microalbuminuria (Table 4). The odds ratio (OR) for microalbuminuria was 1.6 (95% CI 0.9–2.7) in participants with pre-DM and 2.8 (95% CI 1.5–5.4) in participants with newly diagnosed DM compared with normoglycaemia.

### Associations of different measures of glucose metabolism, hyperfiltration and microalbuminuria in the total study population

Higher fasting glucose concentrations were associated with higher eGFR (Figure 1A). Microalbuminuria was associated with higher fasting glucose levels: microalbuminuria was not seen with fasting glucose levels <4 mmol/L, while in participants with fasting glucose levels between 9 and <10 mmol/L, the percentage was almost 14% (Figure 1B).

We examined the associations between different measures of glucose metabolism, hyperfiltration and microalbuminuria (see Table 5). A 1% higher HbA1c level was associated with an OR for hyperfiltration of 1.41 (95% CI 1.06–1.88). Also, higher

**Table 1. Characteristics of the study population of the Netherlands Epidemiology of Obesity study[a]**

| Characteristics | Normoglycaemia (reference) | Pre-DM | DM | Newly diagnosed DM |
|---|---|---|---|---|
| Proportion of participants, % | 54.6 | 34.8 | 6.9 | 3.8 |
| Age (years), mean (SD) | 54.9 (5.4) | 57.4 (6.4) | 58.5 (7.3) | 57.6 (6.8) |
| Sex (male), % | 38 | 57 | 53 | 64 |
| BMI (kg/m$^2$), mean (SD) | 25.4 (3.5) | 27.8 (5.2) | 30.8 (8.0) | 29.7 (7.0) |
| BP (mmHg), mean (SD) | | | | |
| Systolic | 128.1 (15.0) | 134.2 (19.3) | 135.7 (23.5) | 137.2 (21.1) |
| Diastolic | 82.3 (9.1) | 84.7 (11.9) | 84.8 (13.4) | 88.1 (12.8) |
| Hypertension (yes), % | 30 | 42 | 47 | 56 |
| Tobacco smoking (never), % | 41 | 35 | 25 | 29 |
| Ethnicity (Caucasian), % | 95 | 95 | 90 | 94 |
| Waist circumference (cm), mean (SD) | 89.0 (11.0) | 97.5 (14.3) | 106.2 (19.1) | 103.3 (17.1) |
| Hip circumference (cm), mean (SD) | 102.3 (7.5) | 106.0 (10.5) | 109.8 (17.1) | 108.7 (13.6) |
| Use of antihypertensive medication (yes), % | 18 | 30 | 69 | 43 |
| Use of ACEis/ARBs (yes), % | 10 | 18 | 52 | 23 |
| Statin use (yes), % | 6 | 13 | 71 | 19 |
| Family history of diabetes (yes), % | 25 | 34 | 57 | 41 |
| Comorbidity, % | | | | |
| Heart failure | 0.4 | 0.4 | 1.3 | 0.8 |
| Cerebrovascular disease | 1.4 | 2.4 | 7.8 | 1.0 |
| Cardiovascular disease | 1.2 | 2.0 | 6.7 | 4.0 |
| Kidney function | | | | |
| Serum creatinine ($\mu$mol/L), mean (SD) | 75.6 (12.0) | 79.3 (18.1) | 75.7 (25.1) | 78.3 (19.6) |
| CKD-EPI (mL/min/1.73 m$^2$), mean (SD) | 86.6 (10.7) | 85.0 (14.7) | 86.9 (20.7) | 86.7 (18.7) |
| CKD <60 mL/min/1.73 m$^2$ (yes), % | 1.2 | 3.5 | 6.2 | 7.0 |
| Urine (morning spot) | | | | |
| ACR (mg/mmol), mean (SD) | 0.7 (2.5) | 1.1 (6.8) | 2.6 (21.5) | 2.0 (17.4) |
| Micro-albuminuria (yes), % | 1.6 | 3.3 | 6.3 | 8.6 |
| CKD (yes), % | 3.4 | 6.6 | 12.2 | 13.2 |
| Biomarkers (mmol/L), mean (SD) | | | | |
| Total cholesterol | 5.7 (0.9) | 5.8 (1.2) | 4.7 (1.4) | 5.7 (1.6) |
| HDL | 1.6 (0.4) | 1.5 (0.5) | 1.3 (0.5) | 1.3 (0.5) |
| LDL | 3.5 (0.8) | 3.7 (1.1) | 2.7 (1.2) | 3.5 (1.4) |
| Triglycerides | 1.1 (0.7) | 1.5 (1.1) | 1.6 (1.4) | 1.8 (1.4) |
| ALT (U/L) | 24 (11) | 28 (15) | 31 (22) | 34 (23) |
| AST (U/L) | 24 (8) | 25 (9) | 26 (14) | 27 (15) |
| Hb (mmol/L) | 8.6 (0.9) | 8.9 (1.0) | 8.7 (1.0) | 9.3 (0.8) |
| CRP (mg/L) | 1.9 (2.4) | 2.4 (3.6) | 3.0 (5.1) | 3.6 (4.7) |

[a]Results were weighted towards the BMI distribution of the general population ($n = 6338$).
Hypertension was defined as a BP ≥140/90 mmHg. HDL, high-density lipoprotein; LDL, low-density lipoprotein. Cardiovascular disease was defined as myocardial infarction. CKD was defined as an eGFR <60 mL/min/1.73 m$^2$ or the presence of micro-albuminuria.

**Table 2. Glucose metabolism in participants with normoglycaemia, pre-DM, diagnosed DM and newly diagnosed DM[a]**

| Measures of glucose metabolism | Normoglycaemia | Pre-DM | Diagnosed DM | Newly diagnosed DM |
|---|---|---|---|---|
| Fasting glucose (mmol/L) | 5.1 (0.3) | 6.0 (0.4) | 8.0 (3.0) | 7.9 (2.7) |
| HbA1c (%) | 5.2 (0.2) | 5.4 (0.3) | 6.7 (1.6) | 6.2 (1.5) |
| Fasting insulin (mU/L) | 8.0 (4.9) | 12.0 (8.4) | 17.7 (28.7) | 18.5 (23.6) |
| Glucose AUC | 5.5 (0.8) | 6.8 (1.1) | 10.6 (4.5) | 9.8 (3.9) |
| Insulin AUC | 44.0 (23.5) | 57.9 (38.0) | 55.6 (49.3) | 72.7 (58.4) |
| HOMA-IR | 1.8 (1.1) | 3.2 (2.3) | 6.6 (13.7) | 6.4 (8.4) |
| HOMA-B | 104.0 (62.2) | 98.3 (66.9) | 91.0 (124.8) | 92.8 (111.9) |
| Disposition index | 51.8 (38.4) | 30.6 (11.7) | 14.1 (11.8) | 16.6 (12.9) |

[a]Results were weighted towards the BMI distribution of the general population ($n = 5894$). A total of 444 participants were excluded because of protocol violation during the mixed meal test. Data are presented as mean (SD).

levels of fasting plasma glucose, AUC glucose and HOMA-B were associated with increased ORs of hyperfiltration (Table 5). Hyperinsulinaemia, as a measure of insulin resistance, was not associated with hyperfiltration. Data were similar if we included participants who used oral glucose-lowering medication and/or insulin (data not shown). Both fasting plasma glucose and HbA1c were associated with micro-albuminuria (Table 5).

**Table 3. Mean difference in the CKD-EPI in patients with pre-DM, diagnosed DM, newly diagnosed DM compared with normoglycaemia[a]**

| Model | Normoglycaemia (reference) | Pre-DM, OR (95% CI) | Diagnosed DM, OR (95% CI) | Newly diagnosed DM, OR (95% CI) |
|---|---|---|---|---|
| A | 86.3 | 0.0 (−0.9–1.0) | 2.1 (0.0–4.2) | 2.6 (−0.3–5.5) |
| B | 86.3 | 0.1 (−0.9–1.1) | 2.2 (−0.1–4.4) | 2.7 (−0.2–5.7) |
| C | 86.3 | −0.1 (−1.1–0.9) | 2.2 (−0.0–4.5) | 2.7 (−0.3–5.6) |
| D | 86.3 | −0.1 (−1.1–0.9) | 2.1 (−0.2–4.4) | 2.7 (−0.3–5.7) |

[a]Results were weighted toward the BMI distribution of the general population ($n = 5879$). A total of 444 participants were excluded because of protocol violation during the mixed meal test. Model A adjusted for age and sex. Model B additionally adjusted for BMI. Model C additionally adjusted BP, smoking and antihypertensive agents. Model D additionally adjusted for heart failure, cerebrovascular accident and myocardial infarction.

**Table 4. ORs of micro-albuminuria in patients with pre-DM, diagnosed DM, newly diagnosed DM compared with normoglycaemia[a]**

| Model | Normoglycaemia (reference), OR | Pre-DM, OR (95% CI) | Diagnosed DM, OR (95% CI) | Newly diagnosed DM, OR (95% CI) |
|---|---|---|---|---|
| Model A | 1.0 | 2.2 (1.3–3.6) | 3.8 (2.2–6.8) | 5.3 (2.8–10.3) |
| Model B | 1.0 | 1.7 (1.0–2.8) | 2.1 (1.3–3.7) | 3.4 (1.8–6.5) |
| Model C | 1.0 | 1.6 (0.9–2.6) | 1.6 (1.0–2.8) | 2.8 (1.5–5.4) |
| Model D | 1.0 | 1.5 (0.9–2.6) | 1.6 (0.9–2.7) | 2.8 (1.5–5.4) |

[a]Results were weighted toward the BMI distribution of the general population ($n = 5870$). A total of 444 participants were excluded because of protocol violation during the mixed meal test. Model A adjusted for age and sex. Model B additionally adjusted for BMI. Model C additionally adjusted for BP, smoking and antihypertensive agents. Model D additionally adjusted for heart failure, cerebrovascular accident and myocardial infarction.

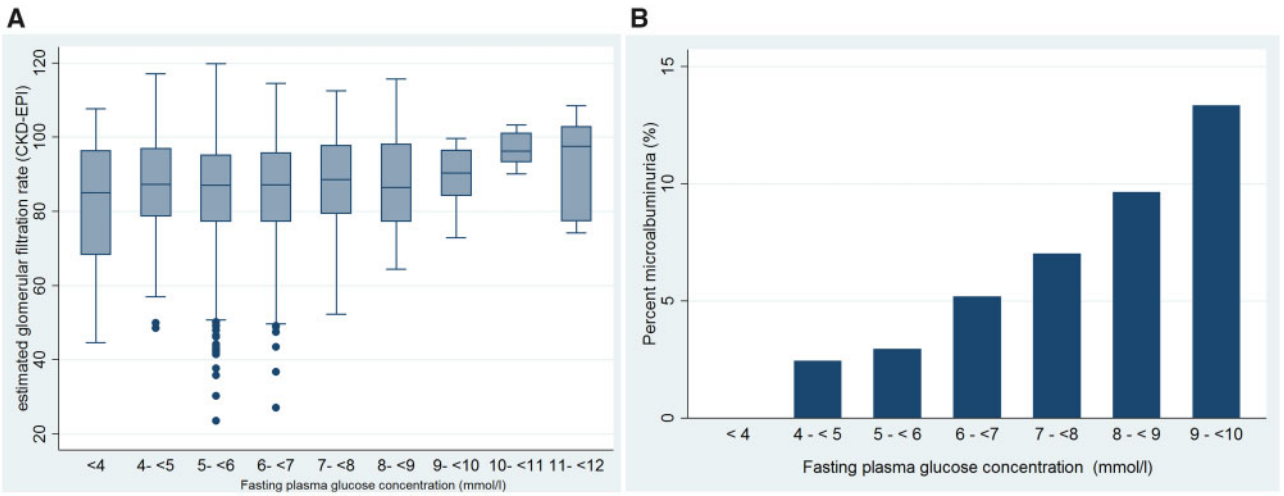


**FIGURE 1:** (**A**) Association between fasting plasma glucose and eGFR. Results were weighted toward the BMI distribution of the general population ($n = 60\,03$). Patients using glucose-lowering drugs were excluded. (**B**) Association between fasting plasma glucose and micro-albuminuria. [a]Results were weighted towards the BMI distribution of the general population ($n = 60\,03$). Patients using glucose-lowering drugs were excluded. Micro-albuminuria was defined as a UACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women.

**Table 5. Association of different measures of glucose metabolism with hyperfiltration and micro-albuminuria[a]**

| Measures of glucose metabolism | OR (95% CI) for hyperfiltration | OR (95% CI) for micro-albuminuria |
|---|---|---|
| Fasting glucose, per mmol/L (18 mg/dL) | 1.27 (1.11–1.46) | 1.21 (1.04–1.42) |
| HbA1c, per % unit | 1.41 (1.05–1.87) | 1.36 (1.00–1.86) |
| Fasting insulin, per mU/L | 0.99 (0.97–1.01) | 1.01 (1.00–1.03) |
| AUC glucose, per unit | 1.22 (1.11–1.34) | 1.11 (0.97–1.26) |
| AUC insulin, per unit | 1.00 (1.00–1.01) | 1.00 (1.00–1.01) |
| HOMA-IR, per unit | 1.00 (0.94–1.05) | 1.05 (0.97–1.14) |
| HOMA-B, per unit | 1.00 (0.99–1.00) | 1.00 (1.00–1.00) |
| IDI-ISI, per unit | 1.00 (1.00–1.01) | 1.00 (0.99–1.01) |

[a]Results were weighted toward the BMI distribution of the general population ($n = 5572$). Patients using glucose-lowering drugs were excluded. Logistic regression analysis with hyperfiltration and micro-albuminuria as the dependent variable. All models were adjusted for age, sex, weight, diastolic and systolic BP, smoking status and the use of ACEis or ARBs.

## DISCUSSION

In this large cross-sectional study of middle-aged men and women, we observed a relatively low proportion of patients with CKD. Furthermore, we found that both fasting and post-prandial glucose and HOMA-B, but not insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with micro-albuminuria.

As expected, our study showed that patients with CKD had higher glucose levels compared with patients without CKD. Also, we demonstrated that the proportion of patients with kidney disease in this Dutch study is much lower than in previous studies [9, 13]. This relatively low proportion of patients with CKD might be explained by relatively good metabolic control in our study as illustrated by good glycaemic, BP and lipid control. Furthermore, it might also be related to different study populations. First, in a US study [9], many patients had no insurance (8.9–19.4%), while in the Netherlands all patients have basic insurance and patients with insurance have better healthcare outcomes [27]. Second, the mean BMI is higher in the USA than in the Netherlands and BMI is a strong risk factor of CKD [28]. Third, almost all our participants were of non-Hispanic Caucasian ethnicity, which might contribute to the lower prevalence of CKD, as the prevalence of CKD in non-White populations is higher [29].

Previous cohort studies showed conflicting results as to whether pre-DM is associated with CKD. Some studies showed a positive association between pre-DM and CKD, as in a higher prevalence of glomerular hyperfiltration and albuminuria compared with participants without DM [11, 30, 31]. Other longitudinal studies showed that pre-DM was not an independent risk factor for CKD [13, 32]. However, information on micro-albuminuria was not available in these studies, meaning that this early sign of kidney damage may have been missed. We showed in participants with pre-DM that eGFR was similar to that in participants with normoglycaemia, but the OR of micro-albuminuria was 1.7 (95% CI 1.0–2.8) times higher. However, after adjustment for vascular risk factors, the OR was attenuated [OR 1.5 (95% CI 0.9–2.7)], which suggests that concomitant vascular disease risk factors explain most of the increased odds of micro-albuminuria development in pre-DM.

The observed higher trend in eGFR in patients with (newly) diagnosed DM is in line with other studies [11, 33–36]. In our study, patients with diagnosed DM, although not recently diagnosed, had a relatively 'mild' DM. This was reflected by good glycaemic control, a small number of patients with insulin use and a low prevalence of diabetic complications. These characteristics might explain the observed higher eGFR, reflecting glomerular hyperfiltration, instead of a decline in eGFR.

Glomerular hyperfiltration is considered as an early manifestation of diabetic kidney nephropathy and may contribute to nephropathy progression and GFR decline [20, 37, 38]. However, a recent study in patients with type 1 DM showed that early hyperfiltration was not associated with a higher long-term risk of decreased GFR, defined as an eGFR $<60$ mL/min/1.73 m$^2$ [39]. A potential limitation of that study was that hyperfiltration was assessed at baseline (median 4 years after diagnosis) and not during long-term follow-up (median 28 years). Furthermore, glucose control was not optimal (mean HbA1c 8.8%). A reason for the negative result in that study, which showed that hyperfiltration was not associated with a higher long-term risk of decreased GFR, might be that glomerular hyperfiltration is (partially) reversible after improvement of glucose control.

In our study, we evaluated different measures of glucose metabolism and showed that both fasting and post-prandial glucose levels and HOMA-B were associated with glomerular hyperfiltration, while only fasting glucose was associated with micro-albuminuria. Our results showed no association between insulin resistance with glomerular hyperfiltration and micro-albuminuria. These results are in line with another study that reported that impaired fasting glucose was associated with glomerular hyperfiltration, whereas hyperinsulinaemia was not [17]. Our results add to the hypothesis that hyperinsulinaemia as a measure of insulin resistance is not associated with a first increase in eGFR (hyperfiltration) but is associated with an immediate decline in eGFR. This might be explained by direct kidney damage, by mechanisms such as inflammatory cytokines and lipotoxicity [40–42]. Other studies have reported that insulin resistance in a non-diabetic population contributes to progressive CKD [43, 44], but hyperfiltration was not assessed in these studies. Our study also showed that hyperinsulinaemia was not associated with micro-albuminuria. This is in line with another study [45], but in contrast with other reports [46, 47]. However, these studies were performed in a different study population (mainly non-White) and no adjustments were made for the use of ACEis or ARBs.

This study adds new knowledge to existing literature. First, the proportion of patients with kidney disease in this Dutch cohort with good metabolic control was relatively small. Second, we showed that insulin resistance was not associated with glomerular hyperfiltration and micro-albuminuria. The strengths of this study are the evaluation of kidney function by eGFR, as well as glomerular hyperfiltration and micro-albuminuria. Micro-albuminuria is a known risk factor for the development of kidney disease in the setting of diabetes [48, 49]. Furthermore, the NEO population consisted of a large study population and included an extensive set of measures of glucose metabolism, including a mixed meal test. This made it possible to evaluate the associations of many different measures of glucose metabolism with measures of kidney function in one large patient cohort.

Our study also has a number of limitations that need to be considered. The cross-sectional design limits inferences on causality. Furthermore, we did not perform a glucose tolerance test, but used a mixed meal test and measured post-prandial glucose levels at 30 and 150 min. A 2-h glucose value was not obtained and therefore impaired glucose tolerance could not be assessed. However, we combined fasting glucose, HbA1c levels and elevated post-prandial levels ($\geq$11.1 mmol/L) and used accepted definitions of pre-DM [2]. Another limitation is the use of eGFR, although the CKD-EPI formula has proven to be more accurate compared with the Modification of Diet in Renal Disease formula, it has not been validated at $>$90 mL/min/1.73 m$^2$ and might underestimate hyperfiltration in obesity [50]. Isotope clearance measurements are the gold standard but are seldom used in large epidemiological studies due to time, high cost and invasiveness. Further, there is no consensus about the definition of hyperfiltration. Some studies referred to hyperfiltration as a GFR exceeding the upper limit of the normal range (eGFR $>$90th percentile) or a measured GFR $>$120 mL/min/1.73 m$^2$ [17, 34, 37]. Another limitation is the lack of confirmation of micro-albuminuria in a second urine portion. Although patients delivered a morning urine sample, which reduces the number of false positives, we cannot exclude that some patients had transient micro-albuminuria.

Further follow-up studies are needed to investigate whether patients with pre-DM or DM and hyperfiltration are at risk of

further progression of kidney disease. If future studies confirm that patients with glomerular hyperfiltration have a high risk of further progression of kidney disease, this will also provide an opportunity for early intervention in diminishing renal disease progression, by modulating intraglomerular pressure with sodium–glucose cotransporter 2 inhibitors and renin–angiotensin–aldosteron system inhibitors.

In conclusion, in contrast with other studies, the proportion of patients with kidney disease in this Dutch study population was relatively small, which might be related to good metabolic control. Furthermore, we showed that both fasting and postprandial glucose and HOMA-B, but not insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with micro-albuminuria. This implies that hyperinsulinaemia as a measure of insulin resistance is not associated with a first increase in eGFR (hyperfiltration) but is associated with a decline in eGFR. The results need further confirmation in cohorts with long-term follow-up.

## SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

## CONFLICT OF INTEREST STATEMENT

None declared.

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