HHS Public Access

Author manuscript

Diabetologia. Author manuscript; available in PMC 2019 August 07.

Published in final edited form as:

Diabetologia. 2009 July ; 52(7): 1290–1297. doi:10.1007/s00125-009-1361-4.

Risk of type 2 diabetes among individuals with high and low glomerular filtration rates

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Abstract

Aims/hypothesis—Metabolic abnormalities frequently develop prior to the diagnosis of type 2 diabetes and chronic kidney disease. However, it is not known whether GFR predicts the onset of type 2 diabetes.

Methods—Incident diabetes was ascertained in the Insulin Resistance Atherosclerosis Study (IRAS) (n = 864; age 40–69 years; median follow-up 5.2 years [4.5–6.6 years]; 141 incident cases of diabetes). GFR was estimated by the Modification of Diet in Renal Disease equation. We assessed the relationship between GFR and incident diabetes by logistic regression analysis. Results were adjusted for age, sex, ethnicity, clinic location, BMI, systolic blood pressure, antihypertensive treatment, family history of diabetes, insulin sensitivity and secretion, albumin to creatinine ratio, and levels of triacylglycerols, HDL-cholesterol, plasminogen activator inhibitor-1, and fasting and 2 h glucose.

Results—The relationship between GFR and incident diabetes was not linear. This relationship was statistically significant (p = 0.039) using a restricted cubic polynomial spline for GFR as a

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

regression modelling strategy. Participants were stratified by GFR quintiles. Mean values for GFR from the first to the fifth quintile were 60.8, 71.6, 79.8, 88.2 and 109.0 ml min^{-1} 1.73 m^{-2}. Relative to the fourth quintile, the odds ratios of incident diabetes for the first, second, third and fifth quintiles were 2.32 (95% CI 1.06–5.05), 1.76 (95% CI 0.80–3.88), 1.26 (95% CI 0.56– 2.84) and 2.59 (95% CI 1.18–5.65), respectively.

Conclusions/interpretation—Individuals in the upper and lower ranges of GFR are at increased risk of future diabetes. GFR and type 2 diabetes may share common pathogenic mechanisms.

Keywords

Chronic kidney disease; Glomerular filtration rate; Hyperfiltration; Incidence; Insulin resistance; Type 2 diabetes

Introduction

In the USA, 20–30% of patients with type 2 diabetes develop early stages of nephropathy [1]. Tests for the presence of microalbuminuria and serum creatinine for the estimation of glomerular filtration rate are annually recommended in order to screen for or stage the level of chronic kidney disease [1]. Microalbuminuria and chronic kidney disease are determinants of nephropathy progression [2] and cardiovascular mortality [3, 4] and are associated with insulin resistance and other metabolic abnormalities [5–8]. Microalbuminuria is considered an early marker of atherosclerosis [9, 10] and a feature of the prediabetic state [11] and is associated with an increased risk of type 2 diabetes [12]. However, it is not known whether low GFR predicts the onset of type 2 diabetes.

GFR tends to increase in newly diagnosed patients with type 2 diabetes as an adaptive response to early glomerular haemodynamic changes [13]. Hyperfiltration is a risk factor for future worsening of diabetic nephropathy, even though its presence may not be sufficient for the deterioration of GFR [14]. Hyperfiltration precedes the development of microalbuminuria [15], reflects early target organ damage [16], and correlates with hypertension, insulin resistance and other metabolic disorders [17]. Nevertheless, an association between hyperfiltration and increased risk of diabetes remains to be elucidated.

The aim of this study was to examine the ability of high and low GFR to predict incident diabetes in the Insulin Resistance Atherosclerosis Study (IRAS). The IRAS is a longitudinal epidemiological study designed to analyse the relationship between cardiovascular disease, type 2 diabetes and insulin resistance [18].

Methods

Participants

The IRAS was designed to have an equal representation of participants across glucose tolerance status (normal, impaired glucose tolerance [IGT] and type 2 diabetes), ethnic origin, sex and age (40–49, 50–59 and 60–69 years). Recruitment strategies and protocols have been already published [18]. In brief, the IRAS study was conducted at four clinical

centres (Oakland and Los Angeles, CA, USA; San Antonio, TX, USA; San Luis Valley, CO, USA). Sampling strategies were used to yield approximately equal numbers of participants by ethnicity, sex and glucose tolerance categories (type 2 diabetes mellitus, IGT and normal glucose tolerance). Individuals with a history of kidney dialysis or transplant, acute or chronic renal failure or serious illnesses were excluded. Study protocols were approved by local Institutional Review Boards. All participants gave written informed consent.

Baseline data were collected in two visits approximately 1 week apart (range 7–28 days). Baseline examination was completed by 1,624 individuals (48% overall recruitment rate; 56% women), which occurred between October 1992 and April 1994. The present report includes information on 864 participants (81.1% of non-diabetic participants at baseline) for whom diabetes status was ascertained after an average of 5.2 years (range 4.5–6.6 years).

Participant examination

Age, ethnicity, education, diet, family history of diabetes and pharmacological treatment were self-reported. Height, weight and waist circumference were measured following a standardised protocol. Resting blood pressure was measured three times, and the second and third measurements were averaged. Participants were asked before each visit to fast for 12 h, to abstain from intense exercise and alcohol for 24 h and to refrain from smoking during the morning of examination. During the first baseline visit, blood specimens were collected to determine the concentration of serum creatinine, blood urea nitrogen and plasma glucose, albumin, lipoproteins and plasminogen activator inhibitor-1 (PAI-1). Glucose tolerance status was ascertained by oral glucose tolerance test during the first baseline and follow-up visits.

During the second baseline visit, insulin resistance and secretion were measured by the frequently sampled intravenous glucose tolerance test. Insulin sensitivity, expressed as the insulin sensitivity index, was calculated by mathematical modelling methods (MINMOD, version 3.0 [1994], Los Angeles, CA, USA; courtesy of R. Bergman, University of Southern California). Comparisons with the hyperinsulinaemic–euglycaemic clamp indicate that insulin sensitivity index was an adequate estimate of insulin resistance [19]. Insulin secretion, expressed as the acute insulin response, was calculated as the mean of 2 and 4 min insulin concentrations after glucose administration. Acute insulin response correlated well with first-phase insulin response during the hyperglycaemic clamp [20].

Levels of albumin, glucose, triacylglycerols and HDL-cholesterol were measured using standard methods [18]. Serum and urine creatinine levels were determined by a modified kinetic Jaffe reaction [21] and urea nitrogen by standard clinical methods at the central IRAS laboratory with a Paramax PLA instrument (Baxter Diagnostic, Chicago, IL, USA) [18]. Fasting insulin concentration was measured using the dextran—charcoal radioimmunoassay, which had considerable cross-reactivity with proinsulin [22]. PAI-1 was measured with a two-site immunoassay that is sensitive to free active and latent PAI-1 but not to PAI-1 complexed with tissue plasminogen activator (inhouse assay, Laboratory for Clinical Biochemistry Research PAI-1 antigen enzyme immunoassay) [23].

Definition of variables

The urinary albumin to creatinine ratio (ACR) (albumin in mg/l and creatinine in mmol/l) was used as a measure of albumin excretion [2]. Diabetes mellitus was defined as fasting plasma glucose level ≥7.0 mmol/l, 2 h plasma glucose level ≥11.1 mmol/l and/or treatment with hypoglycaemic medication. IGT was defined as 2 h plasma glucose level ≥7.8 mmol/l in the absence of diabetes.

GFR categories

GFR was not measured by definitive methods (e.g. inulin or radioisotope studies), which are difficult to apply to epidemiological studies. Neither was cystatin C available for analysis. We chose the Modification of Diet in Renal Disease (MDRD) equation based on six variables to estimate GFR [2, 24]:

$$\begin{aligned}\text{GFR} = {} & 170 \times \text{creatinine}^{-0.999} \times \text{age}^{-0.176} \\ & \times 0.762[\text{if female}] \times 1.18[\text{if African-American}] \\ & \times \text{urea nitrogen}^{-0.17} \times \text{albumin}^{0.318}\end{aligned}$$

In this equation, GFR was expressed in ml min^{-1} 1.73 m^{-2} body surface area, serum creatinine and blood urea nitrogen in mg/dl, albumin in g/dl and age in years. The MDRD equation tends to be more accurate than the Cockcroft—Gault equation in obese adults [2]. In addition, weight is not included in the MDRD formula; therefore, a confounding effect of adiposity on the relation of GFR to incident diabetes is less likely.

We created five strata from low renal function through to high renal function (GFR quintiles). We also generated categories with known clinical relevance such as low GFR (<60 ml min^{-1} 1.73 m^{-2}), high GFR (>95% CI upper limit of GFR in healthy participants [1.96 standard deviations above the mean]), and normal/near-to-normal GFR (any value not classified as high or low). Altman's method was used to calculate the 95% reference range of estimated GFR in healthy participants [25]. Healthy individuals had the following characteristics: no vegetarian diet, no history of cardiovascular disease, BMI ≥18.5 and <25 kg/m^2, normal glucose tolerance and blood pressure, and ACR <17 mg/g in men and <25 mg/g in women ($n = 132$). Because of the decline of GFR with age, linear regression analysis was used to determine the relationship between GFR and age (GFR = 95.03 ml min^{-1} 1.73 m^{-2} − [0.29 × age], $p = 0.045$). Absolute residuals were calculated and were found to be unrelated to age. Because of the distribution of absolute residuals (half normal), 95% of the GFR data in healthy controls were expected to fall within 0 and $1.96 \times \sqrt{\pi/2} \times$ mean of absolute residuals. Therefore, the upper limit of the 95% CI was calculated (122.89 ml min^{-1} 1.73 m^{-2} − [0.29 × age]) and used as the cut-off point for high GFR.

Statistical methods

The analysis was carried out using the SAS statistical software (version 9.1, SAS Institute, Cary, NC, USA) and R project statistical software (version 2.8.1; The R Foundation for Statistical Computing, Vienna, Austria). Stratified by GFR categories, baseline

characteristics were analysed by one-way analysis of covariance (continuous variables) and logistic regression analysis (rates). The relation of GFR to incident diabetes was examined by multiple logistic regression analysis in order to take into consideration the effect of potential determinants of diabetes and GFR. In separate logistic regression models, appropriate interaction terms were introduced to model interactions between GFR category and sex (GFR category and age or GFR category and ethnicity and so forth) in relation to incident diabetes. We performed another logistic regression to model incident diabetes with a restricted cubic polynomial spline for GFR to estimate the varying effects of GFR over its full range [26]. Log_e– transformed values of ACR, acute insulin response and levels of triacylglycerols and PAI-1 were used in all analyses to improve discrimination and calibration of the models and to minimise the influence of extreme observations. We also used the $\log_e$ transformation of (insulin sensitivity index +1) given that some participants had insulin sensitivity index =0. These variables were then back-transformed to their units for presentation in tables.

Results

A total of 1,065 non-diabetic individuals were potentially eligible for analysis; however, baseline GFR was not estimated in 43 participants and incident diabetes was not ascertained in 158 additional participants. Therefore, we used information on 864 participants (81.1% of non-diabetic participants at baseline) for whom diabetes status was ascertained at follow-up. These participants had similar baseline characteristics to counterparts who did not return to follow-up including age, sex, ethnicity, glucose tolerance status, BMI, insulin sensitivity, albuminuria and estimated GFR (all comparisons, $p > 0.2$).

At the baseline examination, 283 participants had IGT and 581 participants had normal glucose tolerance. Only six participants had an albumin excretion rate ≥200 mg/g (range 1.1–558.4 mg/g) and none of the participants had an estimated GFR <39 ml min^{-1} 1.73 m^{-2} (range, 39.9–239.1 ml min^{-1} 1.73 m^{-2}). Measurement variability of GFR was not equal across GFR categories. A change in serum creatinine concentration of 8.84 μmol/l modified the estimated GFR by 2.1 to 6.0 (median 5.0), 4.5 to 18.3 (median 8.4) and 11.1 to 79.7 (median 17.6)ml min^{-1} 1.73 m^{-2} in the low, normal/near-to-normal and high GFR categories, respectively.

Baseline rates of low and high GFR were 7.6% (95% CI 6.0–9.6) and 8.6% (95% CI 6.9–10.6), respectively. Low GFR was less common in African-Americans and more common in older individuals and women (Table 1). High GFR was more frequent in African-Americans and less frequent in non-Hispanic whites. In addition, low GFR was associated with antihypertensive treatment and high GFR with diastolic blood pressure (DBP), albuminuria and PAI-1 concentration.

There were 141 incident cases of diabetes during an average of 5.2 years. Follow-up time ranged from 4.5 to 6.6 years, but 90% of the participants had the follow-up examination 4.8 to 5.8 years after the initial examination. Follow-up time was not associated with incident diabetes (OR × 1 year increase 0.89 [0.49–1.61]).

Crude rates of incident diabetes were 24.2% (95% CI 15.4–36.0), 14.9% (95% CI 12.5–17.7) and 23.0% (95% CI 14.8–33.9) for the low, normal/near-to-normal and high GFR categories, respectively. Compared with the normal/near-to-normal GFR category, the conversion rate in the low GFR category was marginally significant ($p = 0.049$), but that in the high GFR category was not ($p = 0.072$). High GFR was associated with increased odds of incident diabetes independently of the effect of confounding variables (Table 2). Diabetic risk associated with low GFR was near significance. There was no significant interaction of age, sex, race/ethnicity or glucose tolerance status on the association of high and low GFR with incident diabetes ($p > 0.2$).

From the first to the fifth quintile, mean GFR values were 60.8, 71.6, 79.8, 88.2 and 109.0 ml min_{-1} 1.73 m_{-2}, respectively. Corresponding crude rates of incident diabetes were 20.3% (95% CI 15.0–27.0), 16.2% (95% CI 11.4–22.4), 12.7% (95% CI 8.5–18.6), 11.6% (95% CI 7.6–17.2) and 20.8% (95% CI 15.4–27.5). The first and fifth quintiles had higher conversion rates than the fourth quintile (Table 3). We observed no significant interaction of age, sex, race/ethnicity or glucose tolerance status on the relationship between GFR by quintiles and incident diabetes ($p > 0.2$).

As the relationship between GFR and incident diabetes was not linear, we fitted a logistic regression model with the relevant risk factors in it and a smoothed effect of GFR (Fig. 1). The relationship between GFR and incident diabetes was statistically significant ($p = 0.039$). Figure 1a presents the OR relative to an estimated GFR of 80 ml min^{-1} 1.73 m^{-2}. The OR is higher in participants with GFR below 65 and above 100 ml min^{-1} 1.73 m^{-2}. Figure 1b shows the cumulative probability for a hypothetical individual with a relevant set of values for the confounders.

Discussion

To our knowledge, this is the first study that relates GFR to the development of diabetes. Hyperfiltration-related characteristics are present in non-diabetic participants whose estimated GFR is high. High GFR is associated with arterial pressure, chronic inflammation and albuminuria. These associations are not driven by obesity or insulin resistance and do not explain the increased risk of diabetes associated with high GFR. Low GFR is also a predictor of future diabetes independently of the effect of determinants of GFR and diabetes.

Tomaszewski et al. were the first to describe a relationship between hyperfiltration and metabolic risk [17]. Our study validates, in part, their observations. High GFR is directly related to several components of the insulin resistance syndrome, including arterial pressure, chronic inflammation and albuminuria. Therefore, insulin resistance is an attractive causative factor for the relationship between high GFR and incident diabetes. Insulin has been shown to exert a direct effect on glomerular podocytes [27]. Acute insulin infusion stimulates the sympathetic nervous system [28] and produces a vasodilator hypotensive effect [29]. In our study, however, high GFR is not associated with insulin resistance. This unexpected finding has to be evaluated in view of the limitations of the MDRD equation. For example, the high GFR category may group a heterogeneous pool of individuals. Some of these individuals may have low generation of creatinine and, consequently, falsely elevated

GFR. Our analysis also demonstrates that the relation of GFR to metabolic abnormalities is independent of the effect of obesity. Obesity could largely explain the relationship between hyperfiltration and metabolic risk in the study by Tomaszewski et al., because the Cockcroft–Gault equation was used to estimate GFR [17]. Thus, studies with definitive measures of both insulin resistance and GFR are needed to re-examine the relationship between hyperfiltration and insulin resistance.

Epidemiological studies have linked low GFR to insulin resistance and other metabolic abnormalities [7, 8]. In the IRAS, low GFR is associated with hypertensive treatment, which may be a marker for higher blood pressure and/or longer duration of hypertension. However, low GFR was not associated with any other metabolic abnormality. To explain this fact, we advance three possible explanations. First, the number of participants with low GFR is relatively small and none of them has a GFR <39 ml min^{-1} 1.73 m^{-2}. Second, an initial increase in GFR is common in individuals with IGT [13] and obesity-related glomerulopathy [30]. Both obesity and IGT are very prevalent in the IRAS cohort. Finally, worsening GFR in diabetic nephropathy tends to occur after the onset of macroalbuminuria [13].

Mechanisms other than insulin resistance may be important for explaining the relationship between GFR and development of type 2 diabetes. Potential mechanisms are the dysregulation of the autonomic nervous system [31, 32], increased renal gluconeogenesis [33], endothelial dysfunction/chronic inflammation [34–37], oxidative stress [37] and activation of the renin–angiotensin system [38–40]. A marker of chronic inflammation, PAI-1 concentration, is increased in individuals with high GFR. However, PAI-1 concentration does not explain the relationship between GFR and incident diabetes. Future studies need to determine the role of these potential contributory mechanisms.

Using a restricted cubic polynomial spline as a regression modelling strategy is a better method of assessing the non-linear effect of GFR than using GFR categories [26]. Categories may have the advantage of presenting the results in terms of clinically relevant cut-off points. Our results indicate that the increased risk of future diabetes associated with high and low GFR is not the result of arbitrary cut-off points.

Although changes in GFR precede the development of diabetes in men, women and all three ethnic groups, a number of limitations must be considered. First, the assessment of GFR is indirectly estimated. Definitive methods (e.g. with inulin or radioisotope studies) are difficult to apply to epidemiological studies. Second, creatinine concentration is not calibrated for the MDRD equation in the IRAS. However, creatinine concentration was measured by the same laboratory and method for all participants. Third, the MDRD equation may not generate definite GFR estimates in participants with normal or high GFR. Biological and measurement variability associated with normal or high GFR is greater than that associated with low GFR [40]. In the IRAS, a .84 μmol/1 change in serum creatinine concentration represents a 2.1 to 6.0 ml min^{-1} 1.73 m^{-2} change in participants with low GFR and a 11.1 to 79.7 ml min^{-1} 1.73 m^{-2} change in participants with high GFR. Finally, the MDRD equation underestimates GFR measurement in individuals with normal or low serum creatinine concentration [41]. For example, the mean GFR (using the six-variable MDRD equation) was 77 ml min^{-1} 1.73 m^{-2} among adult non-diabetic participants in the

National Health and Nutrition Examination Survey III [42]. Cystatin C may be a better filtration marker [43], but is unavailable in the IRAS. Therefore, an incorrect conclusion may derive from our results: that a GFR level of 80 ml min^{-1} 1.73 m^{-2} is associated with the lowest diabetic risk. To reach this type of conclusion, a definitive method to measure GFR is needed.

In summary, low and high GFR predict incident diabetes independently of confounding risk factors. The exact mechanism is unknown but our results suggest that GFR changes and type 2 diabetes share common pathogenic mechanisms. Studies that use definitive measures of GFR are needed to confirm the hypothesis that changes in GFR may precede the onset of type 2 diabetes independently of ongoing changes in albumin excretion rate.

Acknowledgements

This study was supported by National Heart, Lung, and Blood Institute Grants (HL-47887, HL-47889, HL-47890, HL-47892, HL-47902), the General Clinical Research Centers Program (NCRR GCRC, M01 RR431, M01 RR01346), and CTSA Award (KL2 RR025766) from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Center for Research Resources of the National Institutes of Health

Abbreviations

ACR	Albumin to creatinine ratio
DBP	Diastolic blood pressure
IGT	Impaired glucose tolerance
IRAS	Insulin Resistance Atherosclerosis Study
MDRD	Modification of Diet in Renal Disease
PAI-1	Plasminogen activator inhibitor-1

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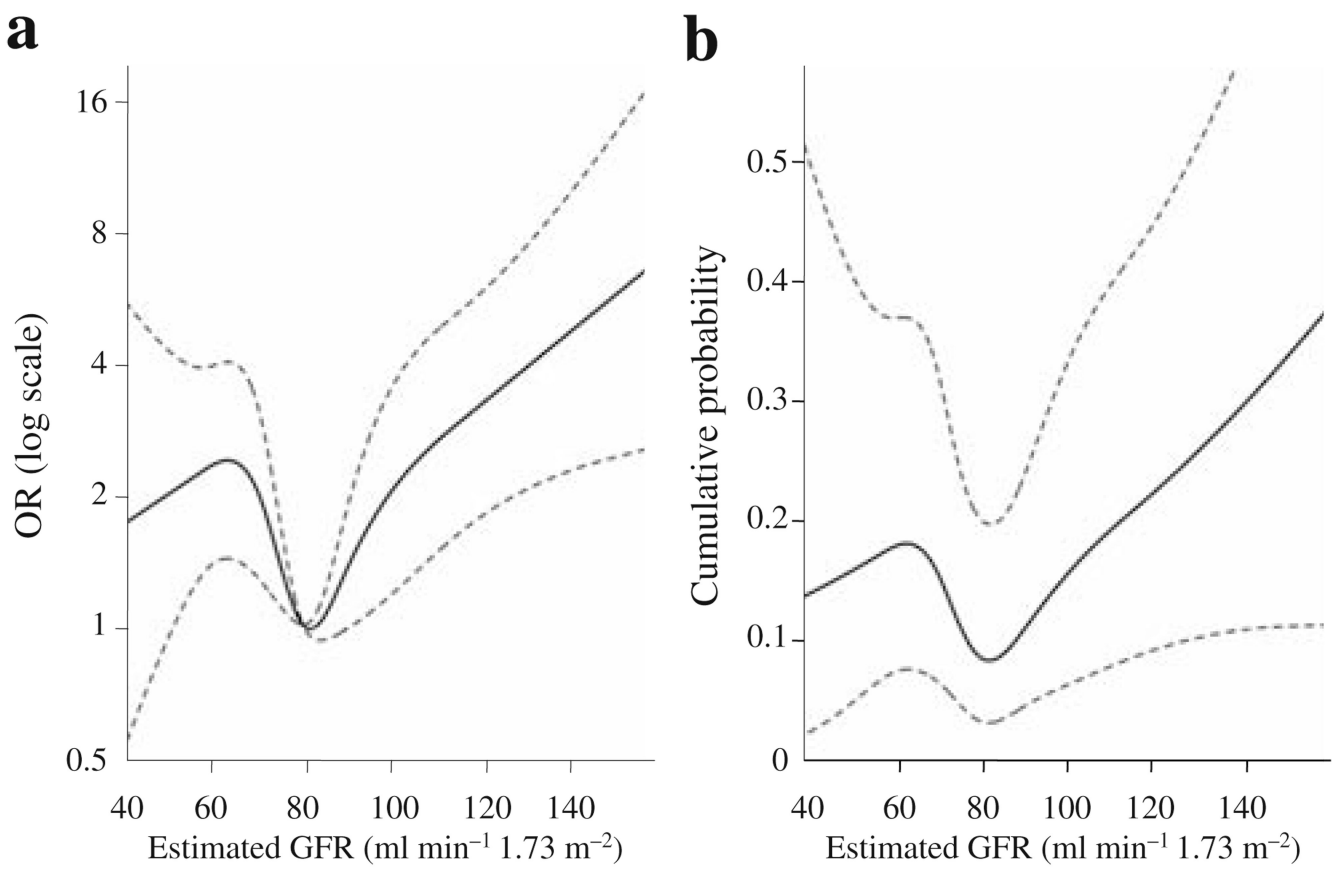

Fig. 1.

Relationship between the 5 year risk of type 2 diabetes and GFR modelled by a smooth function. **a** Probability of incident diabetes adjusted for age, sex, race/ethnicity, clinic location, BMI, systolic blood pressure (SBP), antihypertensive treatment, history of diabetes in first-degree relatives, insulin sensitivity index, acute insulin response and ACR, and levels of triacylglycerols, HDL-cholesterol, PAI-1 and fasting and 2 h glucose. The OR has a reference level GFR of 80 ml min^{-1} 1.73 m^{-2}. **b** The 5 year cumulative probability for a hypothetical individual with a relevant set of values for the confounders. The participant modelled is a 65 year old Hispanic man at the San Antonio clinic with the following risk factors: SBP 140 mmHg, BMI 30 kg/m^2, fasting glucose 6.66 mmol/l and 2 h glucose 6.66 mmol/l. All other risk factors are at the study averages

Table 1

Baseline characteristics by GFR categories after adjusting for age, sex, ethnicity and clinic location

Characteristic	Low GFR	Normal/near-to-normal GFR	High GFR	Low vs normal/near-to-normal *p* value	High vs normal/near-to-normal *p* value
n	66	724	74	–	–
Age (years)[a]	60.0±1.0	54.5±0.3	52.6±1.0	<0.001	0.071
Female sex (%)[a]	75.8 (64.0–84.6)	55.2 (51.6–58.8)	54.1 (42.7–65.0)	0.002	0.844
Ethnicity					
African-American (%)[a]	10.6 (5.1–20.6)	24.9 (21.8–28.1)	41.9 (31.2–53.4)	0.012	0.002
Hispanic (%)[a]	33.3 (23.1–45.5)	34.5 (31.2–38.1)	35.1 (25.2–6.6)	0.846	0.917
Non-Hispanic white (%)[a]	56.1 (44.0–67.5)	40.6 (37.1–44.2)	23.0 (15.8–33.9)	0.016	0.004
BMI (kg/m^2)	28.4±0.7	28.4±0.2	27.8±0.6	0.982	0.321
Waist circumference (cm)	89.5±1.5	90.3±0.4	90.3±1.4	0.633	0.947
Triacylglycerol concentration (mmol/l)	1.39±0.10	1.28±0.03	1.25±0.08	0.296	0.697
HDL-cholesterol (mmol/l)	1.25±0.04	1.20±0.01	1.26±0.04	0.223	0.135
SBP (mmHg)	120.8±1.9	121.4±0.6	124.7±1.8	0.691	0.067
DBP (mmHg)	78.2±1.1	77.4±0.3	79.6±1.0	0.498	0.041
Antihypertensive medications (%)	33.5 (22.6–46.5)	19.2 (16.4–22.4)	20.2 (12.5–31.0)	0.011	0.799
Fasting glucose concentration (mmol/l)	5.35±0.07	5.44±0.02	5.43±0.06	0.232	0.896
2 h glucose concentration (mmol/l)	6.58±0.23	6.91±0.07	7.08±0.21	0.197	0.457
Insulin sensitivity index (MINMOD) ($\times10^{-4}$ min^{-1} μU^{-1} ml^{-1})[b,c]	1.80±0.20	1.77±0.06	1.64±0.16	0.903	0.432
Acute insulin response (pmol/l)[b]	337.0±35.4	298.9±9.1	292.9±27.6	0.221	0.895
PAI-1 concentration (ng/ml)[b]	14.0±1.5	15.8±0.5	19.7±1.8	0.190	0.030
ACR (mg/mmol)[b]	0.98±0.11	0.84±0.02	1.11±0.12	0.138	0.006
Dietary protein (g/day)	80.4±3.9	77.4±1.1	76.8±3.7	0.155	0.891
GFR (ml min^{-1} 1.73 m^{-2})[a]	55.4±1.4	80.3±0.4	121.3±1.4	<0.001	<0.001

[a]Non-adjusted values

[b]Log$_e$-transformed variable and then back-transformed to its natural units for presentation

[c] To convert values to SI units ($\times 10^{-4}$ min^{-1} $pmol^{-1}$ l^{-1}) multiply by 0.167

SBP, systolic blood pressure

Table 2

Adjusted OR for predicting a 5.2 year incidence of diabetes associated with low and high GFR

Model	Adjusted for	Low vs normal/near normal	High vs normal/near normal
1	Unadjusted OR	1.82 (1.00−3.32)	1.70 (0.95−3.03)
2	Adjusted for age, sex, race/ethnicity, clinic location and duration of follow-up	1.40 (0.74−2.63)	1.96 (1.08−3.56)
3	Adjusted for age, sex, race/ethnicity, clinic location, duration of follow-up, BMI, SBP, antihypertensive treatment, history of diabetes in first degree relatives, insulin sensitivity index, acute insulin response, and levels of triacylglycerols, HDL-cholesterol, PAI-1 and fasting and 2 h glucose	2.24 (1.00−5.16)	2.44 (1.15−5.17)
4	Adjusted for all variables in model 3 plus ACR	2.14 (0.94−4.86)	2.29 (1.06−4.97)

Values are OR (95% CI)

SBP, systolic blood pressure

Table 3

Adjusted OR for predicting a 5.2 year incidence of diabetes associated with quintiles of GFR

Model	1st quintile (n = 172)[a]	2nd quintile (n = 173)[b]	3rd quintile (n = 173)[c]	4th quintile (n = 173)[d]	5th quintile (n = 173)[e]
Model 1	1.95 (1.08–3.55)	1.48 (0.80–2.74)	1.11 (0.58–2.13)	Reference	2.01 (1.11–3.64)
Model 2	1.69 (0.90–3.15)	1.46 (0.78–2.74)	1.12 (0.58–2.15)	Reference	2.34 (1.27–4.32)
Model 3	2.35 (1.08–5.12)	1.74 (0.79–3.84)	1.19 (0.53–2.69)	Reference	2.59 (1.19–5.64)
Model 4	2.32 (1.06–5.05)	1.76 (0.80–3.88)	1.26 (0.56–2.84)	Reference	2.59 (1.18–5.65)

Values are OR (95% CI)

Model 1: unadjusted OR

Model 2: OR adjusted for age, sex, race/ethnicity, clinic location and duration of follow-up

Model 3: OR adjusted for age, sex, race/ethnicity, clinic location, duration of follow-up, BMI, systolic blood pressure (SBP), antihypertensive treatment, history of diabetes in first-degree relatives, insulin sensitivity index, acute insulin response and levels of triacylglycerols, HDLcholesterol, PAI-1 and fasting and 2 h glucose

Model 4: OR adjusted for all variables in model 3 plus ACR

GFR (ml min^{-1} 1.73 m^{-2}):

[a]39.9–67.5;

[b]67.6–75.2;

[c]75.3–83.9;

[d]84.0–92.9;

[e]93.0–239.1