**Prediabetes is Associated with Microalbuminuria, Reduced Kidney Function and Chronic Kidney Disease in the General Population**

**The KORA (Cooperative Health Research in the Augsburg Region) F4-Study**

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**Abstract**

**Background and Aims**

We investigated the associations of serum fasting (FG) and 2-hour postload (2HG) glucose from an oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), fasting insulin and the homeostasis model assessment-insulin resistance index (HOMA-IR) with urinary albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR).

**Methods and Results**

We performed cross-sectional analyses of 2,713 subjects (1,429 women; 52.7%) without known type 2 diabetes, aged 31 to 82 years, from the KORA (Cooperative Health Research in the Augsburg Region) F4-Study. FG, 2HG, HbA1c, fasting insulin, HOMA-IR and glucose tolerance categories were analyzed for association with ACR and eGFR in multivariable adjusted linear and median regression models, and with isolated microalbuminuria (i-MA), isolated reduced kidney function (i-RKF) and chronic kidney disease (CKD, defined as MA and/or RKF) in multivariable adjusted logistic regression models. Among the 2,713 study participants, 28% revealed prediabetes (isolated impaired fasting glucose [i-IFG], isolated glucose tolerance [i-IGT] or both by American Diabetes Association definition), 4.2% had unknown type 2 diabetes, 6.5 % had i-MA, 3.1% i-RKF and 10.9% CKD. In multivariable adjusted analysis, all continuous variables (FG, 2HG, HbA1c, fasting insulin and HOMA-IR) were associated with i-MA, i-RKF and CKD. The odds ratios (ORs) for i-MA and CKD were 1.54 (95% confidence interval: 1.02 to 2.33) and 1.58 (1.10 to 2.25) for individuals with i-IFG. Moreover, the OR for i-RKF was 2.57 (1.31 to 5.06) for individuals with IFG + IGT.

**Conclusion**

Our findings suggest that prediabetes might have harmful effects on the kidney.

**Introduction**

Chronic kidney disease (CKD) is increasingly common affecting over 12% of the population in the developed countries today.[[1](#_ENREF_1)] The number of deaths attributed to CKD has doubled in the last 20 years.[[2](#_ENREF_2)] CKD is defined based on the presence of renal damage (usually expressed as urinary albumin-to-creatinine ratio [ACR] ≥30 mg/g) or reduced kidney function (expressed as estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m²) for 3 months or more.[[3](#_ENREF_3)] Importantly, many cases of CKD are undetected, resulting in delayed treatments for CKD-related conditions including hypertension or hyperglycemia that may help avoid the progression to end-stage renal disease and cardiovascular events.[[4](#_ENREF_4)] Among the established risk factors for CKD, diabetes mellitus is thought to be responsible for almost 40% of new cases in the United States.[[3](#_ENREF_3)] Noteworthy, up to 30% of individuals with recently diagnosed diabetes mellitus present some degree of renal disease which suggests that the effects of hyperglycemia on the kidney might begin already at glycemic levels below the diabetic range.[[4](#_ENREF_4)] However, the long-term influences of prediabetes on the kidney are still unknown. It might be possible that screening for CKD in individuals presenting with prediabetes might lead to early detection and interventions resulting in fewer new cases of renal dysfunction.

A report from the National Health and Nutrition Examination Survey (NHANES, from 2009 to 2012) estimated that up to 80.8 million adult Americans (35.3%) have impaired fasting glucose.[[5](#_ENREF_5)] This indicates that the number of individuals with prediabetes might be four times the number of subjects with type 2 diabetes. In previous analyses of our group, we found that 43.1% adults in Northeast and 30.1% adults in Southeast Germany already present the diagnosis of prediabetes (according to the American Diabetes Association definition).[[6](#_ENREF_6)]

The diagnosis of diabetes and also prediabetes is based on a dichotomization of biomarkers such as serum glucose or glycated hemoglobin (HbA1c) for ease of use in primary care. However, the use of discrete thresholds to define abnormalities is artificial and distorts understanding of the underlying pathways. It is most likely that there is a non-linear dose-response association between glycemic levels and renal damage, with no clear cut-point where the risk increases. Because leakage of albumin through the glomerular filter and impaired renal function are separate phenomena, the aim of the present study was to investigate the associations of parameters (continuously and with categorization), from an oral glucose tolerance test (OGTT: fasting [FG] and 2-hour postload [2HG] serum glucose), HbA1c, fasting insulin and the homeostasis model assessment-insulin resistance index (HOMA-IR), as well as the presence of prediabetes and unknown type 2 diabetes (UT2D), with ACR, eGFR, and isolated microalbuminuria, isolated reduced kidney function and chronic kidney disease (microalbuminuria and /or reduced kidney function) in the population-based KORA (Cooperative Health Research in the Augsburg Region) F4-Study.

**Methods**

Please see the Online Data Supplement for a more detailed description.

**Study sample**

**The KORA F4 study**

The present cross-sectional analysis is based on data from the KORA F4 study, a follow-up of the KORA S4 study, a population-based health survey conducted in the city of Augsburg and 16 municipalities from the surrounding counties (about 600,000 inhabitants). A total sample of 6,640 subjects was drawn from the target population consisting of German residents of the region aged 25 to 74 years. Out of these, 4,261 participated in the baseline examination (KORA S4) between 1999 and 2001 (response 64.2%).[[7](#_ENREF_7)] Of the initially examined participants of KORA S4, 176 had died, 206 lived outside the study region or were completely lost to follow-up and 12 had demanded deletion of their address data. Of the remaining 3,867 eligible persons, 174 could not be contacted, 218 were unable to participate because they were too ill or had no time, 395 were not willing to participate in the follow-up. Finally, altogether 3,080 subjects were included in the KORA F4 examination that was conducted between 2006 and 2008. From the 3,080 participants, we excluded individuals with known diabetes mellitus (defined as validated by physician diagnosis or current use of hypoglycemic medication expressed as use of agents with the ATC code A10; n=238) and less than 8 hours of overnight fasting (n=3), as well with missing values for OGTT parameters (n=80), ACR (n=21) and other covariates (n=25). The final analytical sample comprised 2,713 individuals (1,429 women; 52.7%), aged 31 to 82 years.

All study participants gave written informed consent. The study was approved by the ethics committee of the Bavarian Medical Association and complies with the Declaration of Helsinki.

**Oral glucose tolerance test, glycated hemoglobin and classification of prediabetes and unknown type 2 diabetes**

Measurements of FG and 2HG were based on serum samples. FG was sampled, and 75 grams of anhydrous glucose (Dextro OGT; Boehringer Mannheim, Ingelheim, Germany) was given to the participants who had no overt diabetes or were not taking glucose-lowering agents. FG and 2HG levels were measured using a hexokinase method (GLU Flex, Dade Behring, Marburg, Germany).[[6](#_ENREF_6)]

Following the criteria of the American Diabetes Association (ADA),[[8](#_ENREF_8)] we classified individuals as having normal glucose tolerance (NGT) when they had FG values <5.6 mmol/l (<100 mg/dl) and 2HG <7.8 mmol/l (<140mg/dl). UT2D was defined as FG values ≥7.0 mmol/l (≥126 mg/dl) or 2HG ≥11.1 mmol/l (≥200mg/dl). We classified participants as having prediabetes if FG values were between 5.6 and 6.9 mmol/l (100-125 mg/dl, impaired fasting glucose: IFG) and/or 2HG values were between 7.8 and 11.0 mmol/l (140-199 mg/dl, impaired glucose tolerance: IGT).[[6](#_ENREF_6), [8](#_ENREF_8)] We defined three groups of prediabetes: isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and combined IFG and IGT (IFG + IGT).[[6](#_ENREF_6), [8](#_ENREF_8)]

HbA1c was quantified with a reverse-phase cation-exchange high-performance liquid chromatography method using a Menarini–Arkray Analyzer HA-8160 (Menarini Diagnostics, Florence, Italy).[[9](#_ENREF_9)]

Following the criteria of the ADA for HbA1c levels,[[8](#_ENREF_8)] we classified individuals as having normal glucose levels (NGL) when they had HbA1c values <39 mmol/mol (<5.7%). UT2D was defined as HbA1c values ≥48 mmol/mol (≥6.5%). We classified participants as having prediabetes if HbA1c values were between 39 and 47 mmol/mol (5.7 to 6.4%).[[8](#_ENREF_8)]

Fasting insulin from frozen serum was assessed by electrochemiluminescence immunoassay (ECLIA Cobas; Roche Diagnostics GmbH, Mannheim, Germany) and the homeostasis model assessment-insulin resistance index (HOMA-IR) was calculated as (fasting insulin [μU/ml] X fasting glucose [mmol/l])/22.5.[[10](#_ENREF_10)]

**Urinary albumin-to-creatinine ratio and estimated glomerular filtration rate**

Urinary albumin and urinary creatinine were determined from frozen urine (sampled by a random spot urine specimen) with a modified kinetic rate Jaffe method (CREATININ-JK, Greiner, Bahlingen, Germany) on a Cobas Mira analyzer (Roche Diagnostics, Mannheim, Germany) and by nephelometry on a BN II analyzer (Siemens, Erlangen, Germany). ACR was calculated as urinary creatinine / urinary albumin.

Serum creatinine concentration was assessed using a modified kinetic rate Jaffe method (Krea Flex, Dade Behring, Marburg, Germany),[[10](#_ENREF_10)] The eGFR was determined according to the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) formula[[11](#_ENREF_11)] and expressed in ml/min/1.73 m²:

**Isolated** microalbuminuria (i-MA) was defined as an ACR ≥ 30 mg/g (**together** with an eGFR ≥ 60 ml/min/1.73 m²).[[12](#_ENREF_12)]

**Isolated** reduced kidney function (i-RKF) was defined as an eGFR < 60 ml/min/1.73 m² (**together** with an ACR < 30 mg/g).[[12](#_ENREF_12)]

CKD was defined as an ACR ≥ 30 mg/g and/or an eGFR < 60 ml/min/1.73 m².[[12](#_ENREF_12)]

**Statistical analysis**

To characterize the study population, data was reported as median (with 25th and 75th percentiles) for continuous variables and as percentages for categorical variables stratified by OGTT classification.

The associations of FG, 2HG, HbA1c, fasting insulin and HOMA-IR levels with ACR and eGFR were investigated by linear regression models adjusting for sex, age, height, years of school education, smoking status and alcohol consumption. The associations of the outcome ACR were analyzed using quantile regression[[13](#_ENREF_13)] because this variable was neither normally distributed nor homoscedastic, as confirmed by residual analyses. In sensitivity analysis, we estimated an extra model after further adjustment for variables that might be confounders or mediate the associations between exposures and outcomes, namely, waist circumference, total cholesterol and systolic blood pressure levels. In order to evaluate the robustness of our findings in light of dropout from baseline to follow-up examination, we performed inverse probability weighting[[14](#_ENREF_14)] based on sociodemographic and health-related variables in our analyses. We used fractional polynomials to model non-linear relationships between exposure and outcomes. [[15](#_ENREF_15)]

We also analyzed the associations of the OGTT groups and the groups based on HbA1c with ACR and eGFR by quantile and linear regression models adjusted for sex, age, height, years of school education, smoking status and alcohol consumption.

Multiple logistic regression analyses, adjusted for sex, age, height, years of school education, smoking status and alcohol consumption, were used to relate the continuous variables FG, 2HG, HbA1c, fasting insulin and HOMA-IR levels to i-MA, i- RKF and CKD. The reference group had an ACR < 30 mg/g and an eGFR ≥ 60 ml/min/1.73 m². We also analyzed the associations, using the same adjustments and reference group, according to the OGTT groups and the groups based on HbA1c.

A two-sided p-value p<0.05 was considered as statistically significant. Statistical analyses were performed using Stata 14.1 (Stata Corporation, College Station, TX, USA).

**Results**

Among the total study sample of 2,713 individuals (1,429 women, 52.7%), the occurrence of prediabetes (i-IFG, i-IGT, and IFG + IGT) was 28.0%. Isolated IFG (51.8% of all prediabetes individuals) or IFG + IGT (23.3%) was responsible for the majority of the cases. I-IGT was identified in 24.9% of all prediabetes subjects. Moreover, the prevalence of UT2D was 4.2%. Additionally, among all study participants, 6.5% had i-MA, 3.1% had i-RKF and 10.9% had CKD. The clinical and laboratory characteristics of all study participants stratified by OGTT are provided in **Table 1**. Individuals with NGT were younger, more likely female, had a lower BMI and waist circumference and were less likely to suffer from hypertension and hypercholesterolemia, with a concomitant less frequent use of antihypertensive and lipid-lowering medication, and to have previous myocardial infarction and stroke. They also had lower fasting insulin levels, ACR excretion and alcohol intake, higher eGFR and were more likely to be current smokers.

**Associations of FG, 2HG, HbA1c, fasting insulin and HOMA-IR index with ACR, eGFR, i-MA, i-RKF and CKD**

The left side of the **Figure 1** shows the associations of FG, 2HG, HbA1c, fasting insulin and HOMA-IR with ACR. In multivariable adjusted regression analyses, we observed statistically significant positive linear associations of FG, 2HG, HbA1c, fasting insulin and HOMA-IR index with ACR. A 1 mmol/l increase in FG or 2HG was associated with an increase of 0.75 mg/g (95% confidence interval: 0.33 to 1.16; p<0.001) or 0.15 mg/g (0.02 to 0.28; p=0.029), respectively, in ACR excretion, while an increase of 1% in HbA1c was associated with an increase of 1.37 mg/g (0.75 to 1.99; p<0.001) in ACR excretion. Moreover, an increase of 1 µlU/ml in fasting insulin or 1 unit in HOMA-IR was associated with an increase of 0.06 mg/g (0.01 to 0.10; p=0.007) or 0.23 mg/g (0.10 to 0.37; p=0.001), respectively, in ACR excretion (**Figure 1**). The additional further adjustment for waist circumference, total cholesterol and systolic blood pressure levels slightly attenuated the associations of FG and HbA1c with ACR. The results were 0.50 mg/g (0.14 to 0.87; p=0.007) for FG and 1.04 mg/g (0.51 to 1.57; p<0.001) for HbA1c. However, associations of 2HG, fasting insulin and HOMA-IR with ACR became non-significant.

The right side of the **Figure 1** shows the associations of FG, 2HG, HbA1c, fasting insulin and HOMA-IR with eGFR. While FG, fasting insulin levels and HOMA-IR index were inversely nonlinear associated with eGFR (all p<0.001), 2HG and HbA1c were not associated with eGFR (**Figure 1**). After supplementary adjustment for waist circumference, total cholesterol and systolic blood pressure levels, there was no considerable change in the associations (p=0.004 for FG and p<0.001 for fasting insulin and HOMA-IR). In sensitivity analysis, we evaluated the above associations after exclusion of individuals with CKD (defined as an ACR ≥ 30 mg/g and/or an eGFR < 60 ml/min/1.73 m²) and the results (regarding the loss of power because of fewer participants, n= 2,417 instead of 2,713) were largely the same (Supplementary Figure I).

**Table 2** shows the ORs for prevalent i-MA, i-RFK and CKD associated with FG, 2HG, HbA1c, fasting insulin and HOMA-IR. All the continuous variables (FG, 2HG, HbA1c, fasting insulin and HOMA-IR) were associated with higher OR for i-MA, i-RFK and CKD.

**Associations of the OGTT groups and the groups based on HbA1c with ACR, eGFR, i-MA, i-RKF and CKD**

In multivariable adjusted regression analyses, we observed statistically significantly higher mean values of ACR in the groups i-IFG and UT2D, when compared with the NGT group, but the i-IGT and IFG + IGT groups were not significantly different (**Table 3**). Based on HbA1c levels, while there was higher means value of ACR in the group prediabetes, there was no statistically significant difference regarding the mean value of ACR in the group UT2D (there was a trend, but as this group was very small, n=36, the CI was very wide) when compared with the NGL group (**Table 4**).

Regarding eGFR, we observed statistically significantly lower mean values of eGFR in the groups IFG + IGT and UT2D, when compared with the NGT group, but the i-IFG and the i-IGT groups were not significantly different (**Table 3**). Based on HbA1c levels, we did not found differences between the NGL, prediabetes and UT2D groups (**Table 4**).

The UT2D group (based in FG and 2HG levels) was associated with i-MA, i-RKF and CKD (**Table 5**). The i-IFG group was associated with higher ORs for i-MA and CKD, but not for i-RKF. The IFG + IGT group was associated with higher ORs for i-RKF and CKD while the i-IGT group was not associated with any of these groups (**Table 5**).

While the UT2D group (based on HbA1c levels) was associated with i-MA and CKD, but not i-RKF, the prediabetes group was not associated with any of the groups (**Table 6**).

**Discussion**

Our results showed a positive association of both FG (which represents nocturnal hepatic gluconeogenesis, dependent of hepatic insulin sensitivity) and 2HG (which reflects a postprandial hyperglycemia), HbA1c, fasting insulin and HOMA-IR with ACR. We also showed that FG, fasting insulin and HOMA-IR levels, but not 2HG and HbA1c, were inversely associated with eGFR. Moreover, we show a vast number of kidney parameters demonstrating that prediabetes (based on OGTT classification) is associated with higher ACR and lower eGFR and increases in the odds of isolated microalbuminuria, isolated reduced kidney function and chronic kidney disease.

Higher glucose and insulin levels and higher ACR excretion and lower eGFR share several cardiovascular and metabolic risk factors and co-morbidities like older age, obesity, hypercholesterolemia and hypertension that might explain those associations as a parallel event rather than a causal relation. However, we have incorporated various risk factors in our multivariable regression models that might suggest a direct relation between higher glucose and/or insulin levels and higher ACR excretion and lower eGFR. Regrettably, the cross-sectional design of our analyses limits the assessment of temporal ordering.

**In the context of the published literature**

In line with our results, a previous analysis from the Framingham Offspring Study[[16](#_ENREF_16)] found that the ORs for incident microalbuminuria, associated with a 0.28 mmol/l (5 mg/dl) increase in the fasting glucose levels, was 1.12 (1.00 to 1.26) for men and 1.11 (1.01 to 1.22) for women in age-adjusted models. The study also found that insulin levels were positively associated with ACR. Alternatively, contrary to our findings that showed an association of i-IFG and UT2D, but not i-IGT and IFG + IGT with microalbuminuria; a cross-sectional analysis[[17](#_ENREF_17)] among Chinese individuals found that the ORs for microalbuminuria was 1.01 (0.51 to 1.99) for individuals with i-IFG, 2.05 (1.40 to 3.01) with i-IGT, 2.60 (95%CI: 1.65 to 4.09) with IFG + IGT and 4.03 (2.95 to 5.50) with UT2D.

Cross-sectional analysis[[18](#_ENREF_18)] of 1,112 Chinese found that FG, insulin and HOMA-IR, but not 2HG and HbA1c, were inversely associated with eGFR which is in agreement with our findings. On the other hand, contrary to our findings, only FG, but not 2HG, HbA1c, insulin and HOMA-IR, was associated with i-RKF.

Finally, a recent systematic review and meta-analysis[[4](#_ENREF_4)] of 9 cohort studies concluded that prediabetes was associated with an increased risk for CKD of 1.12 (1.02 to 1.21). However, based that the analyzed studies described risks for CKD that varied from 0.97 to 1.84, the authors also concluded that the findings still need more robust confirmation. In line with this statement, and contrary with our findings, the Framingham Heart Study[[19](#_ENREF_19)] found that the odds for developing CKD were 0.98 (95% CI 0.67-1.45) and 1.71 (95% CI 0.83-3.55) among persons with prediabetes (IFG or IGT) and UT2D, respectively, in comparison to subjects with normoglycemia at baseline. The outcome incident CKD was defined as an eGFR < 60 ml/min/1.73 m² without considering microalbuminuria, which might have underestimated the diagnosis. Moreover, the definition of prediabetes included IFG or IGT, but not each of the groups isolated, which might also have had an effect on the results. Finally, the fully adjusted model included correction for multiple vascular disease risk factors that might be just parallel developments, or intermediate factors, leading to a possible over-adjustment. On the other hand, and in agreement with our results (considering that our analyses were just cross-sectional), the Strong Heart Study[[20](#_ENREF_20)] found that IFG was associated with a hazard ratio for developing CKD of 1.40 (1.10 to 1.78).

**Study limitations**

Some limitations of this study ought to be mentioned. First, the sample of our study comprised middle-aged Caucasians; therefore, further analyses of samples with other ethnicity and age groups would be needed to investigate the strength of this association across those groups. Second, the cross-sectional design of the study represents a limitation, implicating that cause and effect relationships cannot be discerned. Finally, even though we have incorporated numerous confounders in our multivariable regression models, we cannot exclude unmeasured confounding.

In spite of these limitations, our analyses have also some significant strengths, including the large number of subjects based on the general population, the standardized assessment of OGTT data after an overnight fast, and the availability of data on lifestyle and multiple metabolic risk factors.

**Conclusions**

Our results showed a positive association of both FG and 2HG and HbA1c, fasting insulin and HOMA-IR with ACR. We also found that FG, fasting insulin and HOMA-IR levels, but not 2HG and HbA1c, were inversely associated with eGFR. Moreover, we found that prediabetes is associated with higher ACR and lower eGFR and increases the chances for isolated microalbuminuria, isolated reduced kidney function and chronic kidney disease.

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**Conflict of interest**

Michael Roden reports personal fees from Sanofi-Aventis, Merck, Genentech, GI Dynamics, Boehringer Ingelheim Novo Nordisk and Poxel S.A.

All other authors declared no competing interests.

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**Figure Legends**

**Figure 1:** Adjusted# line (95% CI) showing the associations between fasting glucose (FG), 2-hour postload (2HG) glucose, glycated hemoglobin (HbA1c) and fasting insulin levels and the homeostasis model assessment-insulin resistance index (HOMA-IR) with urinary albumin-to-creatinine ratio (ACR, left) and estimated glomerular filtration rate (eGFR, right).

#Linear regression adjusted for sex, age, height, waist circumference, years of school education, smoking status and alcohol consumption.

**Table 1:** Characteristics of the study sample at the KORA-F4 examination stratified by oral glucose tolerance test (OGTT) classification: normal glucose tolerance (NGT), isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), combined IFG and IGT (IFG + IGT) and unknown type 2 diabetes (UT2D).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **NGT** | **i-IFG** | **i-IGT** | **IFG + IGT** | **UT2D** | **p-value\*** |
| **N (%)** | 1,840 (67.8) | 393 (14.5) | 189 (7.0) | 177 (6.5) | 114 (4.2) |  |
| **Age (years)** | 51 (41, 62) | 59 (51, 69) | 66 (54, 74) | 65 (59, 71) | 65 (58, 74) | **<0.001** |
| **Women (%)** | 57.8 | 33.3 | 60.3 | 41.2 | 41.2 | **<0.001** |
| **Fasting serum glucose (mmol/l)** | 5.0 (4.7, 5.3) | 5.9 (5.7, 6.1) | 5.2 (4.9, 5.4) | 6.0 (5.7, 6.4) | 6.7 (5.7, 6.5) | **<0.001** |
| **2-hour postload serum glucose (mmol/l)** | 5.3 (4.6, 6.2) | 6.1 (5.3, 6.9) | 8.7 (8.2, 9.6) | 8.9 (8.3, 10.0) | 12.0 (11.2, 13.4) | **<0.001** |
| **Glycated hemoglobin (%)** | 5.3 (5.1, 5.5) | 5.6 (5.4, 5.8) | 5.5 (5.3, 5.7) | 5.7 (5.5, 6.0) | 6.1 (5.7, 6.5) | **<0.001** |
| **Serum insulin (µlU/ml)** | 7.7 (5.6, 10.0) | 11.0 (7.9, 16.0) | 11.0 (7.6, 15.0) | 13.0 (9.6, 21.0) | 17.0 (11.0, 27.0) | **<0.001** |
| **Homeostasis model assessment-insulin**  **resistance index (HOMA-IR)** | 1.71 (1.21, 2.30) | 2.88 (2.04, 4.28) | 2.42 (1.71, 3.67) | 3.45 (2.56, 5.52) | 5.37 (3.18, 7.90) | **<0.001** |
| **Urinary albumin-to-creatinine ratio (mg/g)** | 5.29 (3.44, 9.67) | 6.37 (3.83, 11.9) | 6.33 (3.95, 12.4) | 7.20 (4.02, 14.7) | 7.96 (4.62, 20.4) | **<0.001** |
| **Isolated microalbuminuria (%)** | 5.3 | 9.7 | 5.8 | 8.5 | 13.2 | **<0.001** |
| **Estimated glomerular filtration rate (ml/min/1.73 m²)** | 97.7 (84.9, 108) | 89.8 (77.3, 99.0) | 86.3 (75.2, 97.4) | 82.7 (70.2, 91.8) | 82.2 (66.8, 93.7) | **<0.001** |
| **Isolated reduced kidney function (%)** | 1.85 | 3.56 | 5.29 | 8.47 | 10.5 | **<0.001** |
| **Chronic kidney disease (%)** | 7.9 | 15.0 | 13.2 | 19.8 | 28.1 | **<0.001** |
| **Years of school education (%)** |  |  |  |  |  |  |
| Less than 10 years | 46.1 | 56.7 | 59.3 | 57.1 | 66.7 |  |
| 10 years | 27.4 | 20.6 | 25.4 | 23.2 | 16.7 |  |
| More than 10 years | 26.5 | 22.7 | 15.3 | 19.8 | 16.7 | **<0.001** |
| **Smoking (%)** |  |  |  |  |  |  |
| Never | 44.3 | 39.2 | 51.9 | 51.4 | 43.0 |  |
| Current | 21.1 | 15.3 | 9.5 | 7.3 | 14.0 |  |
| Former | 34.6 | 45.6 | 38.6 | 41.2 | 43.0 | **<0.001** |
| **Alcohol consumption (g/day)** | 5.71 (0.00, 20.0) | 8.57 (0.00, 27.5) | 5.71 (0.00, 19.3) | 10.7 (0.89, 22.9) | 8.57 (0.0.0, 25.7) | **0.003** |
| **Weight (kg)** | 74.1 (64.9, 84.6) | 83.7 (73.2, 92.7) | 76.7 (71.1, 88.1) | 83.1 (75.2, 94.9) | 87.1 (77.2, 92.4) | **<0.001** |
| **Height (cm)** | 169 (162, 176) | 171 (164, 178) | 164 (158, 171) | 169 (161, 175) | 168 (160, 173) | **<0.001** |
| **Body mass index (kg/m2)** | 25.7 (23.4, 28.7) | 28.2 (25.8, 30.9) | 29.1 (25.7, 31.7) | 29.8 (26.8, 33.3) | 30.5 (28.2, 33.4) | **<0.001** |
| **Waist circumference (cm)** | 89.2 (80.2, 97.7) | 98.6 (91.5, 106) | 96.3 (89.1, 105) | 101 (94.2, 110) | 104 (95.3, 111) | **<0.001** |
| **Systolic blood pressure (mm Hg)** | 116 (106, 128) | 127 (117, 139) | 123 (111, 139) | 132 (120, 139) | 133 (119, 144) | **<0.001** |
| **Diastolic blood pressure (mm Hg)** | 73.5 (67.5, 80.5) | 77.0 (71.0, 85.0) | 74.0 (69.0, 82.0) | 78.0 (71.5, 84.5) | 76.0 (71.0, 83.5) | **<0.001** |
| **Hypertension (%)** | 27.3 | 52.9 | 57.7 | 68.9 | 83.3 | **<0.001** |
| **Antihypertensive medications (%)** | 19.2 | 37.2 | 44.4 | 56.5 | 69.3 | **<0.001** |
| **Total cholesterol (mmol/l)** | 5.50 (4.86, 6.15) | 5.68 (5.01, 6.30) | 5.79 (5.01, 6.41) | 5.81 (5.22, 6.59) | 5.52 (5.06, 6.20) | **<0.001** |
| **Hypercholesterolemia (%)** | 39.3 | 58.3 | 59.8 | 62.2 | 64.0 | **<0.001** |
| **Lipid-lowering medication (%)** | 8.1 | 14.0 | 16.9 | 17.5 | 21.1 | **<0.001** |
| **Prevalent myocardial infarction (%)** | 1.41 | 3.56 | 5.82 | 5.62 | 6.14 | **<0.001** |
| **Prevalent stroke (%)** | 1.3 | 2.29 | 1.06 | 3.95 | 6.14 | **<0.001** |

Data are medians (25th, 75th percentile) or percentage.

\*p-values are based on the chi-squared test for categorical variables and the Wilcoxon rank-sum (or Mann-Whitney) tests for continuous variables.

**Table 2:** Adjusted# odds ratio (95% CI) for isolated microalbuminuria (i-MA), isolated reduced kidney function (i-RKF) and for chronic kidney disease (CKD) according to fasting glucose (FG), 2-hours postload glucose (2HG), glycated hemoglobin (HbA1c), fasting insulin levels, and the homeostasis model assessment-insulin resistance index (HOMA-IR).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **FG** | **2HG** | **HbA1c** | **Insulin** | **HOMA-IR** |
| **i-MA** | 1.43 (1.21 to 1.68) | 1.25 (1.09 to 1.44) | 1.00 (1.00 to 1.00) | 1.02 (1.00 to 1.04) | 1.08 (1.02 to 1.15) |
| **p-value\*** | **<0.001** | **0.002** | **0.002** | **0.038** | **0.009** |
| **i-RKF** | 1.91 (1.31 to 2.79) | 1.11 (1.00 to 1.22) | 2.07 (1.16 to 3.68) | 1.03 (1.01 to 1.06) | 1.13 (1.04 to 1.23) |
| **p-value\*** | **0.001** | **0.045** | **0.014** | **0.013** | **0.006** |
| **CKD** | 1.54 (1.31 to 1.81) | 1.29 (1.10 to 1.52) | 1.56 (1.21 to 2.02) | 1.02 (1.01 to 1.04) | 1.63 (1.31 to 2.03) |
| **p-value\*** | **<0.001** | **0.002** | **0.001** | **0.007** | **<0.001** |

#Logistic regression adjusted for sex, age, height, waist circumference, years of school education, smoking status and alcohol consumption. p-value is based on the Wald test.

**Table 3:** Adjusted# mean (95% CI) urinary albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) according to oral glucose tolerance test (OGTT) classification: normal glucose tolerance (NGT), isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), combined IFG and IGT (IFG + IGT) and unknown type 2 diabetes (UT2D).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **NGT** | **i-IFG** | **i-IGT** | **IFG + IGT** | **UT2D** |
| **ACR (mg/g)** | 5.77 (5.48 to 6.07) | 6.63 (6.12 to 7.14) | 5.88 (5.10 to 6.66) | 6.78 (5.55 to 8.02) | 7.89 (6.58 to 9.20) |
| **p-value\*** |  | **0.002** | 0.803 | 0.122 | **0.002** |
| **eGFR (ml/min/1.73 m²)** | 92.5 (92.0 to 93.1) | 91.2 (89.9 to 92.5) | 93.6 (91.8 to 95.5) | 89.6 (87.6 to 91.5) | 89.9 (87.4 to 92.4) |
| **p-value\*** |  | 0.065 | 0.272 | **0.004** | **0.045** |

#Linear regression adjusted for sex, age, height, waist circumference, years of school education, smoking status and alcohol consumption.

\*p-values when compared with NGT group.

**Table 4:** Adjusted# mean (95% CI) urinary albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) according to glycated hemoglobin (HbA1c) classification: normal glucose levels (NGL, n=2,239), prediabetes and unknown type 2 diabetes (UT2D).

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **NGL**  **2,239 (82.5%)** | **Prediabetes**  **438 (16.1%)** | **UT2D**  **36 (1.33%)** |
| **ACR (mg/g)** | 5.89 (5.62 to 6.15) | 6.70 (5.98 to 7.43) | 8.98 (4.00 to 14.0) |
| **p-value\*** |  | **0.041** | 0.224 |
| **EGFR (ml/min/1.73 m²)** | 92.2 (91.7 to 92.7) | 91.7 (90.5 to 92.9) | 89.5 (86.0 to 93.0) |
| **p-value\*** |  | 0.455 | 0.127 |

#Linear regression adjusted for sex, age, height, waist circumference, years of school education, smoking status and alcohol consumption.

\*p-values when compared with NGL group.

**Table 5:** Adjusted# odds ratio (95% CI) for isolated microalbuminuria (i-MA), isolated reduced kidney function (i-RKF) and chronic kidney disease (CKD) according to oral glucose tolerance test (OGTT) classification: normal glucose tolerance (NGT), isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), combined IFG and IGT (IFG + IGT) and unknown type 2 diabetes (UT2D) .

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **NGT** | **i-IFG** | **i-IGT** | **IFG + IGT** | **UT2D** |
| **i-MA** | reference | 1.54 (1.02 to 2.33) | 0.77 (0.39 to 1.55) | 1.28 (0.71 to 2.29) | 1.91 (1.02 to 3.58) |
| **p-value\*** |  | **0.041** | 0.469 | 0.414 | **0.043** |
| **i-RKF** | reference | 1.48 (0.75 to 2.93) | 0.84 (0.37 to 1.90) | 2.57 (1.31 to 5.06) | 2.56 (1.07 to 6.15) |
| **p-value\*** |  | 0.263 | 0.676 | **0.006** | **0.035** |
| **CKD** | reference | 1.58 (1.10 to 2.25) | 0.79 (0.47 to 1.33) | 1.65 (1.07 to 2.55) | 2.20 (1.30 to 3.74) |
| **p-value\*** |  | **0.013** | 0.375 | **0.024** | **0.004** |

#Logistic regression adjusted for sex, age, height, waist circumference, years of school education, smoking status and alcohol consumption.

\* p-value is based on the Wald test.

**Table 6:** Adjusted# odds ratio (95% CI) for isolated microalbuminuria (i-MA), isolated reduced kidney function (i-RKF) and chronic kidney disease (CKD) according to glycated hemoglobin (HbA1c) classification: normal glucose levels (NGL), prediabetes and unknown type 2 diabetes (UT2D).

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **NGL**  **2,239 (82.5%)** | **Prediabetes**  **438 (16.1%)** | **UT2D**  **36 (1.33%)** |
| **i-MA** | reference | 1.15 (0.77 to 1.70) | 3.36 (1.40 to 8.06) |
| **p-value\*** |  | 0.499 | **0.007** |
| **i-RKF** | reference | 1.58 (0.95 to 2.63) | 0.70 (0.07 to 6.68) |
| **p-value\*** |  | 0.081 | 0.760 |
| **CKD** | reference | 1.26 (0.93 to 1.72) | 2.66 (1.09 to 6.48) |
| **p-value\*** |  | 0.141 | **0.031** |

#Logistic regression adjusted for sex, age, height, waist circumference, years of school education, smoking status and alcohol consumption.

\*p-value is based on the Wald test.

**Figure 1:**

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