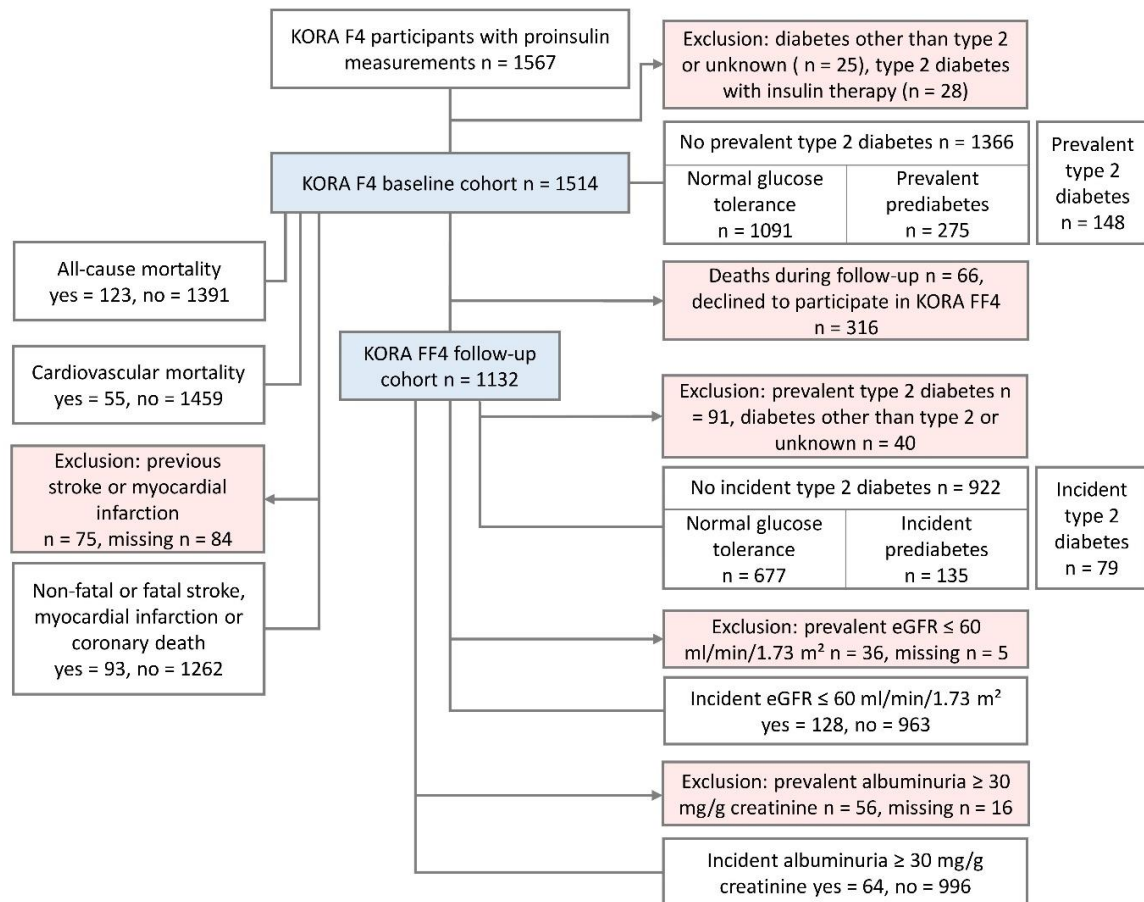


Supplementary Figure 1 Flow chart showing sample sizes and reasons for exclusions. The median (1st; 3rd quartile) follow-up time was 6.6 (6.4; 6.8) years between KORA F and KORA FF4, 9.1 (8.8; 9.4) years for total and cardiovascular mortality and 8.6 (8.1; 9.0) years for incident stroke/myocardial infarction.



Supplementary Table 1 Characteristics of the study participants who initially had no type 2 diabetes at KORA F4, stratified by incident type 2 diabetes status ^a.

	Non-progressors to incident type 2 diabetes	Incident type 2 diabetes	p value
n	922	79	-
Male sex n (%)	436 (47)	48 (61)	0.03 ^e
Age (years)	53.1 ± 11.7	61.4 ± 10.8	<0.001 ^c
BMI (kg/m ²)	26.5 ± 4.2	30.3 ± 4.8	<0.001 ^c
Waist circumference (cm)	90.2 ± 12.5	102.5 ± 13.7	<0.001 ^c
HbA1c (%)	5.3 (5.1; 5.5)	5.8 (5.5; 6.0)	<0.001 ^d
HbA1c (mmol/mol)	34.4 (32.2; 36.6)	39.9 (36.6; 41.5)	<0.001 ^d
Arterial hypertension n (%) ^b	262 (28)	45 (57)	<0.001 ^e
Physically inactive n (%) ^c	327 (36)	42 (53)	0.003 ^e
Proinsulin (pmol/l)	2.5 (1.8; 3.7)	5.1 (3.6; 7.8)	<0.001 ^d
Insulin (pmol/l)	48.6 (36.0; 66.0)	78.0 (55.8; 126.0)	<0.001 ^d
Proinsulin-to-insulin ratio	0.051 (0.037; 0.072)	0.065 (0.046; 0.092)	<0.001 ^d

^a mean ± standard deviation, median (first quartile; third quartile), or number of participants (proportion in %);

^b defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive medication, given that the participants were aware of being hypertensive;

^c T-test; ^d Mann-Whitney U-test; ^e Chi-square test.

Supplementary Table 2 Cross-sectional association estimates between proinsulin-to-insulin ratio and HOMA-IR stratified by glucose tolerance status: β coefficients ± standard error from linear regression models are given per standard deviation proinsulin-to-insulin ratio.

	HOMA-IR	p value
Adjustment for sex, age, BMI, physical activity (Model 2)		
Normal glucose tolerance (n = 1091)	-0.29 ± 0.02	< 0.001
Prediabetes (n = 275)	-0.12 ± 0.05	0.008
Type 2 diabetes (n = 82)	-0.32 ± 0.10	0.002

Supplementary Table 3 Cross-sectional association estimates between proinsulin and components of the metabolic syndrome adjusted for sex, age and physical activity (Model 1): β coefficients \pm standard error from linear regression models are given per standard deviation.

	Adjusted $\beta \pm$ standard error	p value
Elevated waist circumference^a (yes: n = 1011; no: n = 503)	0.42 \pm 0.05	<0.001
Elevated triglycerides^b (yes: n = 371; no: n = 1143)	0.33 \pm 0.05	<0.001
Reduced HDL cholesterol^c (yes: n = 276; no: n = 1238)	0.21 \pm 0.06	<0.001
Elevated fasting glucose^d (yes: n = 463; no: n = 1051)	0.58 \pm 0.05	<0.001
Elevated blood pressure^e (yes: n = 740; no: n = 774)	0.22 \pm 0.05	<0.001

^a defined as ≥ 80 cm in women and ≥ 94 cm in men;

^b defined as ≥ 1.7 mmol/l and/or intake of fibrates or nicotinic acid;

^c defined as < 1.0 mmol/l in men and < 1.3 mmol/l in women and/or intake of fibrates or nicotinic acid;

^d defined as ≥ 5.6 mmol/l and/or intake of anti-diabetic medication;

^e defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or use of antihypertensive medication, given that the participants were aware of being hypertensive.

Supplementary Table 4 Cross-sectional association estimates of the association of proinsulin-to-insulin ratio or proinsulin alone, respectively, with intima-media thickness: β coefficients \pm standard error from linear regression models are given per standard deviation. n = 1239 (type 2 diabetes n = 115; without diabetes n = 1124).

Proinsulin-to-insulin ratio	p value	Proinsulin	p value
Without adjustment			
0.12 \pm 0.03	< 0.001	0.25 \pm 0.03	< 0.001
Adjustment for sex, age, BMI, arterial hypertension, physical activity (Model 3)			
-0.04 \pm 0.02	0.093	-0.04 \pm 0.03	0.072

Supplementary Table 5: Odds ratios (95% confidence interval) for incident albuminuria ≥ 30 mg/g creatinine and incident chronic kidney disease in dependence on proinsulin-to-insulin ratio or proinsulin, respectively, (per standard deviation). Prevalent cases at baseline ($n = 36$ for eGFR < 60 ml/min/1.73 m² and $n = 56$ for albuminuria ≥ 30 mg/g creatinine) were excluded. $N = 16$ values were missing for the analysis of incident albuminuria ≥ 30 mg/g creatinine and $n = 5$ values were missing for the analysis of incident eGFR < 60 ml/min/1.73 m².

Proinsulin-to-insulin ratio		Proinsulin	
Incident albuminuria ≥ 30 mg/g creatinine	Incident eGFR < 60 ml/min/1.73 m ²	Incident albuminuria ≥ 30 mg/g creatinine	Incident eGFR < 60 ml/min/1.73 m ²
n (non-cases) ^a : 996	n (non-cases) ^a : 963	n (non-cases) ^a : 996	n (non-cases) ^a : 963
n (cases) ^b : 64	n (cases) ^b : 128	n (cases) ^b : 64	n (cases) ^b : 128
Without adjustment			
1.44 (1.13-1.88) **	1.40 (1.16-1.69) ***	1.57 (1.21; 2.03) ***	1.93 (1.58; 2.35) ***
Adjustment for sex, age, BMI, arterial hypertension, physical activity, baseline eGFR, baseline albumin/creatinine ratio	Adjustment for sex, age, BMI, arterial hypertension, physical activity, baseline eGFR	Adjustment for sex, age, BMI, arterial hypertension, physical activity, baseline eGFR, baseline albumin/creatinine ratio	Adjustment for sex, age, BMI, arterial hypertension, physical activity, baseline eGFR
1.29 (0.96-1.74)	1.13 (0.88-1.45)	1.14 (0.81; 1.59)	1.30 (0.97; 1.74)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$;

^a number of participants without events;

^b number of events.

Supplementary Table 6: Hazard ratios (95% confidence interval) for all-cause mortality, cardiovascular mortality, non-fatal and fatal stroke, and non-fatal myocardial infarction or coronary death in dependence on proinsulin (per standard deviation).

All-cause mortality	Cardiovascular mortality	Non-fatal or fatal stroke, myocardial infarction, or coronary death
n (non-cases) ^a : 1391	n (non-cases) ^a : 1459	n (non-cases) ^a : 1262
n (cases) ^b : 123	n (cases) ^b : 55	n (cases) ^b : 93
Without adjustment		
1.91 (1.59; 2.28) ***	1.79 (1.37; 2.35) ***	1.67 (1.31; 1.99) ***
Adjustment for sex, age, BMI, arterial hypertension, physical activity		
1.35 (1.07; 1.70) *	1.14 (0.80; 1.62)	0.98 (0.78; 1.26)

* $p < 0.05$; *** $p < 0.001$;

^a number of participants without events;

^b number of events.