

Table S1. Multivariable adjusted linear regression analyses with log-transformed C-peptide as dependent variable in 5176 participants of the PREVEND study.

Variables	Age- and sex-adjusted		Age-, sex-, and insulin-adjusted		Multivariable adjusted (R ² =0.721)	
	Standardized β	<i>p</i> value	Standardized β	<i>p</i> value	Standardized β	<i>p</i> value
Sex, female vs. male	—	—	—	—	0.040	<0.001
Age, years	—	—	—	—
Family history of diabetes, yes vs. no	0.071	<0.001	0.033	<0.001
Alcohol, yes vs. no	-0.09	<0.001
BMI, kg/m ²	0.530	<0.001	0.179	<0.001	0.120	<0.001
Systolic blood pressure, mm Hg	0.235	<0.001	0.060	<0.001	-0.039	0.002
Dystolic blood pressure, mm Hg	0.207	<0.001	0.072	<0.001	0.056	<0.001
Antihypertensive medication, yes vs. no	0.202	<0.001	0.07	<0.001
Total cholesterol, mmol/L	0.108	<0.001	0.023	<0.001
HDL cholesterol, mmol/L	-0.416	<0.001	-0.143	<0.001	-0.052	<0.001
Triglycerides, mmol/L	0.458	<0.001	0.181	<0.001	0.140	<0.001
Lipid-lowering medication, yes vs. no	0.132	<0.001	0.046	<0.001
Plasma ASAT (U/L)	0.150	<0.001	-0.070	<0.001
Plasma ALAT (U/L)	0.333	<0.001	0.084	<0.001	0.103	<0.001
Glucose, mmol/L	0.336	<0.001	0.113	<0.001	0.096	<0.001
Insulin (Mu/L)	0.754	<0.001	—	—	0.549	<0.001
eGFR, mL/min/1.73 m ²	-0.275	<0.001	-0.162	<0.001	-0.151	<0.001
Urinary albumin excretion, mg/24 hours	0.161	<0.001	0.061	<0.001	0.029	0.001

ASAT: L-aspartate aminotransferase; ALAT: L-alanine aminotransferase; eGFR: estimated glomerular filtration rate; PREVEND: Prevention of renal and vascular End-stage Disease

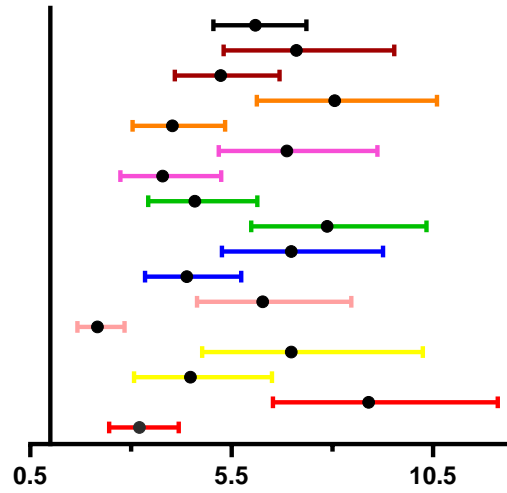
Table S2. Additive Value of C-Peptide and Insulin, for the Prediction of Type 2 Diabetes

	C-statistics (95% CI)	<i>p</i> value for change in C-statistics
FOS risk model	0.888 (0.870-0.907)	
Fos risk model+ C-peptide	0.891 (0.873-0.909)	0.04
Fos risk model+ insulin	0.889 (0.870-0.908)	0.27

FOS: Framingham Offspring risk score

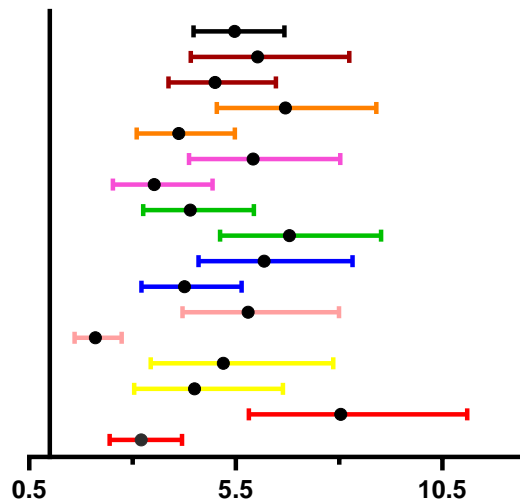
A)

Overall ($n = 5176$; $e = 289$)
 Gender = Female ($n = 2598$; $e = 105$)
 Gender = Male ($n = 2578$; $e = 184$)
 Age < 57 ($n = 3457$; $e = 145$)
 Age ≥ 57 ($n = 1719$; $e = 144$)
 BMI < 29 kg/m² ($n = 4039$; $e = 145$)
 BMI ≥ 29 kg/m² ($n = 1137$; $e = 144$)
 eGFR < 90 mL/min/1.73 m² ($n = 1991$; $e = 143$)
 eGFR ≥ 90 mL/min/1.73 m² ($n = 3185$; $e = 146$)
 UAE < 15 mg/ 24 h ($n = 3915$; $e = 161$)
 UAE ≥ 15 mg/ 24 h ($n = 1261$; $e = 128$)
 Glucose < 5.7 mmol/L ($n = 4671$; $e = 133$)
 Glucose ≥ 5.7 mmol/L ($n = 505$; $e = 156$)
 Insulin < 13.5 mU/L ($n = 4188$; $e = 145$)
 Insulin ≥ 13.5 mU/L ($n = 988$; $e = 146$)
 Hypertension = no ($n = 3753$; $e = 125$)
 Hypertension = yes ($n = 1423$; $e = 164$)



B)

Overall ($n = 5176$; $e = 289$)
 Gender = Female ($n = 2598$; $e = 105$)
 Gender = Male ($n = 2578$; $e = 184$)
 Age < 57 ($n = 3457$; $e = 145$)
 Age ≥ 57 ($n = 1719$; $e = 144$)
 BMI < 29 kg/m² ($n = 4039$; $e = 145$)
 BMI ≥ 29 kg/m² ($n = 1137$; $e = 144$)
 eGFR < 90 mL/min/1.73 m² ($n = 1991$; $e = 143$)
 eGFR ≥ 90 mL/min/1.73 m² ($n = 3185$; $e = 146$)
 UAE < 15 mg/ 24 h ($n = 3915$; $e = 161$)
 UAE ≥ 15 mg/ 24 h ($n = 1261$; $e = 128$)
 Glucose < 5.7 mmol/L ($n = 4671$; $e = 133$)
 Glucose ≥ 5.7 mmol/L ($n = 505$; $e = 156$)
 Insulin < 13.5 mU/L ($n = 4188$; $e = 145$)
 Insulin ≥ 13.5 mU/L ($n = 988$; $e = 146$)
 Hypertension = no ($n = 3753$; $e = 125$)
 Hypertension = yes ($n = 1423$; $e = 164$)



C)

Overall ($n = 5176$; $e = 281$)
 Age < 57 ($n = 3457$; $e = 126$)
 Age ≥ 57 ($n = 1719$; $e = 126$)
 BMI < 29 kg/m² ($n = 4039$; $e = 145$)
 BMI ≥ 29 kg/m² ($n = 1137$; $e = 144$)
 eGFR < 90 mL/min/1.73 m² ($n = 1991$; $e = 143$)
 eGFR ≥ 90 mL/min/1.73 m² ($n = 3185$; $e = 146$)
 UAE < 15 mg/ 24 h ($n = 3915$; $e = 161$)
 UAE ≥ 15 mg/ 24 hours ($n = 1261$; $e = 128$)
 Glucose < 5.7 mmol/L ($n = 4671$; $e = 133$)
 Glucose ≥ 5.7 mmol/L ($n = 505$; $e = 156$)
 Insulin < 13.5 mU/L ($n = 4188$; $e = 145$)
 Insulin ≥ 13.5 mU/L ($n = 988$; $e = 146$)
 Hypertension = no ($n = 3539$; $e = 109$)
 Hypertension = yes ($n = 1282$; $e = 143$)

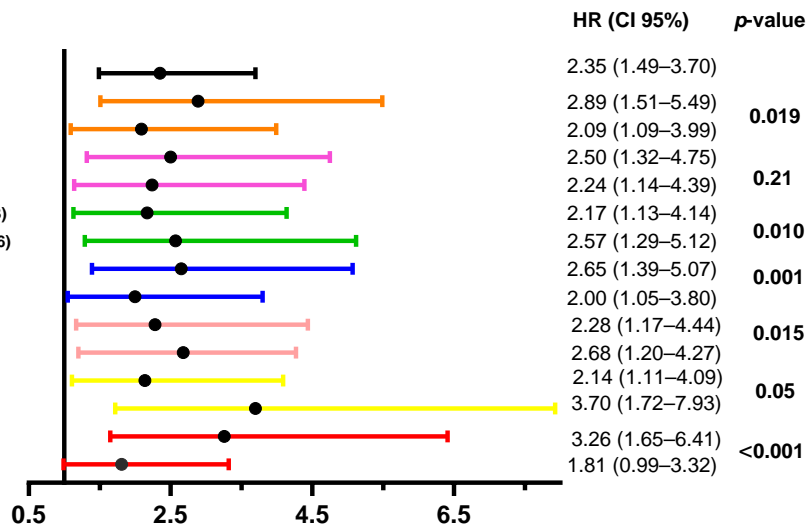


Figure S1. Association between C-peptide and risk of diabetes in the overall population and stratified by selected characteristics (n = number of subjects; e = number of cases). Multivariable hazard ratios (95% confidence

intervals) for risk of diabetes are expressed per Log_2 -unit increase of C-peptide levels. Hazard ratios (95 CIs) were derived from Cox proportional hazards regression models with crude analyses in panel (A), adjusted for age, sex in panel (B), and adjusted for age, sex, smoking status, alcohol consumption, BMI, family history of diabetes, hypertension, triglycerides, total cholesterol, HDL cholesterol, eGFR, urinary albumin excretion, glucose and insulin in panel (C). The p -values denote the p for interaction. BMI: body mass index; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; UAE: urinary albumin excretion

Table S3. Competing risk model of C-peptide to mortality and incident Type 2 Diabetes in 5176 participants without diabetes.

	Subhazard Ratio (95% CI)	<i>p</i> value
Crude analysis	5.96 (4.91–7.23)	<0.001
Model1 [†]	5.48 (4.42–6.74)	<0.001
Model2 [‡]	5.31 (4.29–6.57)	<0.001
Model3 [§]	3.47 (2.67–4.52)	<0.001
Model4	2.88 (2.15–3.87)	<0.001
Model5 [¶]	3.29 (2.39–4.52)	<0.001
Model6 [#]	2.33 (1.49–3.65)	<0.001

Subhazard Ratio (95% CIs) were derived from competing risk analyses by Fine and Gray .

[†]Model 1 is adjusted for age and sex.

[‡]Model 2 is additionally adjusted for smoking status and alcohol consumption.

[§]Model 3 is additionally adjusted for BMI, family history of diabetes and hypertension.

^{||}Model 4 is additionally adjusted for triglycerides, total cholesterol and HDL cholesterol.

[¶]Model 5 is additionally adjusted for eGFR and urinary albumin excretion.

[#]Model 6 is additionally adjusted for glucose and insulin.

eGFR: estimated glomerular filtration rate; PREVEND: Prevention of renal and vascular End-stage Disease.

Table S4. Association between C-peptide and risk of developing Type 2 Diabetes in 5,176 participants of the PREVEND study*

	Sex specific tertiles of plasma C-peptide, pmol/L			C-peptide per Log ₂ unit increase	<i>p</i> value	
	Male	<642	642-890			>890
	Female	<592	592-803	>803		
		1	2	3		
Cases		19	57	213	289	
Crude analysis		1.00 (ref)	3.06 (1.81-5.17)	12.61(7.84-20.26)	7.10 (5.63-8.94)	<0.001
Model1 [†]		1.00 (ref)	2.91 (1.72-4.93)	11.54 (7.13-18.69)	6.60 (5.19-8.40)	<0.001
Model2 [‡]		1.00 (ref)	2.87 (1.70-4.87)	11.21(6.92-18.16)	6.46 (5.07-8.22)	<0.001
Model3 [§]		1.00 (ref)	2.19 (1.29-3.73)	5.55 (3.32-9.28)	4.07 (3.07-5.39)	<0.001
Model4		1.00 (ref)	2.07(1.18-3.63)	4.29 (2.45-7.51)	3.42 (2.49-4.70)	<0.001
Model5 [¶]		1.00 (ref)	1.99(1.12-3.49)	4.09 (2.33-7.19)	3.89(2.78-5.46)	<0.001
Model6 [#]		1.00 (ref)	1.64(0.91-2.95)	2.19 (1.15-4.18)	2.43(1.43-4.13)	0.001

*ORs (95% CIs) were derived from design-based logistic regression models.

[†]Model 1 is adjusted for age and sex.

[‡]Model 2 is additionally adjusted for smoking status and alcohol consumption.

[§]Model 3 is additionally adjusted for BMI, family history of diabetes and hypertension.

^{||}Model 4 is additionally adjusted for triglycerides, total cholesterol and HDL cholesterol.

[¶]Model 5 is additionally adjusted for eGFR and urinary albumin excretion.

[#]Model 6 is additionally adjusted for glucose and insulin.

eGFR: estimated glomerular filtration rate; PREVEND: Prevention of renal and vascular End-stage Disease.