

**Supplementary table 1.** Detailed clinical characteristics of the study participants from different studies.

Trait	Type 2 diabetes patients						Controls								
	n	Breda (n=569)		n	UDES (n=192)		n	Zodiac(n=914)		n	Blood bank controls (n=920)		n	Vlagtwedde (n=768)	
Male/female (%)	567	255 (45.0) / 312 (55.0)		190	103 (54.2) / 87 (45.8)		914	386 (42.2) / 528 (57.8)		911	557 (61.1) / 354 (38.9)		764	409 (53.5) / 355 (46.5)	
Age-at-study (years)	569	69.9±9.9		189	65.2±10.7		914	67.4±11.3		905	47.8±12.7		764	51.2±9.3	
Age at diagnosis (years)	557	62.6±11.1		189	58.3±11.3		912	59.8±±12.4		–	–		–	–	
BMI (kg/m <sup>2</sup> )	564	28.0±4.2		182	28.8±4.7		912	28.9±4.6		NA	NA		764	27.8±4.0	
HbA <sub>1c</sub> (%)	506	7.3±1.1		180	7.1±0.9		914	7.3±1.1		NA	NA		NA	NA	
HDL-cholesterol (mmol/l)	517	1.2±0.3		177	1.2±0.3		914	1.2±0.3		NA	NA		NA	NA	
Total cholesterol (mmol/l)	517	5.3±1.0		185	5.6±1.2		914	5.6±1.1		NA	NA		NA	NA	
Triglyceride (mmol/l)	517	1.9±1.0		177	2.4±1.7		914	2.5±1.5		NA	NA		NA	NA	

The data are presented as mean±SD. BMI: Body Mass Index. HbA<sub>1c</sub>: haemoglobin A<sub>1c</sub> (glucose bound to haemoglobin). HDL: high density lipoprotein. T2D: type 2 diabetes. NA: not applicable

Trait	n	New Hoorn / DCS		New Hoorn / DCS		EPIC-NL controls	
		West-Friesland T2Dn (n=1.969)	West-Friesland controls (n=1.951)	n	EPIC-NL T2D (n=976)	n	EPIC-NL controls (n=1.646)
Male/female (%)	1969	1083 (55.0) / 886 (45.0)	1951	871 (44.6) / 1080 (55.4)	976	172 (17.6) / 804 (82.4)	1646 372 (22.6) / 1274 (77.4)
Age-at-study (years)	1969	64.1 ± 10.5	1951	53.1 ± 6.7	976	58.2 ± 6.9	1646 50.6 ± 117
Age-at-diagnosis (years)	1839	57.0 ± 11.0	-	-	±	-	-
BMI (kg/m <sup>2</sup> )	1917	30.0 ± 5.3	1940	25.6 ± 3.6	975	29.7 ± 4.6	1645 25.6 ± 3.8
HbA <sub>1c</sub> (%)	1809	6.9 ± 1.1	1950	5.3 ± 0.3	961	7.2 ± 1.7	1615 5.5 ± 0.5
Fasting blood glucose (mmol/l)	1808	8.2 ± 2.2	1951	5.3 ± 0.4	-	-	-
HDL (mmol/l)	1649	1.2 ± 0.3	1949	1.6 ± 0.4	930	1.0 ± 0.3	1604 1.3 ± 0.3
Total cholesterol (mmol/l)	1650	4.7 ± 1.1	1949	5.5 ± 1.0	960	5.3 ± 1.1	1622 5.3 ± 1.1
Triglyceride (mmol/l)	1671	1.7 ± 1.1	1949	1.3 ± 0.7	953	2.3 ± 1.4	1615 1.5 ± 1.0

The data are presented as mean±SD. BMI: Body Mass Index. HbA<sub>1c</sub>: haemoglobin A<sub>1c</sub> (glucose bound to haemoglobin). HDL: high density lipoprotein. T2D: type 2 diabetes

**Supplementary table 2.** Data on diabetic complications in type 2 diabetes patients from the DCS West-Friesland, the ZODIAC and the EPIC-NL studies

Study	T2D patients with macrovascular complications	T2D patients with ascertained nephropathy	T2D patients with ascertained neuropathy	T2D patients with ascertained retinopathy
DCS West-Friesland	NA	NA	NA	279
ZODIAC	284	355	247	90
EPIC-NL	NA	87	86	96
Total	284	442	333	465

NA – data not available

**Supplementary table 3.** Clinical characteristics of the individual hyperglycaemic clamp study samples

	Hoorn	Utrecht	NTR
n (NGT/IGT)	138 (0/138)	74 (63/11)	123 (116/ 7)
Gender (M/F)	66/72	17/57	58/65
Age (y)	60.5 ± 8.7	46.0 ± 6.4	31.5 ± 6.4
BMI (kg/m <sup>2</sup> )	28.1 ± 4.1	25.8 ± 3.6	24.2 ± 3.5
Fasting plasma glucose (mmol/l)	6.3 ± 0.7	4.6 ± 0.5	4.6 ± 0.5
2-hr plasma glucose (mmol/l)	8.8 ± 1.7	5.5 ± 1.6	5.4 ± 1.2
Fasting plasma insulin (pmol/l)	62 (46-89)	36 (24-54)	35 (27-52)
First-phase insulin response (pmol/l)	586 (374-892)	852 (584-1169)	805 (602-1168)
Second-phase insulin response (pmol/l)	254 (171-352)	260 (189-354)	218 (164-362)
Insulin sensitivity index (µmol/min/kg/pmol/l)	0.109 (0.068-0.167)	0.180 (0.122-0.281)	0.221 (0.144-0.318)
Disposition index (µmol/min/kg)	66 (43-94)	162 (93-224)	173 (138-226)

Data are represented as means ± SD or median (interquartile range). NTR=Netherlands Twin Register

**Supplementary table 4.** The characteristics of the Zwolle study population

Characteristics	Total number of patients N=914	Deceased patients N=358	Surviving patients N=556
Age (in years)	67.9 ( $\pm$ 11.3)	75.3 ( $\pm$ 8.5)	63.1 ( $\pm$ 10.2) <sup>***</sup>
Sex (% women)	57.8	57.6	58.1
Diabetes duration (in years)	5.0 (2 -10)	6.0 (3-12)	5.0 (2-9) <sup>***</sup>
Smoking (%)	18.1	14.0	21.0 <sup>**</sup>
BMI (kg/m <sup>2</sup> )	28.9 ( $\pm$ 4.6)	28.5 ( $\pm$ 4.5)	29.2 ( $\pm$ 4.6) <sup>*</sup>
Systolic blood pressure (mmHg)	152.5 ( $\pm$ 25.1)	154.7( $\pm$ 26.6)	151.1 ( $\pm$ 24.1) <sup>*</sup>
HbA1c (%)	7.3 ( $\pm$ 1.1)	7.4 ( $\pm$ 1.1)	7.3 ( $\pm$ 1.2)
eGFR (ml/min/1,73 m <sup>2</sup> )	74.3 ( $\pm$ 27.1)	61.3 ( $\pm$ 21.1)	82.7 ( $\pm$ 27.2) <sup>***</sup>
Total cholesterol-HDL ratio	5.0 ( $\pm$ 1.4)	4.9 ( $\pm$ 1.5)	5.0 ( $\pm$ 1.4)
Albumin creatinine ratio	1.9 (1.0-5.9)	3.8 (1.5-11.5)	1.5 (0.8-3.6) <sup>***</sup>
Macrovascular complications (%)	31.1	43.3	23.2 <sup>***</sup>

Data are mean  $\pm$ SD or median with interquartile range for non-normally distributed data or %.\* P<0.05, \*\* P<0.01, \*\*\*P<0.001, tested with Student's t-test or Mann-Whitney U as appropriate.

**Supplementary table 5.** Effect of *KCNQ1* variants rs151290, rs2237892 and rs2237895 on beta-cell function as assessed with hyperglycaemic clamp.

**Hoorn study**

SNP	Genotype (N)		1st phase insulin response (pmol/l)	2nd phase insulin response (pmol/l)	ISI ( $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{pmol/l}^{-1}$ )	DI ( $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )
<b>rs151290</b>						
	AA (11)					
	<b>CA</b> (36)	$\beta$ (sem) <sup>a</sup>	-0.072 (0.032)	-0.026 (0.030)	+0.076 (0.034)	+0.002 (0.039)
	<b>CC</b> (91)	<i>p</i> -value <sup>a</sup>	<b>0.024</b>	0.39	<b>0.028</b>	0.96
<b>rs2237892</b>						
	TT (0)					
	<b>CT</b> (11)	$\beta$ (sem) <sup>a</sup>	+0.097 (0.054)	+0.181 (0.074)	-0.166 (0.080)	-0.038 (0.071)
	<b>CC</b> (123)	<i>p</i> -value <sup>a</sup>	0.075	<b>0.014</b>	<b>0.037</b>	0.60
<b>rs2237895</b>						
	AA (32)					
	<b>AC</b> (74)	$\beta$ (sem) <sup>a</sup>	-0.033 (0.031)	+0.018 (0.032)	+0.038 (0.037)	+0.016 (0.036)
	<b>CC</b> (31)	<i>p</i> -value <sup>a</sup>	0.29	0.56	<b>0.31</b>	0.65

**Utrecht and NTR studies combined**

SNP	Genotype (N)		1st phase insulin response (pmol/l)	2nd phase insulin response (pmol/l)	ISI ( $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{pmol/l}^{-1}$ )	DI ( $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )
<b>rs151290</b>						
	AA (8)					
	<b>CA</b> (54)	$\beta$ (sem) <sup>a</sup>	-0.028 (0.026)	-0.042 (0.029)	+0.043 (0.026)	+0.014 (0.024)
	<b>CC</b> (135)	<i>p</i> -value <sup>a</sup>	0.28	0.15	0.094	0.56
<b>rs2237892</b>						
	TT (0)					
	<b>CT</b> (17)	$\beta$ (sem) <sup>a</sup>	+0.026 (0.047)	+0.109 (0.045)	-0.056 (0.050)	-0.027 (0.048)
	<b>CC</b> (178)	<i>p</i> -value <sup>a</sup>	0.57	<b>0.017</b>	<b>0.27</b>	0.57
<b>rs2237895</b>						
	AA (54)					
	<b>AC</b> (106)	$\beta$ (sem) <sup>a</sup>	-0.021 (0.029)	-0.069 (0.029)	+0.060 (0.028)	+0.035 (0.020)
	<b>CC</b> (32)	<i>p</i> -value <sup>a</sup>	0.47	0.018	<b>0.034</b>	0.084

<sup>a</sup> Adjusted for glucose tolerance status (NGT/IGT), study center, age, gender and BMI.

All variables were log-transformed before analysis. *p*-values were computed for different additive models using linear generalized estimating equations (GEE) which takes into account the family relatedness when computing the standard errors.

Alleles in bold are the risk alleles for type 2 diabetes identified by previous studies.

DI, disposition index; IGT, impaired glucose tolerance; ISI, insulin sensitivity index;

ND, not determined; NGT, normal glucose tolerance