SUPPLMENTARY MATERIAL

Title: The prevalence of polyneuropathy in type 2 diabetes subgroups based on indices of beta-cell function and insulin sensitivity

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Supplementary Table 1. Registries, codes and definitions used in the study.

Database	Description
Danish Diabetes Database for Adults (DDDA)	Danish Diabetes Database for Adults has recorded detailed clinical information on lifestyle and laboratory measurements including lipids, eGFR, glucose, and blood pressure since 2004 from diabetes outpatient clinics and since 2006 from GPs (1).
Danish National Patient Registry	The Danish National Patient Registry has recorded diagnosis codes, surgical procedures, and certain medical treatments provided during an inpatient hospitalization since 1977 and during outpatient clinic visits, emergency room and psychiatric inpatient contacts since 1995. Records are coded according to the International Classification of Disease (ICD) revision eight since 1977 and tenth revision since 1994 (2).
Danish National Prescription Registry	The Danish National Prescription Registry has recorded information on redeemed prescriptions from community pharmacies since 1995, including date of dispensing, Anatomical Therapeutical Chemical (ATC) code, product name, amount, volume and strength. (3)

Variable	Description	Definition of variables used in regression models and to define patient subgroups.
Type 2 diabetes subgroups	Patients were categorized into classical, hyperinsulinemic, or insulinopenic T2D subgroups using version 2 of the revised homeostatic assessment model (HOMA2), which estimates insulin sensitivity (HOMA2-S) and beta-cell function (HOMA2-B) based on fasting C-peptide and plasma glucose values obtained at DD2 enrollment. High and low HOMA2-S and HOMA2-B were defined as being above or below the median values for HOMA2-S (63.5%) and HOMA2-B (115.3%) measured in a non-diabetes cohort randomly sampled from all residents (360,921) of one Danish county, as previously described (4,5).	All regression analyses: classical, hyperinsulinemic, and insulinopenic. The classical subgroup was the reference group. HOMA2-B and HOMA2-S were both inserted as continuous variables in regression analyses.
Diabetic polyneuropathy (DPN)	DPN was defined as a total score ≥4 based on answers to the 15-item Michigan Neuropathy Screening Instrument questionnaire in June 2016.	All regression analyses: dichotomous variable with a MNSIq score ≥4 points.
Biomarkers	Information about biomarkers were recorded in the Danish Diabetes Database for Adults (DDDA). If more than one measurement of the biomarkers was available, we chose the one closest to date of DD2 enrollment. Measurements taken after the date of MNSIq completion were not considered. We obtained measures on: • Triglycerides (mmol/L, missing values: 27%) • Low density lipoprotein (mmol/L, missing values: 24%) • High density lipoprotein (mmol/L, missing values: 52%) • HbA1c (mmol/mol, missing values: 22%) • Albumin/creatinine ratio (mg/g, missing values: 26%) • Plasma creatinine was converted to eGFR by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (missing values: 32%).(6)	All regression analyses: • Triglycerides ≥1.7 mmol/L or treatment with any lipid-lowering medication (dichotomous variable) • HDL cholesterol <1.0/1.3 mmol/L [male/female] or treatment with lipid-lowering medication (dichotomous variable) • HbA1c (continuous variable) Categories used to define subgroups: • Hypertriglyceridemia: triglycerides ≥1.7 mmol/L or treatment with any lipid-lowering medication (dichotomous variable) • HDL cholesterol: <1.0/1.3 mmol/L [male/female] or treatment with lipid-lowering medication (dichotomous variable) • HbA1c: <53 mmol/mol [7%]/≥53 mmol/mol (dichotomous variable)

High sensitivity C-reactive protein	High-sensitivity C-reactive protein was measured at enrollment in DD2.	All regression analyses: continuous variable Categories used to define subgroups: </≥3.0 mg/dL
Diabetes duration	Time from first diabetes diagnosis or first glucose-lowering drug prescription redemption until enrollment in DD2.	All regression analyses: continuous variable Categories used to define subgroups: <1 year, 1-3 years, ≥3 years
Smoking	Recorded in the DDDA and when completing the DPN questionnaire in June 2016. We primarily considered information about smoking habits from the DDDA answered closest to the date of DD2 enrollment, but if this information was missing, we used the response to the DPN questionnaires. Information on smoking habits was obtained from 729 participants who answered the DPN questionnaire (21% of the total cohort)	Categorized into groups of never, former, current smokers. The categorization was used in all regression analyses.
Alcohol intake	Recorded on the date of DD2 enrollment.	Categorized as (M/F) 1) ≤21/14 units; >21/14 units per week. The categorization was used in all regression analyses.
Physical activity	Recorded on the date of enrollment.	Categorized into groups of days per week with 30 minutes of physical activity: all week days, 5-6 days, 3-4 days, 1-2 days, none. The categorization was used in all regression analyses.
Blood pressure	Recorded on the date of enrollment and in the DDDA. If blood pressure was missing at enrollment, we considered the blood pressure recorded in the DDDA and chose the measurement closest to the date of enrollment. We disregarded measurements taken after completing the DPN questionnaire. 48% of those with a blood pressure measurement had their blood pressure measured after enrollment in DD2 (median days after DD2 enrollment: 160 [IQR 84-329]). 25% of the total cohort had missing blood pressure values.	All regression analyses: • Hypertension: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg and/or use of any antihypertensive medication (dichotomous variable). Similar definition was used to define a subgroup with hypertension.
Hip and waist circumference	Patients had hip and waist circumference measured on the date of DD2 enrollment. 5 had no measurements. WHO provided guidance on cut-off points for waist circumference (>102/88 cm [M/F]) (Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008).	All regression analyses: waist circumference (continuous variable) Categories used to define subgroups: • Obesity: waist circumference (>102/88 cm [M/F]) • No obesity: waist circumference (≤102/88 cm [M/F])
Height and weight	Height and weight were included as predictors in our imputation model. The measurements were recorded on the date of enrollment in the DDDA, and self-reported in the DPN questionnaire. We primarily used the measurements obtained on the date of DD2 enrollment; however, if the measurements were missing, we obtained the information from the DDDA and chose the measurement closest to enrollment. If missing in the DDDA, we used the self-reported measures provided as responses to the DPN questionnaire. The values from the DPN questionnaires were used in 1233 (36%) patients for height and in 1424 (42%) patients for weight.	Used as continuous variables.

Metabolic syndrome	At least three characteristics had to be present for a diagnosis of the metabolic syndrome(7): 1) Increased waist-circumference: ≥102 cm for men; ≥88 cm for women; 2) Hypertriglyceridemia: triglycerides ≥1.7 mmol/L or use of any lipid-lowering drugs. 3) HDL-cholesterol: HDL cholesterol <40 mg/dl (1.0 mmol/L) for men; <50 mg/dl (1.3 mmol/L) for women or use of any lipid-lowering drugs 4) Hypertension: Systolic blood pressure ≥130 and/or diastolic blood pressure ≥85 mmHg or use of any antihypertensive medication Medications for dyslipidemia and hypertension were also used as metabolic syndrome markers in accordance with guidelines (7). Thus, patients were categorized as having dyslipidemia or hypertension if they used lipid-lowering or antihypertensive medication, even if they had normal lipid or blood pressure values.		Definitions of the covariates used in regression analyses and to define subgroups are shown above.
Exclusion criteria	**ICD-10 codes**	**ICD-8 codes**	**Categorization**
Rare diabetes subtypes	E22.0, D35.0A, D13.7B, E16.8C, Q87.1E, Q96, G10, G11.1C, Q87.8B, Q98, E80.0, E80.1, E80.2, E24, E84	25300, 25301, 25529, 19509, 157, 21169, 23069, 31058, 31059, 31158, 31159, 31258, 31259, 31358, 31359, 31458, 31459, 31558, 31559, 31054, 31154, 31254, 31354, 31454, 31554, 75950, 33109, 33209, 75981, 31053, 31153, 31253, 31353, 31453, 31553, 75951, 27310-19, 25809, 25800, 27309	Dichotomous variable
Potential LADA	GAD≥20		Dichotomous variable
Secondary diabetes; A record of acute or chronic pancreatitis or pancreas resection within ten years prior to index date.	K85.0, K86.0, K86.1 KJLC (operation code)	48380-48640 (operation codes before 1996)	Dichotomous variable
Glucocorticoid-associated diabetes	Patients who redeemed a prescription for oral steroids (ATC: H02AB) within 3 months prior to the index date		Dichotomous variable
Any neuropathies *(used in a sensitivity analysis)*	E104, E114, E124, E134, E144, G60, G61, G62, G63, G64, G57, G58, G59		Dichotomous variable
Comorbidities			
Myocardial infarction	I21, I23	410	Dichotomous variable
Overall stroke	I63, I64, I65, I66, I67, G45, I60, I61, I62, I69 S06.6	433-435, 437, 430-432	Dichotomous variable
Percutaneous coronary intervention (PCI)/ Coronary artery bypass grafting (CABG)	Surgical codes: KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF		Dichotomous variable
Heart failure	I500, I501, I502, DI503, I508, I509, I110, I130, I132, I420, I426 I427, I428, I429	42709, 42710, 42711, 42719, 42899, 78249	Dichotomous variable

Lower limb revascularization or lower limb amputation	Surgical codes: KPDE, KPDF, KPDH, KPDN, KPDP, KPDQ KPEE, KPEF, KPEH, KPEN, KPEP, KPEQ, KPEU74, KPEU82, KPEU83, KPEU84 KPFE, KPFH, KPFN, KPFP, KPFQ, KPFU74, KPFU84. KNFQ, KNGQ, KNHQ			Dichotomous variable
Peripheral artery disease	I70, I71, I72, I73, I74, I77	440, 441, 442, 443, 444, 445		Dichotomous variable
Angina pectoris	I20, I251, I259	411, 413		Dichotomous variable
Cardiovascular disease	Above codes for myocardial infarction, stroke, PCI/CABG, heart failure, lower limb revascularization or amputation, peripheral artery disease, angina pectoris			Dichotomous variable
Atrial fibrillation	I48	42792		Dichotomous variable
Chronic pulmonary disease	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3	490-493, 515-518		Dichotomous variable
Chemotherapy treatment	Z082, Z542, Z092, Z926, K529B1, T808E, BOHJ, BWHA, BWHB, BWHC, BOHE, BJCZ01, BJHE11, BJHE12 (treatment code)			Dichotomous variable
Hospital-diagnosed obesity	E65, E66, E68	27799		Dichotomous variable
Chronic liver disease	B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0, B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85	571, 573.01, 57304, 07000, 07002, 07004, 07006, 07008, 57300, 45600–45609		Dichotomous variable
Hypothyroidism	E03, E06	243, 244, 245		Dichotomous variable
Alcoholism-related disorders	F10.2-10.9, G31.2, G62.1, G72.1, K29.2. K70 K86.0, Z72.1, E24.4, E52.9A, K85.2, L27.8A, Z50.2, Z71.4, BRHE2 (treatment code)	291, 303, 57109, 57110, 57710	N07BB	Dichotomous variable

Diabetes with kidney disease	E102, E112, DE122, E132, E142, I12, I13, N083, N06, N00–N05, N07, N163, N17, N18, N19, R809, Z992 Procedure code: BJFD	25002, 24902, 403, 404, 580–583, 584, 59009, 59319, 792	Dichotomous variable
Diabetes with eye disease	E103, E113, E123, E133, E143, H330, H332, H333, H334, H335, H36, H34, H450, H46, H540, H541, H542, H543, H544, H547, H25, H280 H281, H282, H269, H430, H431, H438 H439, I708A Surgical codes: KCKC10, KCKC15, KCKD65	25001, 24901 36101, 36102, 374, 377, 37909, 37919	Dichotomous variable
Cancer	C00–C99		Dichotomous variable
Medications		**ATC codes**	
Aspirin		B01AC06, N02BA01 N02BA51	Dichotomous variable
Insulin		A10A	Dichotomous variable
Metformin		A10BA, A10BD (02, 03, 05, 07, 08, 10, 11, 13-18, 20, 22, 23, 25)	Dichotomous variable
Sulfonylureas		A10BB, A10BD01, A10BD04, A10BD02, A10BD06, A10BC01	Dichotomous variable
DPP4-inihitors		A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD22, A10BD25	Dichotomous variable
GLP-1-analogues		A10BX04, A10BJ, A10BX07, A10BX10, A10BX13, A10BX14, A10AE54, A10AE56	Dichotomous variable
SGLT-2 inhibitors		A10BX09, A10BK, A10BX11, A10BX12, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25	Dichotomous variable
Other anti-hyperglycemic drugs		A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12, A10BD14, A10BD17, A10BX02, A10BX03, A10BX08, A10BF	Dichotomous variable
Non-insulin GLD monotherapy		A single redeemed prescription of either metformin, sulfonylureas, DPP4-inhibitors, GLP1-analogues, SGLT-2 inhibitors, or other anti-hyperglycemic drugs.	Categorized into groups of no use of GLD, non-insulin GLD monotherapy, non-insulin GLD polytherapy, use of insulin. The categorization was used in all regression analyses and to define subgroups.
Non-insulin GLD polytherapy		Two or more redeemed prescription of either metformin, sulfonylureas, DPP4-inhibitors, GLP1-analogues, SGLT-2 inhibitors, or other anti-hyperglycemic drugs.	Categorized into groups of no use of GLD, non-insulin GLD monotherapy, non-insulin GLD polytherapy, use of insulin. The categorization was used in all regression analyses and to define subgroups.
Statins		C10AA, C10BA, C10BX	Dichotomous variable

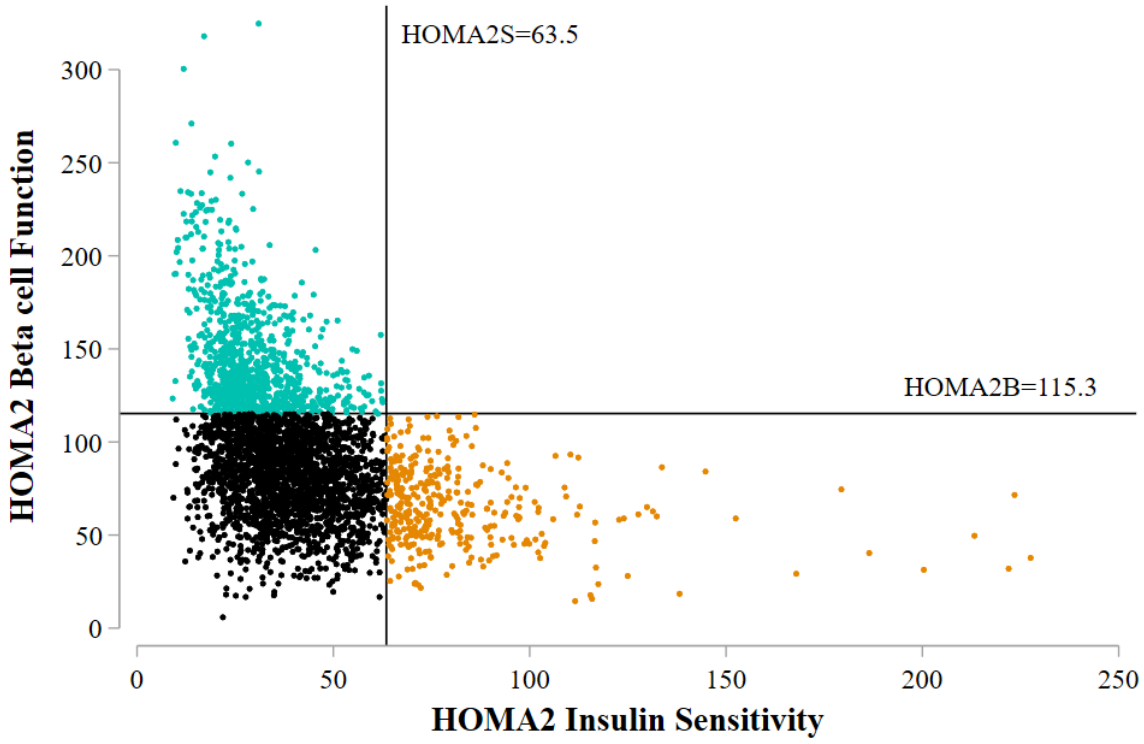
Other lipid-lowering drugs	Fibrates: C10AB Ezetimibe: C10BA05, C10BA10, C10AX09, C10BA011, C10BA012, C10BA06, C10BA02 Other lipid-lowering drugs: B04AC, C10AC, B04AD, C10AD, B04AE, C10AX, B04AX	Dichotomous variable
Loop diuretics	C03EB, C03C	Dichotomous variable
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	C09	Dichotomous variable
Ca-antagonists	C08	Dichotomous variable
Beta-blockers	C07	Dichotomous variable
α-adrenergic anti-hypertensives	C02A, C02B, C02C	Dichotomous variable
Thiazides	C02DA, C02L, C03A, C03B,	Dichotomous variable
Potassium-sparing agents	C03D C03EA, C03X	Dichotomous variable

The look-back period was not restricted for ICD discharge diagnosis codes and procedure codes but was limited to 1 year for all ATC codes. Surgical codes began to be registered in 1996

Subgrouping T2DM patients

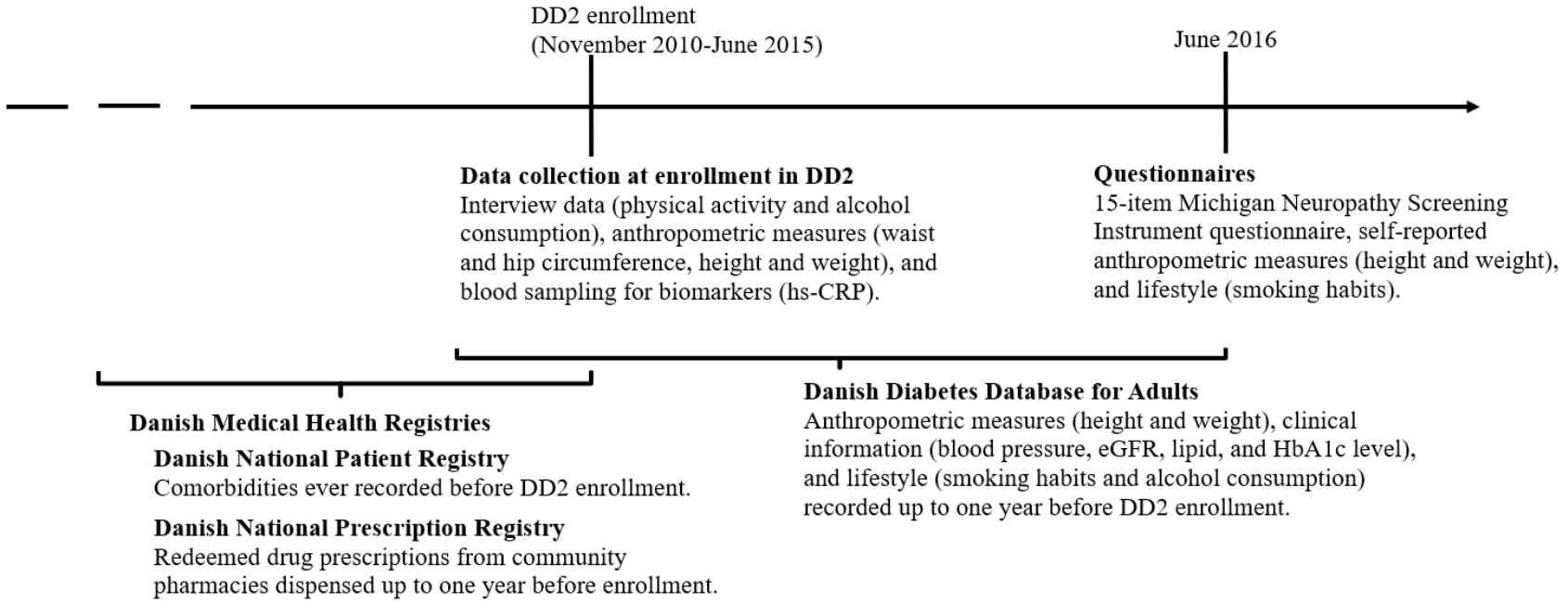
A detailed description of the definition of T2D subgroups has been provided elsewhere.(4,5) In brief, we identified persons aged 25 to 75 years with and without diabetes in a county of Southern Denmark using Danish Health Registries.(8) Patients either had been diagnosed with diabetes in a hospital setting or had redeemed a glucose-lowering drug at a community pharmacy. Diabetes patients were then age- and sex-matched with non-diabetes patients, and a random sample from the non-diabetes cohort was invited to undergo fasting glucose measurement (n= 11,065). Among 4,980 persons with fasting glucose values, 578 persons without diabetes were randomly selected for C-peptide measurements. After exclusion of patients with abnormal fasting glucose values (FPG >6.1 mmol/L) (n=95), the remaining 483 persons without diabetes were used to calculate median HOMA2 values (4,5). These median cut-off values were applied to the DD2 cohort, to divide patients into groups with low and/or high HOMA2-B and HOMA2-S (high/low beta-cell function = HOMA2-B ≥/<115.3% and high/low insulin sensitivity = HOMA2-S ≥/<63.5%): hyperinsulinemic, classical, and insulinopenic. Patients with hyperinsulinemic T2DM had high HOMA2-B and low HOMA2-S, patients with classical T2DM had low HOMA2-B and low HOMA2-S, and patients with insulinopenic T2DM had low HOMA2-B and high HOMA2-S. The names were established in 2018 where the subgroups were introduced(4) and has since then been used in several studies (4,9,10). Despite the names are simple, it is important that the subgroups are based on both indices of HOMA2.

Supplementary Figure 1. Distribution of HOMA2-B, HOMA2-S, and corresponding pathophysiological subgroups in T2DM patients.



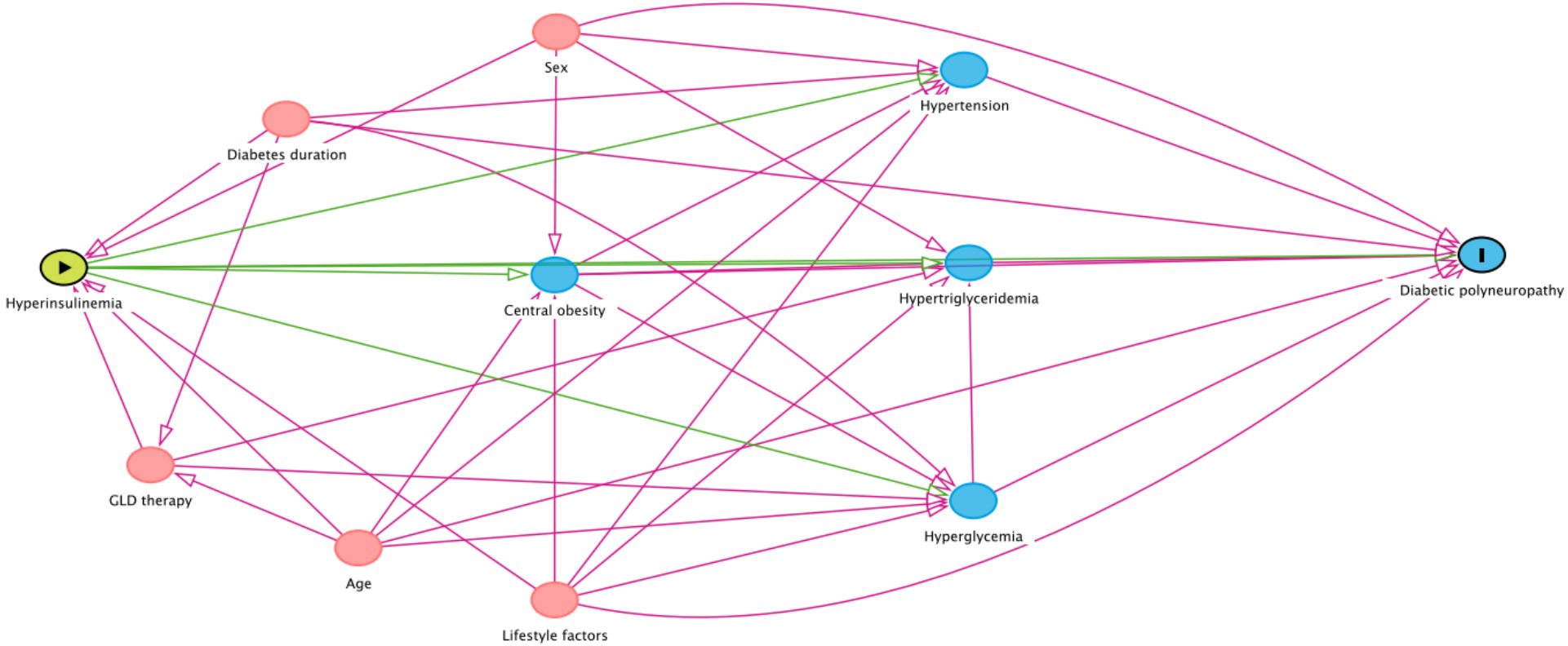
We estimated insulin sensitivity (HOMA2-S, %) and beta-cell function (HOMA2-B, %) from the homeostatic model assessment-2 (HOMA2) computational model based on fasting serum C-peptide and plasma glucose values. One outlier with HOMA2-S above 300 was excluded from the plot. Patients were grouped into three groups: hyperinsulinemic (low HOMA2-S and high HOMA2-B; *green dots*), classical (low HOMA2-S and HOMA2-B; *black dots*), and insulinopenic (high HOMA2-S and low HOMA2-B; *orange dots*) T2D. High and low HOMA2-S and HOMA2-B were defined as being above or below the median values for HOMA2-S (63.5%) and HOMA2-B (115.3%) measured in a non-diabetic background cohort random sampled from all residents of one Danish county (360,921 persons), as previously described (4,5). Patients with high HOMA2-B and HOMA2-S were excluded since the low number of patients makes interpretation of regression coefficients impossible (n=16).

Supplementary Figure 2. Overview of the study design and data sources.



This cross-sectional study used several data sources. Upon enrollment in the DD2, patients answered a short questionnaire about physical activity and alcohol consumption. At this time anthropometric measures were recorded and a blood sample was collected. In June 2016, the 15-item Michigan Neuropathy Screening Instrument questionnaire (MNSIq) and follow-up questions on height and weight and lifestyle behaviors were sent to participants (median 3.0 years [IQR 2.3-3.8 years] after DD2 enrollment). Linkage to the DDDA provided additional clinical information on DPN risk factors. The measurement closest to DD2 enrollment was used if more than one was available. Supplementary Table 1 provided a detailed description of covariate definitions and data sources. Abbreviations: hs-CRP, high-sensitivity C-reactive protein; DD2, Danish Centre for Strategic Research in Type 2 Diabetes; eGFR, estimated glomerular filtration rate.

Supplementary Figure 3. Directed acyclic graph (DAG) of the association between higher beta-cell function (hyperinsulinemia) and diabetic polyneuropathy.



Crude and age and sex adjusted odds ratios for each arrow are shown in Supplementary Table 2A-G. Suggested in the above DAG, the minimal adjustment model included the following variables: age, sex, diabetes duration, GLD therapy, obesity, and lifestyle factors including smoking, alcohol consumption, and physical activity. Central obesity, hypertension, hypertriglyceridemia, and hyperglycemia (measured by HbA1c) may act as intermediates between hyperinsulinemia and DPN; thus, we did not adjust for these covariates in the main model, to avoid lowering the true total effect. Abbreviations: DPN, diabetic polyneuropathy; GLD; glucose-lowering drug

Supplementary Table 2A. Crude and age- and sex-adjusted odds ratios for study covariates and DPN.

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Hypersinsulinemia, n=3,397	No	2,497	1.0	1.0
	Yes	900	1.60 (1.32-1.93)	1.59 (1.31-1.92)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	0.89 (0.67-1.18)	0.80 (0.54-1.20)
	60-69	1,313	0.77 (0.60-1.01)	0.65 (0.36-1.17)
	≥70	790	0.60 (0.44-0.81)	0.46 (0.20-1.05)
Sex, n=3,397	Female	1,433	1.0	1.0
	Male	1,964	0.76 (0.63-0.90)	0.76 (0.63-0.90)
Alcohol (units/week [F/M]), n=3,397	< 14/21	3,164	1.0	1.0
	≥14/21	233	1.18 (0.85-1.65)	1.34 (0.95-1.88)
Physical activity (PA), n=3,397	No PA	495	1.0	1.0
	At least 30 min. PA one time per week	2,902	0.67 (0.53-0.84)	0.67 (0.53-0.85)
Smoking, n=3,397	Never smoker	1,513	1.0	1.0
	Former or current smoker	1,884	1.22 (1.02-1.47)	1.30 (1.08-1.56)
GLD therapy, n=3,397	No GLD	551	1.0	1.0
	Non-insulin GLD monotherapy	2,325	1.15 (0.89-1.50)	1.13 (0.87-1.47)
	Non-insulin GLD polytherapy	359	1.85 (1.32-2.60)	1.77 (1.25-2.49)
	Insulin therapy	162	2.20 (1.44-3.34)	2.17 (1.42-3.32)
Hypertension*, n=3,397	No	254	1.0	1.0
	Yes	2,886	1.21 (0.85-1.72)	1.41 (0.98-2.02)
Obesity (waist circumference ≥88/102 cm [F/M], n=3,392	No	850	1.0	1.0
	Yes	2,542	1.92 (1.52-2.43)	1.80 (1.42-2.29)
Hypertrigyceridemia†, n=3,104§	No	352	1.0	1.0
	Yes	2,752	1.08 (0.80-1.45)	1.08 (0.80-1.46)
HbA1c (mmol/mol [%]), n=2,658	<48 (6.5)	1,491	1.0	1.0
	48-53 (6.5-7.0)	639	1.01 (0.79-1.29)	0.99 (0.77-1.26)
	≥53 (7.0)	528	1.44 (1.13-1.84)	1.38 (1.07-1.77)
Diabetes duration (years), n=3,397	<1	1,413	1.0	1.0
	1-3	1,253	1.10 (0.90-1.35)	1.15 (0.94-1.42)
	>3	731	1.14 (0.90-1.44)	1.17 (0.92-1.48)

Each association represent an arrow on above DAG. DPN was defined as a MNSIq score of >=4 points. A logistic regression model was used to estimate the odds ratio of DPN for each covariate. *Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg and/or use of any antihypertensive medication. †Triglycerides ≥1.7 mmol/L or treatment with lipid-lowering drugs. Abbreviations: CI, confidence interval; DPN, diabetic polyneuropathy; OR, odds ratio; PA, physical activity; GLD, glucose-lowering drug

Supplementary Table 2B. Crude and age- and sex-adjusted odds ratios for study covariates and being in the hyperinsulinemic subgroup (low HOMA2-S and high HOMA2-B)

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	1.00 (0.77-1.29)	1.09 (0.77-1.56)
	60-69	1,313	0.87 (0.69-1.11)	1.04 (0.62-1.73)
	≥70	790	1.16 (0.90-1.49)	1.48 (0.73-3.01)
Sex, n=3,397	Female	1,433	1.0	1.0
	Male	1,964	0.84 (0.72-0.99)	0.84 (0.72-0.99)
Alcohol (units/week [F/M]), n=3,397	< 14/21	3,164	1.0	1.0
	≥14/21	233	0.85 (0.62-1.16)	0.88 (0.64-1.21)
Physical activity (PA), n=3,397	No PA	495	1.0	1.0
	At least 30 min. PA one time per week	2,902	0.60 (0.49-0.74)	0.60 (0.49-0.74)
Smoking, n=3,397	Never smoker	1,513	1.0	1.0
	Former or current smoker	1,884	1.21 (1.04-1.41)	1.24 (1.06-1.45)
GLD therapy, n=3,397	No GLD	551	1.0	1.0
	Non-insulin GLD monotherapy	2,325	1.05 (0.85-1.29)	1.05 (0.85-1.29)
	Non-insulin GLD polytherapy	359	0.79 (0.58-1.08)	0.80 (0.58-1.10)
	Insulin therapy	162	0.52 (0.33-0.82)	0.53 (0.34-0.85)
Hypertension*, n=3,397	No	254	1.0	1.0
	Yes	2,886	1.74 (1.25-2.42)	1.76 (1.26-2.47)
Obesity (waist circumference ≥88/102 cm [F/M], n=3,392	No	850	1.0	1.0
	Yes	2,542	3.44 (2.75-4.31)	3.48 (2.77-4.37)
Hypertrigyceridemia†, n=3,104§	No	352	1.0	1.0
	Yes	2,752	1.25 (0.96-1.62)	1.24 (0.95-1.61)
HbA1c (mmol/mol [%]), n=2,658	<48 (6.5)	1,491	1.0	1.0
	48-53 (6.5-7.0)	639	0.61 (0.49-0.75)	0.60 (0.49-0.75)
	≥53 (7.0)	528	0.30 (0.22-0.39)	0.29 (0.22-0.38)
Diabetes duration (years), n=3,397	<1	1,413	1.0	1.0
	1-3	1,253	0.89 (0.75-1.05)	0.88 (0.74-1.05)
	>3	731	0.59 (0.47-0.73)	0.58 (0.47-0.72)

Each association represent an arrow on above DAG. *Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg and/or use of any antihypertensive medication. †Triglycerides ≥1.7 mmol/L or treatment with lipid-lowering drugs. A logistic regression model was used to estimate the odds ratio of being in the hyperinsulinemic subgroup for each covariate. Abbreviations: CI, confidence interval; OR, odds ratio; PA, physical activity; GLD, glucose-lowering drug

Supplementary Table 2C. Crude and age- and sex-adjusted odds ratios for study covariates and being obese.

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	0.93 (0.71-1.22)	1.46 (1.01-2.12)
	60-69	1,313	0.91 (0.71-1.18)	2.28 (1.33-3.93)
	≥70	790	0.64 (0.49-0.84)	2.40 (1.13-5.10)
Sex, n=3,397	Female	1,433	1.0	1.0
	Male	1,964	0.38 (0.32-0.46)	0.38 (0.32-0.45)
Alcohol (units/week [F/M]), n=3,397	< 14/21	3,164	1.0	1.0
	≥14/21	233	0.91 (0.67-1.23)	1.21 (0.89-1.65)
Physical activity (PA), n=3,397	No PA	495	1.0	1.0
	At least 30 min. PA one time per week	2,902	0.64 (0.50-0.81)	0.64 (0.50-0.81)
Smoking, n=3,397	Never smoker	1,513	1.0	1.0
	Former or current smoker	1,884	1.09 (0.93-1.27)	1.27 (1.08-1.49)

Each association represent an arrow on above DAG. Obesity was defined as waist circumference ≥88/102 cm [F/M]. A logistic regression model was used to estimate the odds ratio of obesity for each covariate. Abbreviations: CI, confidence interval; OR, odds ratio; PA, physical activity.

Supplementary Table 2D. Crude and age- and sex-adjusted odds ratios for study covariates and hypertension.

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	2.12 (1.51-2.98)	1.26 (0.76-2.10)
	60-69	1,313	4.05 (2.88-5.71)	1.53 (0.71-3.29)
	≥70	790	7.47 (4.65-12.01)	1.81 (0.60-5.44)
Sex, n=3,397	Female	1,433	1.0	1.0
	Male	1,964	1.39 (1.08-1.80)	1.43 (1.10-1.86)
Alcohol (units/week [F/M]), n=3,397	< 14/21	3,164	1.0	1.0
	≥14/21	233	3.99 (1.63-9.77)	3.09 (1.25-7.62)
Physical activity (PA), n=3,397	No PA	495	1.0	1.0
	At least 30 min. PA one time per week	2,902	0.76 (0.51-1.13)	0.74 (0.49-1.11)
Smoking, n=3,397	Never smoker	1,513	1.0	1.0
	Former or current smoker	1,884	1.19 (0.92-1.54)	1.03 (0.79-1.34)
Obesity (waist circumference ≥88/102 cm [F/M], n=3,392	No	850	1.0	1.0
	Yes	2,542	2.14 (1.64-2.80)	2.90 (2.17-3.86)
Diabetes duration (years), n=3,397	<1	1,413	1.0	1.0
	1-3	1,253	1.19 (0.90-1.59)	1.03 (0.77-1.38)
	>3	731	1.44 (1.01-2.05)	1.30 (0.90-1.88)

Each association represent an arrow on above DAG. Hypertension was defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg and/or use of any antihypertensive medication. A logistic regression model was used to estimate the odds ratio of having hypertension for each covariate. Abbreviations: CI, confidence interval; OR, odds ratio; PA, physical activity.

Supplementary Table 2E. Crude and age- and sex-adjusted odds ratios for study covariates and hypertriglyceridemia.

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	1.24 (0.87-1.76)	1.55 (0.95-2.55)
	60-69	1,313	1.37 (0.98-1.90)	2.10 (1.01-4.38)
	≥70	790	1.69 (1.16-2.46)	3.19 (1.13-9.01)
Sex, n=3,397	Female	1,433	1.0	1.0
	Male	1,964	0.86 (0.68-1.08)	0.86 (0.69-1.08)
Alcohol (units/week [F/M]), n=3,397	< 14/21	3,164	1.0	1.0
	≥14/21	233	0.87 (0.57-1.31)	0.87 (0.58-1.33)
Physical activity (PA), n=3,397	No PA	495	1.0	1.0
	At least 30 min. PA one time per week	2,902	0.84 (0.60-1.17)	0.83 (0.59-1.16)
Smoking, n=3,397	Never smoker	1,513	1.0	1.0
	Former or current smoker	1,884	1.29 (1.03-1.61)	1.30 (1.04-1.63)
GLD therapy, n=3,397	No GLD	551	1.0	1.0
	Non-insulin GLD monotherapy	2,325	2.04 (1.57-2.66)	2.17 (1.66-2.84)
	Non-insulin GLD polytherapy	359	3.31 (2.05-5.34)	3.84 (2.36-6.26)
	Insulin therapy	162	2.69 (1.43-5.06)	3.16 (1.67-6.00)
Obesity (waist circumference ≥88/102 cm [F/M], n=3,392	No	850	1.0	1.0
	Yes	2,542	1.48 (1.17-1.89)	1.49 (1.17-1.91)

Each association represent an arrow on above DAG. Hypertriglyceridemia was defined as triglycerides ≥1.7 mmol/L or treatment with lipid-lowering drugs. A logistic regression model was used to estimate the odds ratio of having hypertriglyceridemia for each covariate. Abbreviations: CI, confidence interval; OR, odds ratio; PA, physical activity; GLD, glucose-lowering drug

Supplementary Table 2F. Crude and age- and sex-adjusted odds ratios for study covariates and increased HbA1c.

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	0.69 (0.54-0.90)	1.46 (0.89-2.41)
	60-69	1,313	0.57 (0.45-0.72)	1.98 (0.94-4.16)
	≥70	790	0.42 (0.32-0.55)	2.96 (1.04-8.46)
Sex, n=3,397	Female	1,433	1.0	1.0
	Male	1,964	1.02 (0.87-1.19)	0.84 (0.66-1.05)
Alcohol (units/week [F/M]), n=3,397	<14/21	3,164	1.0	1.0
	≥14/21	233	0.66 (0.49-0.90)	0.90 (0.59-1.38)
Physical activity (PA), n=3,397	No PA	495	1.0	1.0
	At least 30 min. PA one time per week	2,902	0.97 (0.78-1.21)	0.87 (0.62-1.22)
Smoking, n=3,397	Never smoker	1,513	1.0	1.0
	Former or current smoker	1,884	1.03 (0.89-1.20)	1.23 (0.98-1.54)
GLD therapy, n=3,397	No GLD	551	1.0	1.0
	Non-insulin GLD monotherapy	2,325	1.86 (1.47-2.35)	2.22 (1.69-2.91)
	Non-insulin GLD polytherapy	359	5.69 (4.09-7.92)	3.98 (2.41-6.57)
	Insulin therapy	162	7.20 (4.67-11.10)	3.51 (1.84-6.69)
Obesity (waist circumference ≥88/102 cm [F/M], n=3,392	No	850	1.0	1.0
	Yes	2,542	1.39 (1.16-1.66)	1.53 (1.19-1.97)
Diabetes duration (years), n=3,397	<1	1,413	1.0	1.0
	1-3	1,253	0.72 (0.61-0.86)	1.38 (1.08-1.77)
	>3	731	1.26 (1.02-1.54)	2.16 (1.53-3.06)

Each association represent an arrow on above DAG. Increased HbA1c was defined as HbA1c ≥48 mmol/mol. A logistic regression model was used to estimate the odds ratio of having increased HbA1c for each covariate. Abbreviations: CI, confidence interval; OR, odds ratio; PA, physical activity; GLD, glucose-lowering drug

Supplementary Table 2G. Crude and age- and sex-adjusted odds ratios for study covariates and use of glucose-lowering drugs.

	Categorization	Numbers	Crude OR (95% CI)	Age and sex adjusted OR (95% CI)
Age group, n=3,397	<50	470	1.0	1.0
	50-59	824	0.67 (0.51-0.88)	0.97 (0.65-1.45)
	60-69	1,313	0.50 (0.39-0.65)	0.98 (0.54-1.80)
	≥70	790	0.23 (0.17-0.33)	0.62 (0.26-1.48)
Diabetes duration (years), n=3,397	<1	1,413	1.0	1.0
	1-3	1,253	1.93 (1.51-2.47)	2.28 (1.77-2.93)
	>3	731	4.71 (3.68-6.02)	5.75 (4.45-7.44)

Each association represent an arrow on above DAG. Glucose-lowering drug therapy was defined as use of GLD ≥2 different GLDs (GLD polytherapy) or insulin. A logistic regression model was used to estimate the odds ratio of using GLD polytherapy or insulin for each covariate. Abbreviations: CI, confidence interval; OR, odds ratio.

Missing values and data imputation

Missingness of covariates included in our adjustment models varied from 0.1%-27% except for HDL cholesterol which had 52% missing (Supplementary Table 1). Missing values were most often seen in DDDA laboratory data due to physicians not completing the record in the DDDA during routine clinical care (1). In a preliminary analysis, we investigated whether missingness in the DDDA depended on certain comorbidities by grouping patients according to missing LDL cholesterol. Patients with missing LDL cholesterol in our cohort also had missing values for most other laboratory measurements, but presence of comorbidities similar to those for patients with measured LDL cholesterol (data not shown). This suggests that laboratory missingness is random and indicates that the observed data sufficiently predicts missingness, although it may be impossible to fully prove the missing-at-random assumption (11).

We employed multiple imputation with chained equations (MICE) to account for potential selection problems, using a complete case analysis (11). Linear regression was used as the underlying model since the incomplete covariates were continuously measured covariates. 50 complete data sets were imputed with 10 iterations each (11,12).

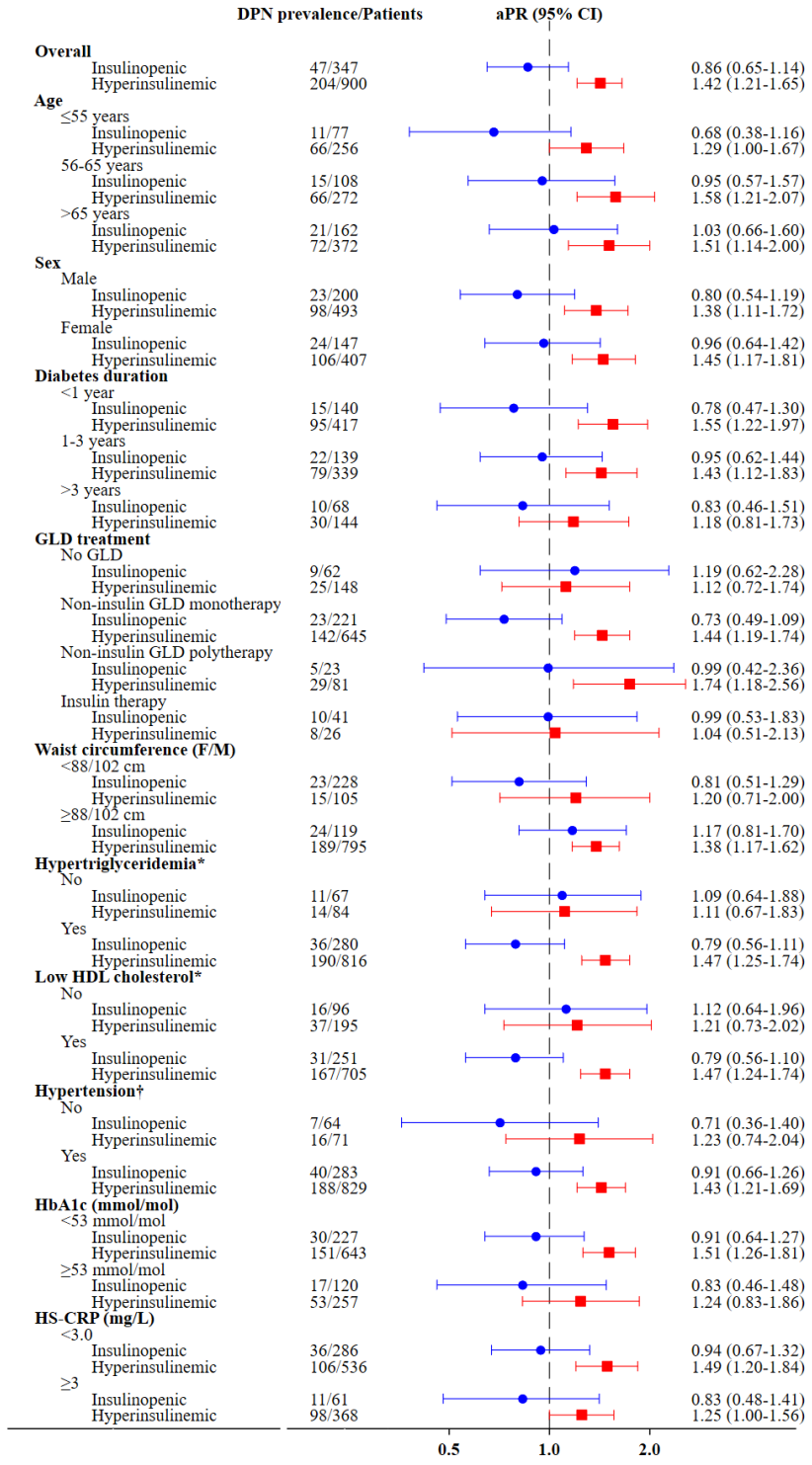
The imputation model included covariates also included in the fully adjusted model, as well as important auxiliary variables for enhancing prediction of the given covariate and missingness. The auxiliary covariates were chosen based on clinical knowledge of a potential correlation between covariates as well as on the calculation of pairwise correlation coefficients for each covariate.

We imputed missing values for waist circumference, triglycerides, HDL cholesterol, hs-CRP, systolic and diastolic blood pressure, and HbA1c. LDL cholesterol, creatinine, height and weight were also imputed to improve prediction of other missing values.

Other predictors with complete data included age, sex, site of enrollment (GP or outpatient clinic), year of inclusion, diabetes duration, T2DM subgroups, HOMA2-B, HOMA2-S, C-peptide, glucose values, smoking, family history of T2DM, self-reported physical activity, alcohol consumption, Charlson Comorbidity Index scores, preexisting cardiovascular disease (myocardial infarction, ischemic stroke, percutaneous coronary intervention/coronary artery bypass grafting, heart failure, hemorrhagic stroke, lower limb revascularization or lower limb amputation, peripheral artery disease, and angina pectoris), arterial fibrillation, chronic pulmonary disease, diabetes with eye disease, diabetes with kidney disease, cancer, chronic liver disease, hospital-diagnosed obesity, hypothyroidism, mono- or poly-glucose-lowering/insulin therapy, blood pressure- and lipid-lowering therapy, use of aspirin and loop diuretics, and presence of diabetic polyneuropathy according to the Michigan Neuropathy Screening Instrument questionnaire. All codes for these covariates are presented in Supplementary Table 1. Continuous variables with clearly non-normal (skewed) distributions were zero-skewness log-transformed, *i.e.*, transformed to approximate normality before imputation. After imputation, the values were transformed back to the original scale before analysis.(12) No trend toward convergence was observed in imputed values when plotting mean values and variances. The imputed models were validated by comparing the mean, median, and interquartile range of the first and last imputed dataset with the complete dataset. Rubin's rule was used when combining estimates from multiple imputed datasets.(12) After imputing missing values, we created new variables to be used in our regression analysis: triglycerides ≥1.7 mmol/L or treatment with lipid-lowering

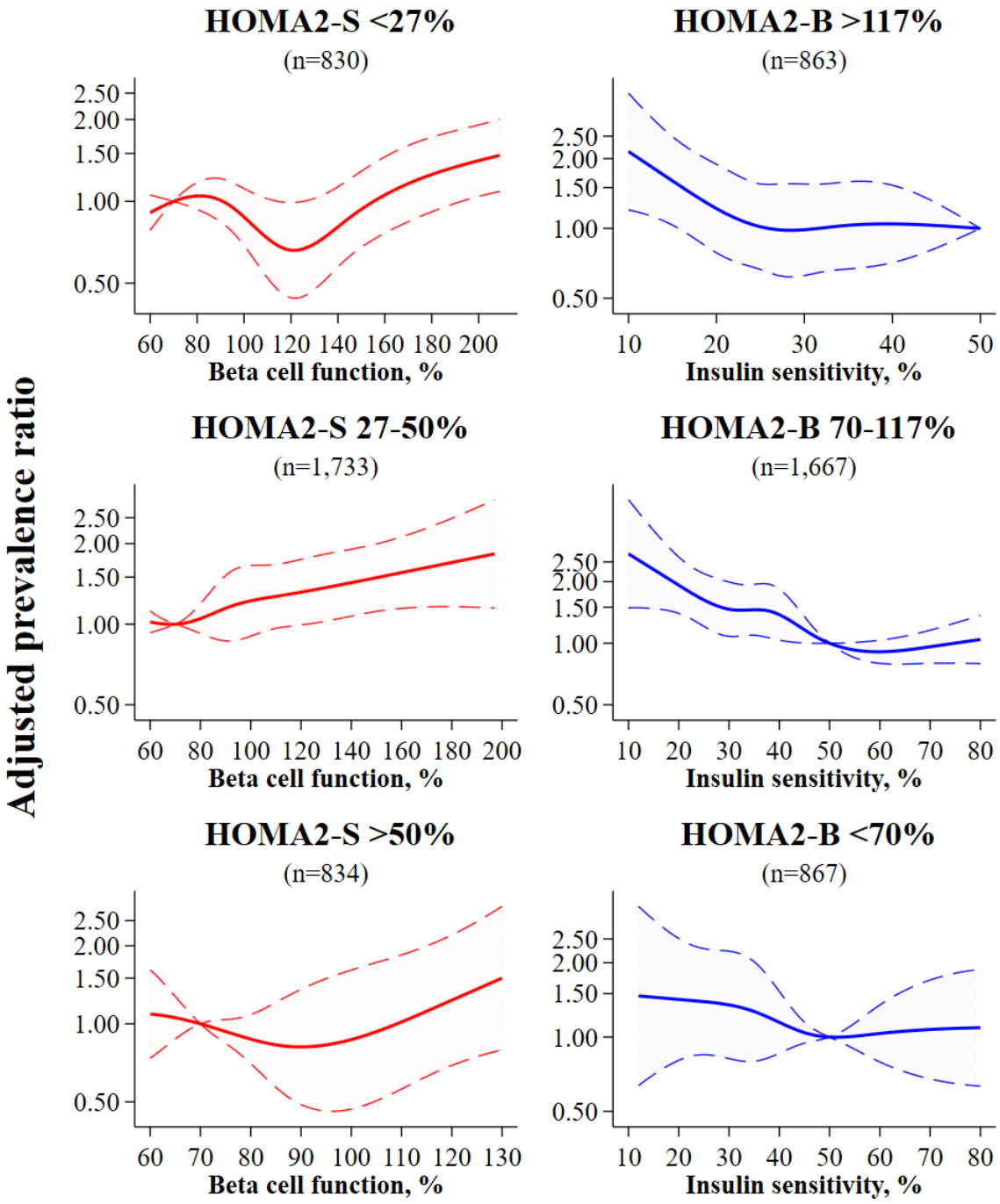
drugs, HDL-cholesterol <1.0/1.3 mmol/L [male/female] or treatment with lipid-lowering drugs, and hypertension (≥130/85 [systolic/diastolic blood pressure] or treatment with antihypertensive medication). Waist circumference and HbA1c was included in the regression analysis as continuous variables.

Supplementary Figure 4. Adjusted prevalence ratios of DPN associated with T2DM subgroups according to age, sex, diabetes duration, and treatment and metabolic syndrome components.



Adjusted for age, sex, diabetes duration and drug therapy, physical activity, smoking, and alcohol consumption. *Triglycerides ≥1.7 mmol/L or treatment with lipid-lowering drugs. Low HDL cholesterol <1.0/1.3 mmol/L [male/female] or treatment with lipid-lowering drugs.
† Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg and/or use of any antihypertensive medication. Missing data were handled by multiple imputation using chained equations. A detailed description of this procedure is available in the Supplementary Material. Abbreviations: CI, confidence interval; DPN, diabetic polyneuropathy; aPR, adjusted prevalence ratios; GLD, glucose-lowering drug; HS-CRP, high-sensitivity C-reactive protein.

Supplementary Figure 5. Continuous measures of HOMA-2B and HOMA2-S associated with DPN, categorized according to quartiles of HOMa2-B and HOMA2-S.



We assessed estimates of insulin sensitivity (HOMA2-S) and beta-cell function (HOMA2-B) from the homeostasis model 2 assessment based on fasting serum C-peptide and plasma glucose values. Splines were obtained for subgroups categorized based on 25th- and 75th quartiles (<25th, 25-75th, and >75th percentile) of the beta-cell function and insulin sensitivity measured in the total study cohort. The reference value for beta-cell function was the 25th percentile of the study cohort (70%), while it was the 75th quartile for insulin sensitivity (49%). Splines were adjusted for age, sex, diabetes duration and drug therapy, physical activity, smoking, and alcohol consumption. Dotted lines indicate 95% confidence intervals. Abbreviations: CI, confidence interval; DPN, diabetic polyneuropathy; HOMA2, homeostatic assessment model 2.

Supplementary Table 3. Adjusted prevalence ratios of DPN associated with T2DM subgroups adjusted for metabolic syndrome components and HS-CPR as well as in a complete case cohort.

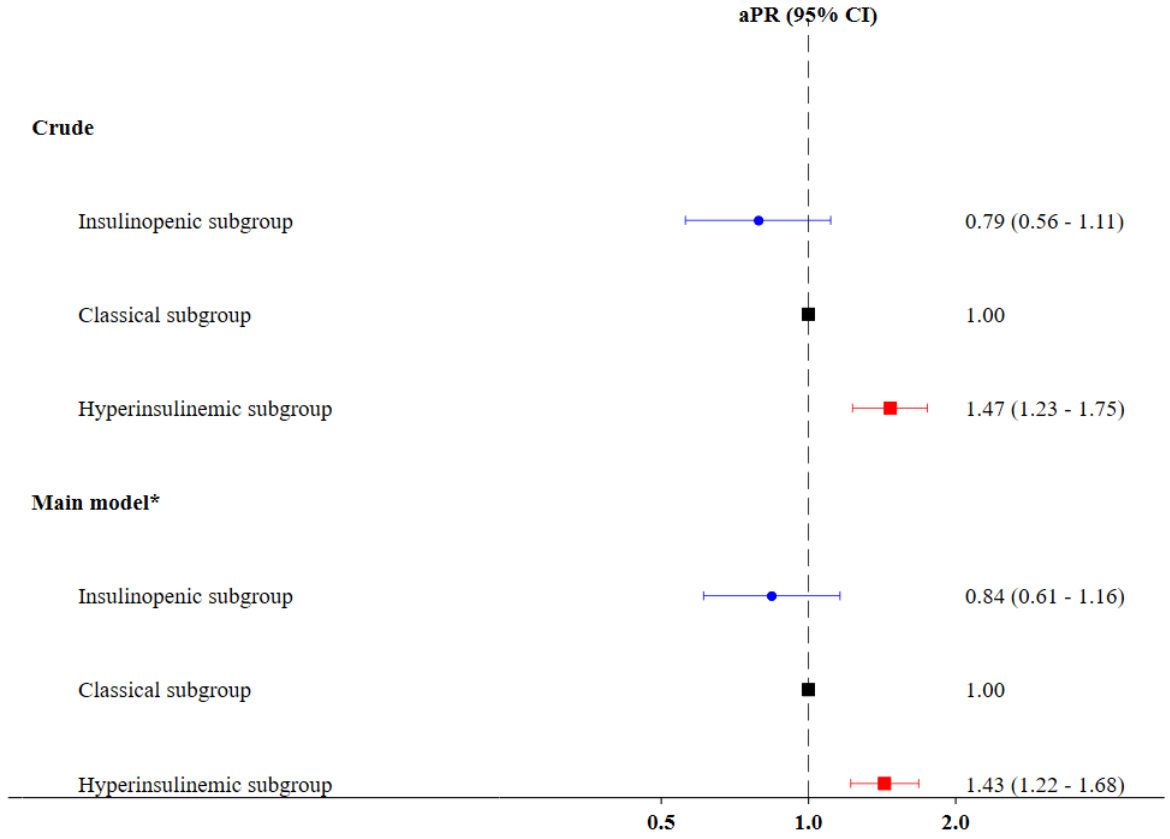
Adjustment model	T2DM subgroup	Number of patients/DPN prevalence	Adjusted PR (95% CI)
Model 1*	**Insulinopenic**	347/47	0.86 (0.63-1.16)
	Classical	2,150/340	1.0
	Hypersinulinemic	900/204	1.43 (1.20-1.71)
Model 2†: Model 1 + waist circumference, triglycerides, HDL cholesterol, hypertension, and HbA1c	**Insulinopenic**	347/47	1.04 (0.77-1.38)
	Classical	2,150/340	1.0
	Hypersinulinemic	900/204	1.35 (1.15-1.57)
Model 2: without HDL cholesterol	**Insulinopenic**	347/47	1.04 (0.77-1.38)
	Classical	2,150/340	1.0
	Hypersinulinemic	900/204	1.34 (1.15-1.57)
Model 2: + HS-CRP	**Insulinopenic**	347/47	1.04 (0.78-1.39)
	Classical	2,150/340	1.0
	Hypersinulinemic	900/204	1.34 (1.15-1.57)
Complete case analysis			
Model 1* (n=3,397)	**Insulinopenic**	347/47	0.86 (0.65-1.14)
	Classical	2,150/340	1.0
	Hypersinulinemic	900/204	1.42 (1.21-1.65)
Complete case analysis	**Insulinopenic**	233/35	1.17 (0.83-1.65)
Model 2†: Model 1 + waist	**Classical**	1,443/230	1.0
circumference, triglycerides, HDL cholesterol, hypertension, and HbA1c (n=2,291)	**Hypersinulinemic**	615/150	1.44 (1.20-1.73)

*Model 1 was adjusted for demographic factors (age and sex), diabetes duration and therapy, and lifestyle behaviors (physical activity, smoking, and alcohol consumption).

†Model 2 was additionally adjusted for metabolic syndrome components: waist circumference (continuous variable), triglycerides ≥1.7 mmol/L or treatment with any lipid lowering medication, HDL cholesterol <1.0/1.3 mmol/L [male/female] or treatment with any lipid-lowering medication**,** systolic/diastolic blood pressure ≥130/85 mmHg or use of any anti-hypertensive medication, and HbA1c (continuous variable). Missing data were handled by multiple imputation using chained equations.

Abbreviations: CI, confidence interval; PR, prevalence ratio; DPN, diabetic polyneuropathy; HDL, high-density lipoprotein cholesterol, T2DM, type 2 diabetes mellitus; HS-CRP, high-sensitive C-reactive protein.

Supplementary Figure 6. Crude and adjusted PRs of DPN associated with T2D subgroups, excluding 162 patients on insulin therapy.



*The main model (model 1) included age, sex, diabetes duration and drug therapy, physical activity, smoking, and alcohol consumption. Missing data were handled by multiple imputation using chained equations. A detailed description of this procedure is available in the Supplementary Material. Abbreviations: CI, confidence interval; DPN, diabetic polyneuropathy; aPR, adjusted prevalence ratios; GLD, glucose-lowering drug

Supplementary Table 4. Adjusted prevalence ratios of DPN associated with T2DM sub-groups adjusted for metabolic syndrome components, excluding patients with a hospital record of any neuropathies (n=103).

Adjustment model	T2DM subgroup	Number of patients/DPN prevalence	Adjusted PR (95% CI)
Model 1*	**Insulinopenic**	335/44	0.88 (0.66-1.18)
	Classical	2092/316	1.0
	Hypersinulinemic	867/186	1.42 (1.21-1.67)
Model 2†: Model 1 + waist circumference, triglycerides, HDL cholesterol, hypertension, and HbA1c	**Insulinopenic**	335/44	1.07 (0.79-1.44)
	Classical	2092/316	1.0
	Hypersinulinemic	867/186	1.35 (1.15-1.59)

*Model 1 was adjusted for demographic factors (age and sex), diabetes duration and therapy, and lifestyle behaviors (physical activity, smoking, and alcohol consumption).

†Model 2 was additionally adjusted for metabolic syndrome components: waist circumference (continuous variable), triglycerides ≥1.7 mmol/L or treatment with any lipid lowering medication, HDL cholesterol: <1.0/1.3 mmol/L [male/female] or treatment with any lipid-lowering medication**,** systolic/diastolic blood pressure ≥130/85 mmHg or use of any anti-hypertensive medication, and HbA1c (continuous variable). Missing data were handled by multiple imputation using chained equations.

Abbreviations: CI, confidence interval; PR, prevalence ratio; DPN, diabetic polyneuropathy; HDL, high-density lipoprotein cholesterol, T2DM, type 2 diabetes mellitus; HS-CRP, high-sensitive C-reactive protein.

Supplementary Table 5. Baseline characteristics of the study cohort *vs.* the cohort available for further T2DM subgrouping.

	Cohort answering the MNSI questionaire (median three years after enrollment).				Overall cohort available for T2DM subgrouping			
	Hyperinsulinemic	**Classical**	**Insulinopenic**	**Total**	**Hyperinsulinemic**	**Classical**	**Insulinopenic**	**Total**
Number of patients	**N=900 (27%)**	**N=2,150 (63%)**	**N=347 (10%)**	**N=3,397**	**N=1,179 (27%)**	**N=2,778 (63%)**	**N=431 (10%)**	**N=4,388**
Median age at enrollment (quartiles)	63 (54-70)	62 (54-69)	65 (56-70)	63 (55-69)	63 (54-70)	62 (53-69)	64 (56-70)	62 (54-69)
Male	493 (55%)	1,271 (59%)	200 (58%)	1,964 (58%)	654 (55%)	1,670 (60%)	249 (58%)	2,573 (59%)
Year of enrollment								
2010-2012	324 (36%)	753 (35%)	119 (34%)	1,196 (35%)	442 (37%)	1,013 (36%)	156 (36%)	1,611 (37%)
2013-2015	576 (64%)	1,397 (65%)	228 (66%)	2,201 (65%)	737 (63%)	1,765 (64%)	275 (64%)	2,777 (63%)
Median diabetes duration, days, (quartiles)	430 (135-871)	566 (174-1077)	483 (157-971)	518 (160-1004)	418 (125-849)	551 (163-1070)	487 (156-953)	504 (152-1001)
Excessive alcohol intake	55 (6%)	160 (7%)	18 (5%)	233 (7%)	72 (6%)	202 (7%)	25 (6%)	299 (7%)
Median hip circumference, cm (quartiles)	112 (105-119)	107 (101-114)	99 (94-105)	107 (101-115)	112 (105-120)	107 (101-115)	99 (94-105)	107 (101-115)
Median waist circumference, cm (quartiles)	112 (102-121)	105 (97-114)	92 (85-100)	105 (97-115)	112 (102-121)	105 (97-115)	92 (85-100)	106 (97-116)
Median hs-CRP, (quartiles)	2.3 (1.0-5.0)	1.7 (0.8-3.7)	0.8 (0.4-1.8)	1.7 (0.8-3.8)	2.5 (1.1-5.3)	1.8 (0.8-3.9)	0.9 (0.4-2.1)	1.8 (0.8-4.1)
Median fasting glucose, mmol/L (quartiles)	6.4 (5.9-6.9)	7.6 (6.9-8.7)	6.5 (5.8-7.3)	7.1 (6.4-8.1)	6.4 (5.9-6.9)	7.6 (6.9-8.8)	6.5 (5.9-7.4)	7.1 (6.4-8.2)
Median c-peptide, pmol/L (quartiles)	1542.0 (1224.0-1869.0)	1050.0 (856.0-1286.0)	556.3 (476.4-608.4)	1108.0 (835.5-1466.0)	1548.0 (1247.0-1901.0)	1056.0 (859.0-1308.0)	552.9 (471.2-603.6)	1118.0 (841.8-1486.5)
Median HOMA2-B, % (quartiles)	136.0 (124.7-157.7)	82.3 (66.5-97.4)	64.2 (49.8-80.8)	91.2 (69.5-117.4)	137.6 (125.0-159.8)	82.4 (66.3-97.3)	62.2 (48.6-78.4)	91.4 (69.4-118.0)
Median HOMA2-S, % (quartiles)	27.3 (22.1-34.8)	37.6 (29.9-46.9)	74.2 (68.4-85.9)	36.2 (27.3-48.7)	26.9 (21.8-34.7)	37.3 (29.3-46.8)	74.7 (68.4-88.1)	35.8 (26.7-48.4)
Median HbA1c, mmol/mol (quartiles)*	44.0 (41.0-48.0)	47.5 (43.0-53.0)	46.0 (41.0-51.0)	46.0 (42.0-52.0)	44.1 (41.0-49.0)	48.0 (43.0-54.0)	46.0 (42.0-51.9)	46.4 (42.0-52.0)
Median LDL cholesterol, mmol/L (quartiles)*	2.1 (1.6-2.7)	2.2 (1.7-2.8)	2.1 (1.7-2.7)	2.2 (1.7-2.7)	2.1 (1.7-2.7)	2.2 (1.7-2.8)	2.2 (1.7-2.7)	2.2 (1.7-2.8)
Median triglycerides, mmol/L (quartiles)*	1.8 (1.3-2.5)	1.6 (1.1-2.4)	1.0 (0.8-1.4)	1.6 (1.1-2.3)	1.8 (1.3-2.5)	1.6 (1.2-2.4)	1.1 (0.8-1.5)	1.6 (1.1-2.4)
Median total cholesterol, mmol/L (quartiles)*	4.3 (3.6-5.1)	4.3 (3.7-5.1)	4.3 (3.7-5.1)	4.3 (3.7-5.1)	4.3 (3.6-5.1)	4.3 (3.7-5.1)	4.4 (3.8-5.1)	4.3 (3.7-5.1)
Median eGFR, ml/min/1.73 m2, (quartiles)*	85.0 (70.0-96.0)	89.0 (76.0-98.0)	90.0 (82.0-96.0)	88.0 (75.0-97.0)	85.0 (67.0-96.0)	90.0 (77.0-100.0)	91.0 (82.0-97.0)	89.0 (75.0-99.0)
Modified Charlson Comorbidity Index score (excluding diabetes)								
0	585 (65%)	1,553 (72%)	269 (78%)	2,407 (71%)	734 (62%)	1,980 (71%)	330 (77%)	3,044 (69%)
1-2	252 (28%)	515 (24%)	63 (18%)	830 (24%)	361 (31%)	683 (25%)	80 (19%)	1,124 (26%)
3+	63 (7%)	82 (4%)	15 (4%)	160 (5%)	84 (7%)	115 (4%)	21 (5%)	220 (5%)
No GLD use	148 (16%)	341 (16%)	62 (18%)	551 (16%)	203 (17%)	448 (16%)	77 (18%)	728 (17%)
Non-insulin GLD monotherapy	645 (72%)	1,459 (68%)	221 (64%)	2,325 (68%)	833 (71%)	1,859 (67%)	267 (62%)	2,959 (67%)
Non-insulin GLD polytherapy	81 (9%)	255 (12%)	23 (7%)	359 (11%)	102 (9%)	335 (12%)	29 (7%)	466 (11%)
Insulin therapy	26 (3%)	95 (4%)	41 (12%)	162 (5%)	41 (3%)	136 (5%)	58 (13%)	235 (5%)
Loop diuretics	126 (14%)	136 (6%)	15 (4%)	277 (8%)	197 (17%)	194 (7%)	20 (5%)	411 (9%)
Aspirin	291 (32%)	569 (26%)	75 (22%)	935 (28%)	397 (34%)	744 (27%)	95 (22%)	1,236 (28%)
Statins	652 (72%)	1,564 (73%)	240 (69%)	2,456 (72%)	847 (72%)	1,976 (71%)	292 (68%)	3,115 (71%)

Please see definitions of covariates in Supplementary Table 1. *Missing values of laboratory tests varied from 20% to 66% in the overall cohort of patients who responded to the MNSI questionaire. The proportion of missing values for the study cohort is described in Supplementary Table 1. Abbreviations: MNSI, Michigan Neuropathy Screening Instrument; IQR, interquartile range; HS-CRP, high senstivity C-reactive protein; GLD, glucose-lowering drug; T2DM, type 2 diabetes mellitus

Supplementary Table 6. Baseline characteristics of the study cohort *vs.* the cohort of non-responders to the MNSIq, according to T2D subgroups.

	Cohort answering the MNSI questionaire (median three years after enrollment).				**Cohort of non-responders to the MNSI questionaire**			
	Hyperinsulinemic	Classical	Insulinopenic	Total	Hyperinsulinemic	Classical	Insulinopenic	Total
Number of patients	N=900 (27%)	N=2,150 (63%)	N=347 (10%)	N=3,397	N=163 (27%)	N=384 (65%)	N=47 (8%)	N=594
Median age at enrollment (quartiles)	63 (54-70)	62 (54-69)	65 (56-70)	63 (55-69)	57 (47-66)	56 (48-63)	54 (48-61)	56 (48-64)
Male	493 (55%)	1,271 (59%)	200 (58%)	1,964 (58%)	96 (59%)	253 (66%)	28 (60%)	377 (63%)
Year of enrollment								
2010-2012	324 (36%)	753 (35%)	119 (34%)	1,196 (35%)	60 (37%)	148 (39%)	21 (45%)	229 (39%)
2013-2015	576 (64%)	1,397 (65%)	228 (66%)	2,201 (65%)	103 (63%)	236 (61%)	26 (55%)	365 (61%)
Median diabetes duration, days, (quartiles)	430 (135-871)	566 (174-1077)	483 (157-971)	518 (160-1004)	427 (102-779)	494 (135-1037)	509 (119-722)	468 (125-964)
Excessive alcohol intake	55 (6%)	160 (7%)	18 (5%)	233 (7%)	6 (4%)	30 (8%)	5 (11%)	41 (7%)
Median hip circumference, cm (quartiles)	112 (105-119)	107 (101-114)	99 (94-105)	107 (101-115)	114 (106-124)	107 (102-116)	103 (96-109)	109 (102-117)
Median waist circumference, cm (quartiles)	112 (102-121)	105 (97-114)	92 (85-100)	105 (97-115)	113 (102-125)	107 (99-118)	93 (86-100)	108 (99-119)
Median hs-CRP, (quartiles)	2.3 (1.0-5.0)	1.7 (0.8-3.7)	0.8 (0.4-1.8)	1.7 (0.8-3.8)	2.8 (1.3-5.6)	2.3 (1.1-5.2)	1.3 (0.5-3.2)	2.4 (1.1-5.2)
Median fasting glucose, mmol/L (quartiles)	6.4 (5.9-6.9)	7.6 (6.9-8.7)	6.5 (5.8-7.3)	7.1 (6.4-8.1)	6.5 (5.9-7.0)	7.9 (7.0-9.3)	7.2 (6.0-8.1)	7.4 (6.5-8.7)
Median c-peptide, pmol/L (quartiles)	1542.0 (1224.0-1869.0)	1050.0 (856.0-1286.0)	556.3 (476.4-608.4)	1108.0 (835.5-1466.0)	1665.0 (1300.0-2054.0)	1116.5 (871.9-1432.5)	496.4 (437.9-561.9)	1182.0 (884.2-1553.0)
Median HOMA2-B, % (quartiles)	136.0 (124.7-157.7)	82.3 (66.5-97.4)	64.2 (49.8-80.8)	91.2 (69.5-117.4)	141.7 (126.7-160.4)	80.7 (59.7-95.8)	51.5 (39.5-69.1)	90.4 (66.6-119.9)
Median HOMA2-S, % (quartiles)	27.3 (22.1-34.8)	37.6 (29.9-46.9)	74.2 (68.4-85.9)	36.2 (27.3-48.7)	25.6 (20.0-32.2)	34.8 (26.4-45.2)	80.3 (69.7-91.6)	32.9 (24.6-46.0)
Median HbA1c, mmol/mol (quartiles)*	44.0 (41.0-48.0)	47.5 (43.0-53.0)	46.0 (41.0-51.0)	46.0 (42.0-52.0)	47.0 (42.0-51.0)	51.0 (45.0-61.9)	50.0 (43.6-61.5)	49.0 (44.0-58.0)
Median LDL cholesterol, mmol/L (quartiles)*	2.1 (1.6-2.7)	2.2 (1.7-2.8)	2.1 (1.7-2.7)	2.2 (1.7-2.7)	2.2 (1.7-2.8)	2.4 (1.8-3.1)	2.2 (2.0-2.8)	2.3 (1.8-3.0)
Median triglycerides, mmol/L (quartiles)*	1.8 (1.3-2.5)	1.6 (1.1-2.4)	1.0 (0.8-1.4)	1.6 (1.1-2.3)	1.9 (1.5-2.6)	1.9 (1.3-2.6)	1.1 (0.8-1.6)	1.8 (1.3-2.6)
Median total cholesterol, mmol/L (quartiles)*	4.3 (3.6-5.1)	4.3 (3.7-5.1)	4.3 (3.7-5.1)	4.3 (3.7-5.1)	4.3 (3.6-5.1)	4.2 (3.6-5.1)	4.3 (3.9-4.4)	4.3 (3.6-5.0)
Median eGFR, ml/min/1.73 m2, (quartiles)*	85.0 (70.0-96.0)	89.0 (76.0-98.0)	90.0 (82.0-96.0)	88.0 (75.0-97.0)	89.0 (69.0-102.0)	96.0 (83.0-107.0)	97.0 (86.0-107.0)	95.0 (81.0-106.0)
Modified Charlson Comorbidity Index scores (excluding diabetes)								
0	585 (65%)	1,553 (72%)	269 (78%)	2,407 (71%)	99 (61%)	283 (74%)	38 (81%)	420 (71%)
1-2	252 (28%)	515 (24%)	63 (18%)	830 (24%)	57 (35%)	88 (23%)	7 (15%)	152 (26%)
3+	63 (7%)	82 (4%)	15 (4%)	160 (5%)	<10 (4%)	13 (3%)	<5 (4%)	22 (4%)
No GLD use	148 (16%)	341 (16%)	62 (18%)	551 (16%)	32 (20%)	62 (16%)	7 (15%)	101 (17%)
Non-insulin GLD monotherapy	645 (72%)	1,459 (68%)	221 (64%)	2,325 (68%)	108 (66%)	241 (63%)	24 (51%)	373 (63%)
Non-insulin GLD polytherapy	81 (9%)	255 (12%)	23 (7%)	359 (11%)	14 (9%)	54 (14%)	6 (13%)	74 (12%)
Insulin therapy	26 (3%)	95 (4%)	41 (12%)	162 (5%)	9 (6%)	27 (7%)	10 (21%)	46 (8%)
Loop diuretics	126 (14%)	136 (6%)	15 (4%)	277 (8%)	28 (17%)	23 (6%)	<1 (2%)	<60 (9%)
Aspirin	291 (32%)	569 (26%)	75 (22%)	935 (28%)	53 (33%)	82 (21%)	7 (15%)	142 (24%)
Statins	652 (72%)	1,564 (73%)	240 (69%)	2,456 (72%)	117 (72%)	243 (63%)	26 (55%)	386 (65%)

Please see definitions of covariates in Supplementary Table 1. *Missing values of laboratory tests varied from 15% to 47% in the cohort of MNSI questionaire non-reponders. The proportion of missing values for the study cohort is decribed in Supplementary Table 1. Abbreviations: MNSI, Michigan Neuropathy Screening Instrument; IQR, interquartile range; HS-CRP, high senstivity C-reactive protein; GLD, glucose-lowering drug; T2DM, type 2 diabetes mellitus

Supplementary Table 7. Baseline characteristics of the study cohort *vs.* the cohort with non-valid respons to the MNSI questionaire, according to T2DM subgroups.

	Cohort with validanswer to the MNSI questionaire (median three years after enrollment)				Cohort of patients with non-valid answers to the MNSI questionaire*			
	Hyperinsulinemic	**Classical**	**Insulinopenic**	**Total**	**Hyperinsulinemic**	**Classical**	**Insulinopenic**	**Total**
Number of patients	**N=900 (27%)**	**N=2,150 (63%)**	**N=347 (10%)**	**N=3,397**	**N=68 (29%)**	**N=147 (62%)**	**N=21 (9%)**	**N=236**
Median age at enrollment (quartiles)	63 (54-70)	62 (54-69)	65 (56-70)	63 (55-69)	66 (58-74)	67 (60-74)	65 (61-71)	67 (59-74)
Male	493 (55%)	1,271 (59%)	200 (58%)	1,964 (58%)	32 (47%)	72 (49%)	11 (52%)	115 (49%)
Year of enrollment								
2010-2012	324 (36%)	753 (35%)	119 (34%)	1,196 (35%)	32 (47%)	67 (46%)	9 (43%)	108 (46%)
2013-2015	576 (64%)	1,397 (65%)	228 (66%)	2,201 (65%)	36 (53%)	80 (54%)	12 (57%)	128 (54%)
Median diabetes duration, days, (quartiles)	430 (135-871)	566 (174-1077)	483 (157-971)	518 (160-1004)	391 (72-622)	473 (145-1041)	420 (202-844)	424 (128-891)
Excessive alcohol intake	55 (6%)	160 (7%)	18 (5%)	233 (7%)	4 (6%)	7 (5%)	1 (5%)	12 (5%)
Median hip circumference, cm (quartiles)	112 (105-119)	107 (101-114)	99 (94-105)	107 (101-115)	113 (107-126)	106 (100-114)	99 (93-106)	108 (101-116)
Median waist circumference, cm (quartiles)	112 (102-121)	105 (97-114)	92 (85-100)	105 (97-115)	113 (101-123)	101 (95-111)	91 (84-100)	103 (95-114)
Median hs-CRP, (quartiles)	2.3 (1.0-5.0)	1.7 (0.8-3.7)	0.8 (0.4-1.8)	1.7 (0.8-3.8)	3.1 (1.4-6.1)	1.6 (0.8-3.5)	0.9 (0.5-4.1)	2.0 (0.8-4.5)
Median fasting glucose, mmol/L (quartiles)	6.4 (5.9-6.9)	7.6 (6.9-8.7)	6.5 (5.8-7.3)	7.1 (6.4-8.1)	6.4 (5.9-7.0)	7.5 (6.7-8.4)	6.6 (5.9-7.0)	7.0 (6.4-7.9)
Median c-peptide, pmol/L (quartiles)	1542.0 (1224.0-1869.0)	1050.0 (856.0-1286.0)	556.3 (476.4-608.4)	1108.0 (835.5-1466.0)	1502.0 (1256.5-1911.0)	1031.0 (842.2-1317.0)	556.5 (491.8-599.1)	1099.0 (840.9-1490.5)
Median HOMA2-B, % (quartiles)	136.0 (124.7-157.7)	82.3 (66.5-97.4)	64.2 (49.8-80.8)	91.2 (69.5-117.4)	141.3 (123.8-165.3)	85.4 (69.6-101.7)	60.0 (52.5-68.6)	95.5 (72.0-119.8)
Median HOMA2-S, % (quartiles)	27.3 (22.1-34.8)	37.6 (29.9-46.9)	74.2 (68.4-85.9)	36.2 (27.3-48.7)	27.8 (21.4-34.6)	38.8 (29.6-47.7)	73.5 (68.9-88.6)	36.8 (27.1-48.4)
Median HbA1c, mmol/mol (quartiles)*	44.0 (41.0-48.0)	47.5 (43.0-53.0)	46.0 (41.0-51.0)	46.0 (42.0-52.0)	44.0 (40.0-49.7)	47.0 (43.0-52.0)	46.0 (41.0-51.0)	46.0 (42.1-51.0)
Median LDL cholesterol, mmol/L (quartiles)*	2.1 (1.6-2.7)	2.2 (1.7-2.8)	2.1 (1.7-2.7)	2.2 (1.7-2.7)	2.1 (1.8-3.2)	2.2 (1.7-2.9)	3.0 (2.0-3.7)	2.2 (1.8-3.1)
Median triglycerides, mmol/L (quartiles)*	1.8 (1.3-2.5)	1.6 (1.1-2.4)	1.0 (0.8-1.4)	1.6 (1.1-2.3)	1.8 (1.4-2.3)	1.4 (1.1-2.0)	1.1 (0.9-1.4)	1.5 (1.2-2.2)
Median total cholesterol, mmol/L (quartiles)*	4.3 (3.6-5.1)	4.3 (3.7-5.1)	4.3 (3.7-5.1)	4.3 (3.7-5.1)	4.4 (3.6-5.1)	4.5 (3.7-5.2)	5.1 (4.5-5.8)	4.5 (3.7-5.2)
Median eGFR, ml/min/1.73 m2, (quartiles)*	85.0 (70.0-96.0)	89.0 (76.0-98.0)	90.0 (82.0-96.0)	88.0 (75.0-97.0)	70.0 (59.0-87.0)	80.5 (67.0-94.0)	84.5 (69.0-93.5)	78.0 (65.0-92.0)
Modified Charlson Comorbidity Index scores (without diabetes)								
0	585 (65%)	1,553 (72%)	269 (78%)	2,407 (71%)	36 (53%)	99 (67%)	17 (81%)	152 (64%)
1-2	252 (28%)	515 (24%)	63 (18%)	830 (24%)	27 (40%)	39 (27%)	2 (10%)	68 (29%)
3+	63 (7%)	82 (4%)	15 (4%)	160 (5%)	5 (7%)	9 (6%)	2 (10%)	16 (7%)
No GLD use	148 (16%)	341 (16%)	62 (18%)	551 (16%)	13 (19%)	28 (19%)	5 (24%)	46 (19%)
Non-insulin GLD monotherapy	645 (72%)	1,459 (68%)	221 (64%)	2,325 (68%)	50 (74%)	97 (66%)	14 (67%)	161 (68%)
Non-insulin GLD polytherapy	81 (9%)	255 (12%)	23 (7%)	359 (11%)	<5 (6%)	14 (10%)	0 (0%)	<20 (8%)
Insulin therapy	26 (3%)	95 (4%)	41 (12%)	162 (5%)	<5 (1%)	8 (5%)	<5 (10%)	<20 (5%)
Loop diuretics	126 (14%)	136 (6%)	15 (4%)	277 (8%)	22 (32%)	14 (10%)	<5 (10%)	<40 (16%)
Aspirin	291 (32%)	569 (26%)	75 (22%)	935 (28%)	29 (43%)	43 (29%)	<10 (33%)	<80 (33%)
Statins	652 (72%)	1,564 (73%)	240 (69%)	2,456 (72%)	46 (68%)	108 (73%)	15 (71%)	169 (72%)

Please see definitions of covariates in Supplementary Table 1. Non-valid answers consisted of partial completion of the MNSIq or return of a blank questionaire.

*Missing values of laboratory tests varied from 24% to 66% in the cohort of patients with non-valid MNSI responses. The proportion of missing values for the study cohort is decribed in Supplementary Table 1. Abbreviations: MNSI, Michigan Neuropathy Screening Instrument; IQR, interquartile range; HS-CRP, high senstivity C-reactive protein; GLD, glucose-lowering drug; T2DM, type 2 diabetes mellitus

Supplementary Table 8. Mortality rate and mortality rate ratios associated with T2D subgroups within the total cohort of patients with available data for T2D subgrouping (n=4,388).

	Classical	**Hyperinsulinemic**	**Insulinopenic**
Number of patients	2,778 (63%)	1,179 (27%)	431 (10%)
Died	91	47	15
Median follow-up years (IQR)	3.0 (2.3-3.8)	3.0 (2.3-3.8)	2.9 (2.3-3.9)
Mortality rates per 1.000 person-years	10.8 (8.8-13.2)	13.1 (9.9-17.4)	11.4 (6.9-18.9)
Crude MRR (95% CI)	1.0	1.22 (0.86-1.72)	1.06 (0.62-1.82)
Age- and sex adjusted MRR (95% CI)	1.0	1.14 (0.82-1.60)	1.00 (0.59-1.71)

Patients were followed from enrollment until death, emigration, or end of follow up on June 1, 2016, when the MNSI questionnaire was answered. Mortality rate ratios were estimated based on Poisson regression with robust variance. Abbreviations: MNSI, Michigan Neuropathy Screening Instrument; IQR, interquartile range; CI, confidence interval; MMR, mortality rate ratio

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