Risk of cardiovascular events associated with pathophysiological phenotypes of type 2 diabetes

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Abstract

Objective: Hyperglycaemia in type 2 diabetes is caused by varying degrees of two defects: low insulin sensitivity and beta-cell dysfunction. We assessed if subgrouping of patients into three pathophysiological phenotypes according to these defects could identify individuals with high or low risk of future cardiovascular events.
Design: This is a prospective cohort study.
Methods: We assessed estimates of insulin sensitivity and beta-cell function from the homeostasis model assessment-2 in 4209 individuals with recently diagnosed type 2 diabetes enrolled from general practitioners and outpatient clinics in Denmark. Individuals were followed for a composite cardiovascular endpoint (either atherosclerotic outcomes (myocardial infarction, unstable angina pectoris, stroke, coronary or peripheral revascularization), heart failure, or cardiovascular death) and all-cause mortality.
Results: Totally 417 individuals with the insulinopenic phenotype (high insulin sensitivity and low beta-cell function) had substantially lower risk of cardiovascular events (5-year cumulative incidence: 4.6% vs 10.1%; age-/sex-adjusted hazard ratio (aHR): 0.49; 95% CI: 0.30–0.82) compared with 2685 individuals with the classical phenotype (low insulin sensitivity and low beta-cell function), driven by atherosclerotic events. Conversely, 1107 individuals with the hyperinsulinaemic phenotype (low insulin sensitivity and high beta-cell function) had more cardiovascular events (5-year cumulative incidence: 12.6%; aHR: 1.33; 95% CI: 1.05–1.69), primarily driven by increased heart failure and cardiovascular death and increased all-cause mortality.
Conclusions: Simple phenotyping based on insulin sensitivity and beta-cell function predicts distinct future risks of cardiovascular events and death in patients with type 2 diabetes. These results suggest that precision medicine according to underlying type 2 pathophysiology potentially can reduce diabetes complications.

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Introduction

Hyperglycaemia in type 2 diabetes is caused by varying degrees of two fundamental defects: low insulin sensitivity and beta-cell dysfunction (1, 2). Recently, two novel classifications from Denmark and Sweden have used these pathophysiological defects to stratify individuals with type 2 diabetes into several subgroups (3, 4). Other

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researchers have suggested the existence of different type 2 diabetes archetypes (5) or clusters informed by genetic loci (6), and such sub-stratification holds the promise of more individualized risk prediction and therapy in the future.

Based on Danish data, we have previously proposed the existence of three distinct type 2 diabetes phenotypes: an insulinopenic phenotype (high insulin sensitivity and low beta-cell function), a classical phenotype (low insulin sensitivity and low beta-cell function), and a hyperinsulinaemic phenotype (low insulin sensitivity and high beta-cell function) (4). We documented an increased prevalence of pre-existing cardiovascular disease already at diabetes diagnosis in individuals with the hyperinsulinaemic phenotype compared with the classical phenotype (4). However, longitudinal follow-up data on cardiovascular risks associated with the new type 2 diabetes phenotypes have hitherto been scarce.

A genetic disposition to hyperinsulinaemia (7, 8) increases the risk of cardiovascular events, suggesting a causal relationship. This does not disentangle the coupling between hyperinsulinaemia and insulin resistance, however (9, 10). Targeted treatment of insulin resistance with pioglitazone reduces risk of stroke in normoglycaemic individuals (11), and insulin resistance and hyperinsulinaemia may both independently cause atherosclerosis (12, 13, 14). However, the individual and separate contribution of the two pathophysiological mechanisms, insulin sensitivity and beta-cell dysfunction, to the risk of cardiovascular events in type 2 diabetes remains to be clarified.

Here, we aimed to investigate whether three pathophysiological phenotypes of type 2 diabetes according to the degree of low insulin sensitivity and beta-cell dysfunction around time of diabetes diagnosis could identify individuals with subsequently high or low risks of cardiovascular events and all-cause mortality.

Subjects and methods

Study population and data sources

This nationwide study drew on a study base of 5988 consecutively enrolled individuals with recently diagnosed type 2 diabetes within the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort from November 2010 to February 2015 (15). All persons with recently diagnosed type 2 diabetes in Denmark with diabetes debut after 2009 were eligible for enrollment in the DD2 cohort; recruitment was done from all hospital diabetes outpatient clinics in Denmark (currently $n = 33$) and from approximately 25% (462 out of 1853) of general practitioner (GP) clinics throughout the country. The patient's GP or hospital physician/nurse informed the patient about the existence of the DD2 project, and patients interested in participating received detailed information and signed a written informed consent. Participants underwent a clinical examination and interview and had a blood sample taken at enrollment (a fasting sample in 80.9%), either at GP offices (53%) or at outpatient clinics (47%). Glucose-lowering treatment was not paused prior to blood sampling. Further details of the DD2 cohort are summarized in the Supplementary methods (see section on supplementary materials given at the end of this article). Data collected at DD2 enrollment were subsequently linked with nationwide, population-based healthcare registries at the individual level using the unique civil personal registration number assigned to all Danish citizens at birth or migration (16). This provided clinical and biochemical data (e.g. HbA_{1c}, systolic and diastolic blood pressures, blood lipid levels) from the Danish Adult Diabetes Registry and data on redeemed medical prescriptions from the Danish National Prescription Registry at the time of registration. Longitudinal follow-up data on hospital diagnosis, procedure, and operation codes were drawn from the Danish National Patient Registry; migration status and exact date of death (if any) were obtained from the Danish Civil Registration System; and causes of death were provided by the Danish Registry of Causes of Death. A detailed description of data sources and variable definitions is presented in the Supplementary Tables 1, 2, 3 and 4.

Definition of type 2 diabetes phenotypes

Of the 5988 participants, we excluded 1447 individuals without available fasting serum C-peptide, fasting plasma glucose, or glutamic acid decarboxylase antibody (GADA) measurements. To ensure proper stratification of pre-existing cardiovascular disease diagnoses, an additional 11 participants who did not have residence in Denmark for at least 1 year before enrollment were excluded (Fig. 1). Of the remaining 4530 participants, we excluded 4 (0.1%) who had rare subtypes of diabetes, 127 (2.8%) who had latent autoimmune diabetes in adults (LADA), 35 (0.8%) who had secondary diabetes, and 140 (3.1%) who had potential glucocorticoid-induced diabetes (Fig. 1 and Supplementary Table 3), as previously described (4). No individuals had type 1 diabetes (GADA-positive patients with age< 30 years and fasting C-peptide<300 pmol/L). The remaining individuals were determined to have type 2 diabetes (17). The analytic methods for serum C-peptide and plasma glucose analysis

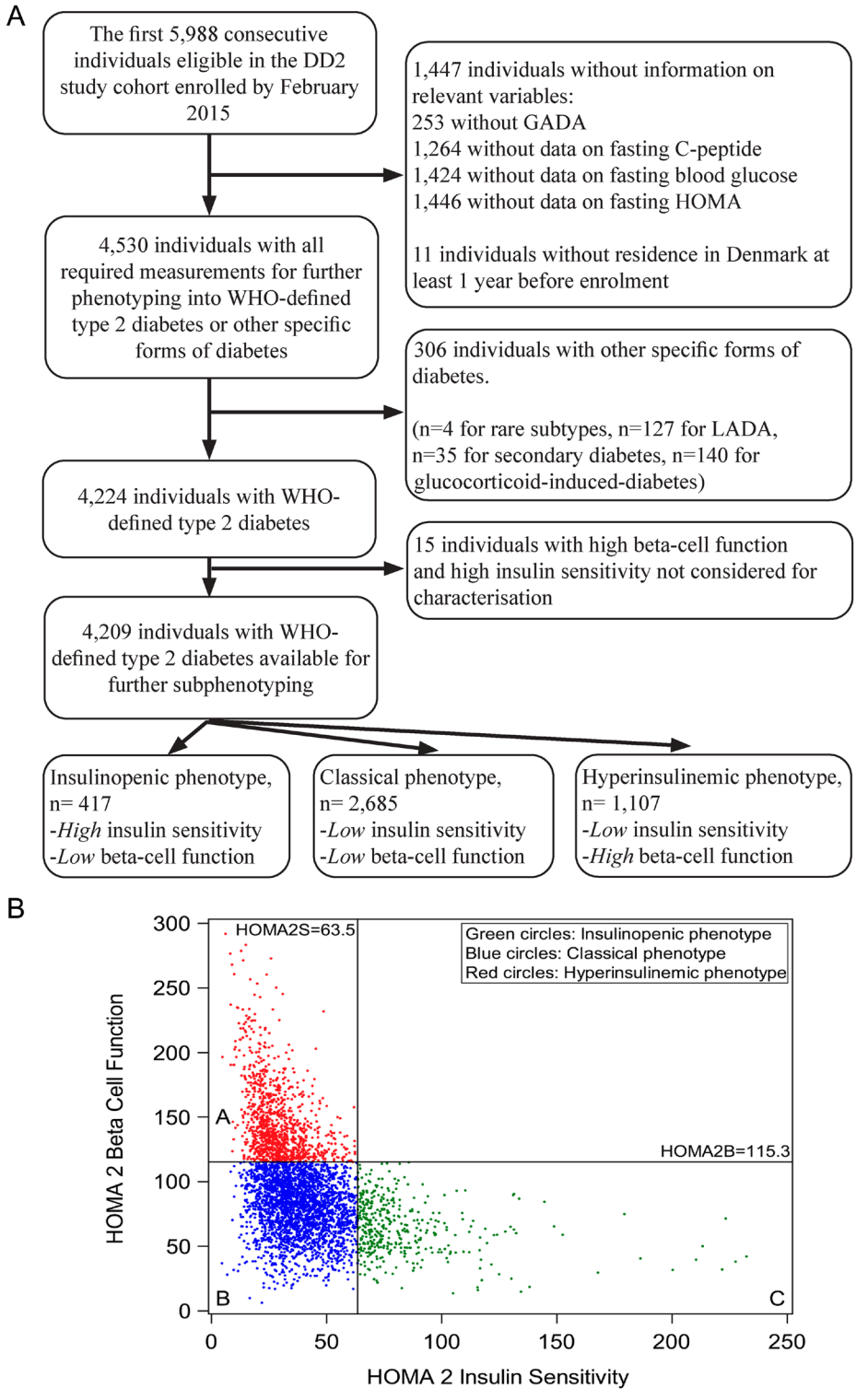

Figure 1

(A) Flow diagram of the study population. DD2, The Danish Centre for Strategic Research in Type 2 Diabetes; HOMA2, version 2 of the revised homeostatic assessment model; LADA, latent autoimmune diabetes in adults. (B) Plot of insulin sensitivity and beta-cell function for individuals with WHO-defined type 2 diabetes. Reference lines depict the median of the insulin sensitivity and beta-cell function in a background population with normal glucose tolerance.

have been described in detail previously (4). Fasting serum C-peptide and plasma glucose levels measured at DD2 enrollment were used to estimate insulin sensitivity and beta-cell function by the homeostatic assessment model 2 (HOMA2) (18, 19, 20). The discrimination between high and low insulin sensitivity (HOMA2-S) and beta-cell function (HOMA2-B) was defined by the median of HOMA2-B and HOMA2-S in a matched background population with normal glucose tolerance, as described previously (4). The individuals who had WHO-defined type 2 diabetes were categorized into either an insulinopenic phenotype with high insulin sensitivity and low beta-cell function (HOMA2-S ≥ 63.5% and HOMA2-B < 115.3%), a classical phenotype with low insulin sensitivity and low beta-cell function (HOMA2-S < 63.5% and HOMA2-B < 115.3%), or a hyperinsulinaemic phenotype with low insulin sensitivity and high beta-cell function (HOMA2-S < 63.5% and HOMA2-B ≥ 115.3%). Fifteen individuals with high insulin sensitivity and high beta-cell function (HOMA2-S ≥ 63.5% and HOMA2-B ≥ 115.3%) were not considered for characterization due to the small numbers and were excluded.

Outcomes

We assessed the first occurrence of a composite cardiovascular endpoint (atherosclerotic outcomes, i.e. myocardial infarction, unstable angina pectoris, stroke, coronary or peripheral revascularization; heart failure; or cardiovascular death) and all-cause mortality (Supplementary Table 2). We further assessed the individual components of the composite endpoint and non-cardiovascular death.

Statistical analysis

The index date for all analyses was defined as the date of DD2 enrollment (i.e. the date of phenotype allocation). We constructed cumulative incidence curves and calculated the corresponding 3- and 5-year cumulative incidence estimates for the composite endpoint, taking the competing risk of non-cardiovascular death into account. The procedures were repeated for the individual endpoints, taking death into account, except for cardiovascular death and non-cardiovascular death where non-cardiovascular death and cardiovascular death were taken into account, respectively. We then constructed cumulative mortality curves and estimated the 3- and 5-year cumulative all-cause mortality rates for each phenotype using the Kaplan–Meier estimator.

Participants were followed from the index date until the first occurrence of either an outcome event, death, migration, enrollment in the DD2 embedded intervention trial 'specialist supervised individualised multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA)' (21), or end of study period (10 August 2018). For follow-up analyses including cause-of-death as an outcome (non-cardiovascular or cardiovascular death, including the composite cardiovascular endpoint), follow-up ended 31 December 2016 due to latest data availability in the Danish Registry of Causes of Death. For all other endpoints, data were available until 10 August 2018, at which follow-up was terminated. The ongoing IDA trial is based on treatment according to phenotype allocation, and its results could affect this study. Therefore, 183 IDA participants were censored at the date of their IDA enrollment in the analyses terminated on 31 December 2016, while 260 were censored in the analyses terminated on 10 August 2018. We used Cox regression analysis to estimate adjusted hazard ratios (aHRs) of the endpoints comparing the insulinopenic and hyperinsulinaemic phenotypes with the classical phenotype, adjusted for age and sex (model 1, main model). We refrained from additional multivariable adjustments in our main model, because the different metabolic and lifestyle factors may act as intermediates and clusters in the same incompletely understood pathophysiological pathways between insulin sensitivity, beta-cell function, and outcomes. For example, obesity and inflammation – well-known risk factors for cardiovascular disease – may cause insulin resistance but may also be an effect of insulin resistance, leading to potential over-adjustment for intermediates. In exploratory analyses, we additionally adjusted for variables that might potentially fulfil criteria of being a confounder (model 2: age, sex, diabetes duration at index date, waist circumference, self-reported physical activity, family history of diabetes, smoking, and alcohol consumption). In a third model, we adjusted both for potential confounders and for likely mediators (model 3: model 2 + systolic and diastolic blood pressure, fasting plasma glucose, HbA_{1c}, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, urine albumin-creatinine ratio, use of glucose-lowering, lipid-lowering, anti-hypertensive, or anti-thrombotic drugs, pre-existing kidney disease, and pre-existing cardiovascular disease). We also performed a stratified analysis of individuals with (19.8%) and without (81.2%) pre-existing cardiovascular disease at the time of enrollment.

Covariates were defined at the index date (Supplementary Table 4). We used multiple imputation by chained equations to impute missing values of covariates used in the additional exploratory multivariable analyses, as described in the Supplementary methods.

The Cox proportional hazards assumption was (see Supplementary methods) without violations, except for all-cause mortality for the insulinopenic phenotype, thus, that specific aHR should be interpreted as an average estimate of the follow-up period.

We performed three sensitivity analyses, restricting the population to individuals with a maximum known diabetes duration of 1 year at DD2 enrolment date (index date), to those not treated with glucocorticoids within 3 months before the index date, and to those not treated with insulin before the index date.

A restricted cubic spline model, adjusted for age and sex, with six knots was used to examine the association between HOMA2-B or HOMA2-S levels, as a continuous variable, and the risk of the composite cardiovascular endpoint or all-cause mortality. All analyses were performed using SAS 9.4.

The study was approved by the Regional Ethical Committee on Health Research (record number, S-20100082) and the Danish Data Protection Agency (record number, 2008-58-0035). All participants received oral and written information and gave written informed consent.

Results

Descriptive data

Characteristics of individuals with the insulinopenic (n=417, 9.9%), classical (n=2,685, 63.8%), and hyperinsulinaemic (n=1,107, 26.3%) type 2 diabetes phenotypes at enrollment are shown in Table 1. Of clinical importance, blood pressure and LDL cholesterol did not differ among the three phenotypes, whereas fasting plasma glucose was higher in the classical phenotype. Waist circumference, BMI, physical inactivity, and pre-existing cardiovascular disease were highest in the hyperinsulinaemic phenotype and lowest in the insulinopenic phenotype, compared with the classical phenotype. In addition, the insulinopenic phenotype had higher HDL cholesterol and lower triglycerides.

Composite cardiovascular outcome and all-cause mortality

A total of 319 individuals experienced the composite cardiovascular endpoint during a median follow-up time of 3.4 years (IQR: 2.6–4.2 years). The crude 5-year cumulative incidence of the composite cardiovascular endpoint (Fig. 2A) was 4.6% in the insulinopenic phenotype compared with 10.1% in the classical phenotype and 12.6% in the hyperinsulinaemic phenotype. After adjustment for age and sex, the insulinopenic phenotype was associated with only half the risk (aHR: 0.49; 95% CI: 0.30–0.82; Fig. 3A), whereas the hyperinsulinaemic phenotype was associated with a clearly higher risk of the composite cardiovascular endpoint (aHR: 1.33; 95% CI: 1.05–1.69; Fig. 3A), as compared with the classical phenotype. During follow-up, 262 individuals died. The crude 5-year, cumulative, all-cause mortality rates (Fig. 2B) were 6.2% in the insulinopenic phenotype, 5.3% in the classical phenotype, and 8.2% in the hyperinsulinaemic phenotype during a median follow-up of 5.0 years (IQR: 4.2–5.9 years). After adjustment for age and sex, the insulinopenic phenotype was associated with similar all-cause mortality as the classical phenotype (aHR: 1.10; 95% CI: 0.73–1.64; Fig. 3A), whereas the hyperinsulinaemic phenotype had a higher risk (aHR: 1.30; 95% CI: 1.00–1.68; Fig. 3A).

Individual cardiovascular and non-cardiovascular outcomes

The insulinopenic phenotype was associated with lower risk for all the individual components of the composite cardiovascular endpoint except for cardiovascular mortality, although statistical precision was limited because of the small number of events (Figs 2C, D, E, F, G, H, I, J and 3B). Importantly, both myocardial infarction (aHR: 0.44; 95% CI: 0.16–1.21) and stroke (aHR: 0.76; 95% CI: 0.36–1.58) were numerically reduced in the insulinopenic phenotype. For the individual components of the composite cardiovascular endpoint, the hyperinsulinaemic phenotype was associated with a substantially increased risk of cardiovascular death and heart failure (aHR: 2.21; 95% CI: 1.27–3.83 and aHR: 2.02; 95% CI: 1.38–2.96, respectively; Figs 2H, I and 3B). The hyperinsulinaemic phenotype had no clear association with the coronary endpoints, but a minor increase in stroke was seen. Of note, the risk of non-cardiovascular death was numerically increased in individuals with the insulinopenic phenotype, whereas there was no association for individuals with the hyperinsulinaemic phenotype (Figs 2J and 3B).

Potential confounders and mediators

When we adjusted for additional potential confounders in addition to age and sex in model 2 (i.e. physical activity, central obesity, and other lifestyle factors that

Table 1 Characteristics of the three type 2 diabetes phenotypes at enrollment. All continuous variables are reported as the median (interquartile range). For variables with missing values, the number with non-missing values is given.

	Insulinopenic phenotype	Classical phenotype	Hyperinsulinaemic phenotype
n	417	2685	1107
Male sex, n (%)	242 (58.0)	1610 (60.0)	614 (55.5)
Age, years	63.8 (55.6–69.7)	62.0 (53.6–68.6)	63.0 (53.8–70.2)
Diabetes duration, years	1.5 (0.6–3.0)	1.8 (0.5–3.3)	1.4 (0.4–2.6)
Waist circumference, cm, *n* = 4204	92.0 (85.0–100.0)	105.0 (97.0–115.0)	112.0 (102.0–121.0)
BMI, kg/m^2, *n* = 1942	25.8 (23.1–28.7)	30.1 (27.1–34.0)	33.1 (29.4–36.7)
Fasting plasma glucose, mmol/L	6.5 (5.9–7.4)	7.6 (6.9–8.8)	6.4 (5.9–6.9)
Fasting C-peptide, pmol/L	554.0 (471.7–603.6)	1,055 (859.3–1308)	1,545 (1243-1903)
HbA_{1c}, %, *n* = 2269	6.6 (6.1–7.2)	6.7 (6.2–7.3)	6.4 (6.0–6.8)
LDL cholesterol, mmol/L, *n* = 2186	2.3 (1.8–2.9)	2.2 (1.8–2.9)	2.2 (1.7–2.8)
HDL cholesterol, mmol/L, *n* = 984	1.4 (1.2–1.8)	1.2 (1.0–1.4)	1.1 (0.9–1.3)
Total cholesterol, mmol/L, *n* = 987	4.4 (3.8–5.3)	4.4 (3.8–5.1)	4.3 (3.6–5.1)
Triglycerides, mmol/L, *n* = 2083	1.1 (0.8–1.5)	1.7 (1.2–2.4)	1.9 (1.3–2.6)
Urine albumin–creatinine ratio, mg/g, *n* = 2098	7.6 (4.0–16.0)	10.0 (4.0–24.0)	10.0 (4.0–30.0)
Diastolic blood pressure, mmHg, *n* = 2147	80.0 (72.0–85.0)	80.0 (75.0–85.0)	80.0 (72.0–85.0)
Systolic blood pressure, mmHg, *n* = 2147	130.0 (125.0–137.0)	130.0 (124.0–140.0)	130.0 (120.0–140.0)
Smoking, *n* = 3866			
Never	195 (50.9%)	1,141 (46.0%)	422 (42.2%)
Former	121 (31.6%)	887 (35.7%)	378 (37.8%)
Current	67 (17.5%)	455 (18.3%)	200 (20.0%)
Excess alcohol intake	24 (5.8%)	197 (7.3%)	69 (6.2%)
Family history of diabetes, number of relatives			
0	191 (45.8%)	1,208 (45.0%)	583 (52.7%)
1–2	196 (47.0%)	1,261 (47.0%)	456 (41.2%)
≥3	30 (7.2%)	216 (8.0%)	68 (6.1%)
Self-reported physical activity, days/week			
0	34 (8.2%)	400 (14.9%)	252 (22.8%)
1–2	61 (14.6%)	544 (20.3%)	241 (21.8%)
≥3	322 (77.2%)	1,741 (64.8%)	614 (55.5%)
HOMA2-B, %	62.5 (48.7–78.4)	82.4 (66.5–97.2)	137.0 (124.9–158.6)
HOMA2-S, %	74.6 (68.4–88.0)	37.3 (29.4–46.8)	27.0 (21.8–34.7)
Pre-existing cardiovascular disease	61 (14.6%)	466 (17.4%)	263 (23.8%)
Pre-existing acute myocardial infarction	24 (5.8%)	150 (5.6%)	98 (8.9%)
Pre-existing stroke	8 (1.9%)	117 (4.4%)	48 (4.3%)
Pre-existing heart failure	5 (1.2%)	63 (2.3%)	51 (4.6%)
Pre-existing COPD	25 (6.0%)	196 (7.3%)	116 (10.5%)
Pre-existing cancer	37 (8.9%)	205 (7.6%)	81 (7.3%)
Chronic renal disease	3 (0.7%)	44 (1.6%)	44 (4.0%)
Glucose-lowering drug-naive	78 (18.7%)	455 (16.9%)	203 (18.3%)
Metformin	320 (76.7%)	2140 (79.7%)	870 (78.6%)
DPP-4 inhibitors	29 (7.0%)	236 (8.8%)	54 (4.9%)
GLP-1 analogues	10 (2.4%)	142 (5.3%)	61 (5.5%)
SGLT2 inhibitors	1 (0.2%)	11 (0.4%)	4 (0.4%)
SU and meglitinides	25 (6.0%)	190 (7.1%)	44 (4.0%)
Insulin	53 (12.7%)	121 (4.5%)	33 (3.0%)
Anti-hypertensive drugs	242 (58.0%)	1892 (70.5%)	872 (78.8%)
Lipid-lowering drugs	268 (64.3%)	1844 (68.7%)	779 (70.4%)
Anti-thrombotic drugs	106 (25.4%)	786 (29.3%)	409 (36.9%)

Excess alcohol intake was defined as more than 21 or 14 standard drinks (12 g of alcohol) per week for men and women, respectively.
COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like protein 1; HOMA2, version 2 of the revised homeostatic assessment model; SGLT2, sodium glucose co-transporter 2; SU, sulfonylurea.

might be precursors of the different phenotypes), the risk estimate of the composite cardiovascular endpoint for the insulinopenic phenotype was only slightly altered (aHR: 0.57; 95% CI: 0.34–0.97; Fig. 4A and Supplementary Table 9). Additional adjustment for likely mediators in model 3 revealed only a small dependency of the reduced cardiovascular risk on known cardiovascular risk factors (aHR: 0.68; 95% CI: 0.39–1.17; Fig. 4A and Supplementary Table 9), such as those included in the metabolic syndrome. In contrast, after adjustment for potential confounders in

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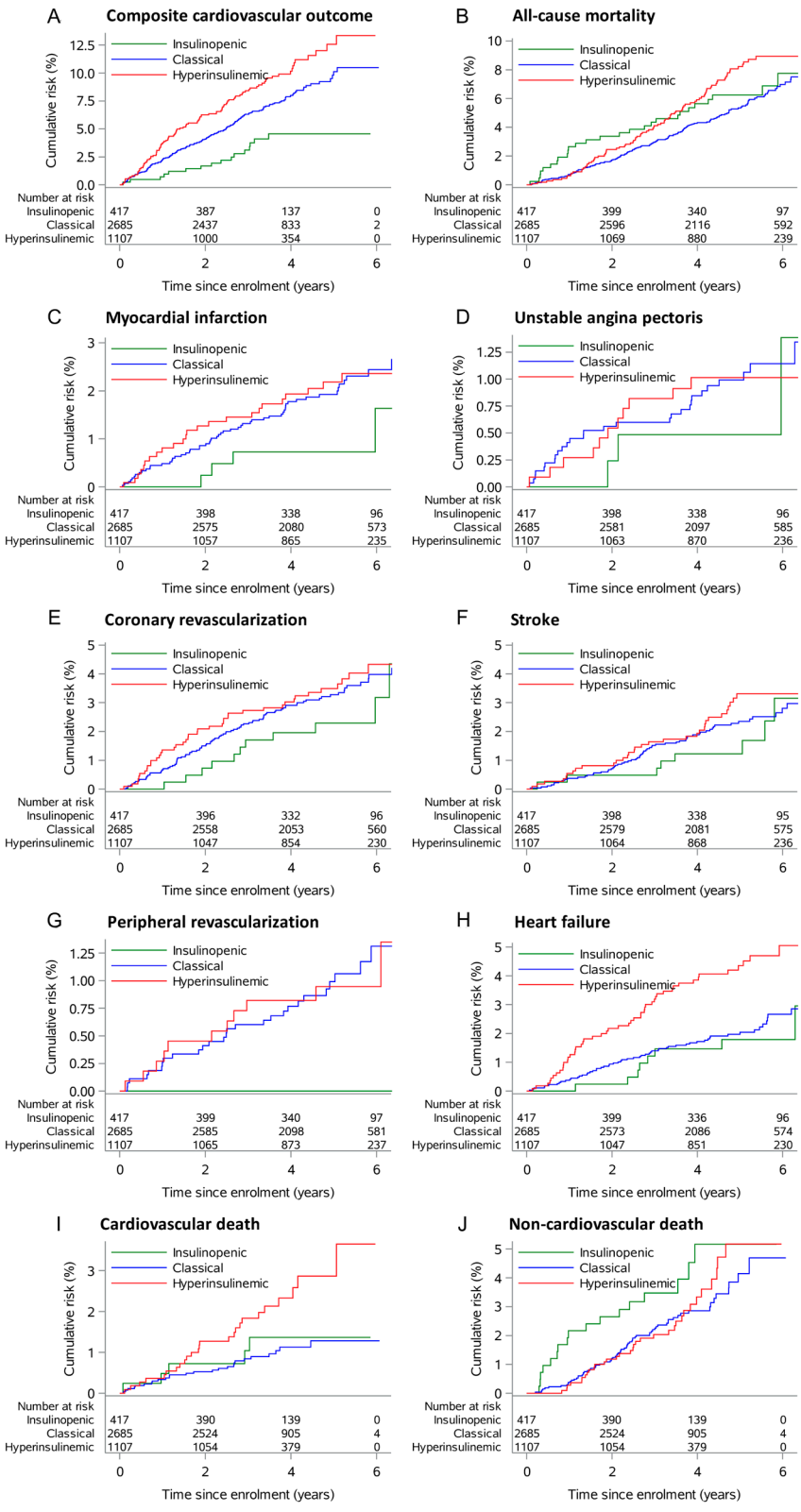

Figure 2

Crude cumulative incidence of the composite cardiovascular endpoint (A), all-cause mortality (B), myocardial infarction (C), unstable angina pectoris (D), coronary revascularization (E), stroke (F), peripheral revascularization (G), heart failure (H), cardiovascular death (I), and non-cardiovascular death (J) by type 2 diabetes phenotype. The cumulative incidence of the composite cardiovascular endpoint (A) was estimated taking the competing risk from non-cardiovascular deaths into account, while death was taken into account for (C, D, E, F, G, and H). For cardiovascular death (I) and non-cardiovascular death (J), non-cardiovascular death and cardiovascular death were taken into account, respectively. All-cause mortality was estimated by the Kaplan–Meier method.

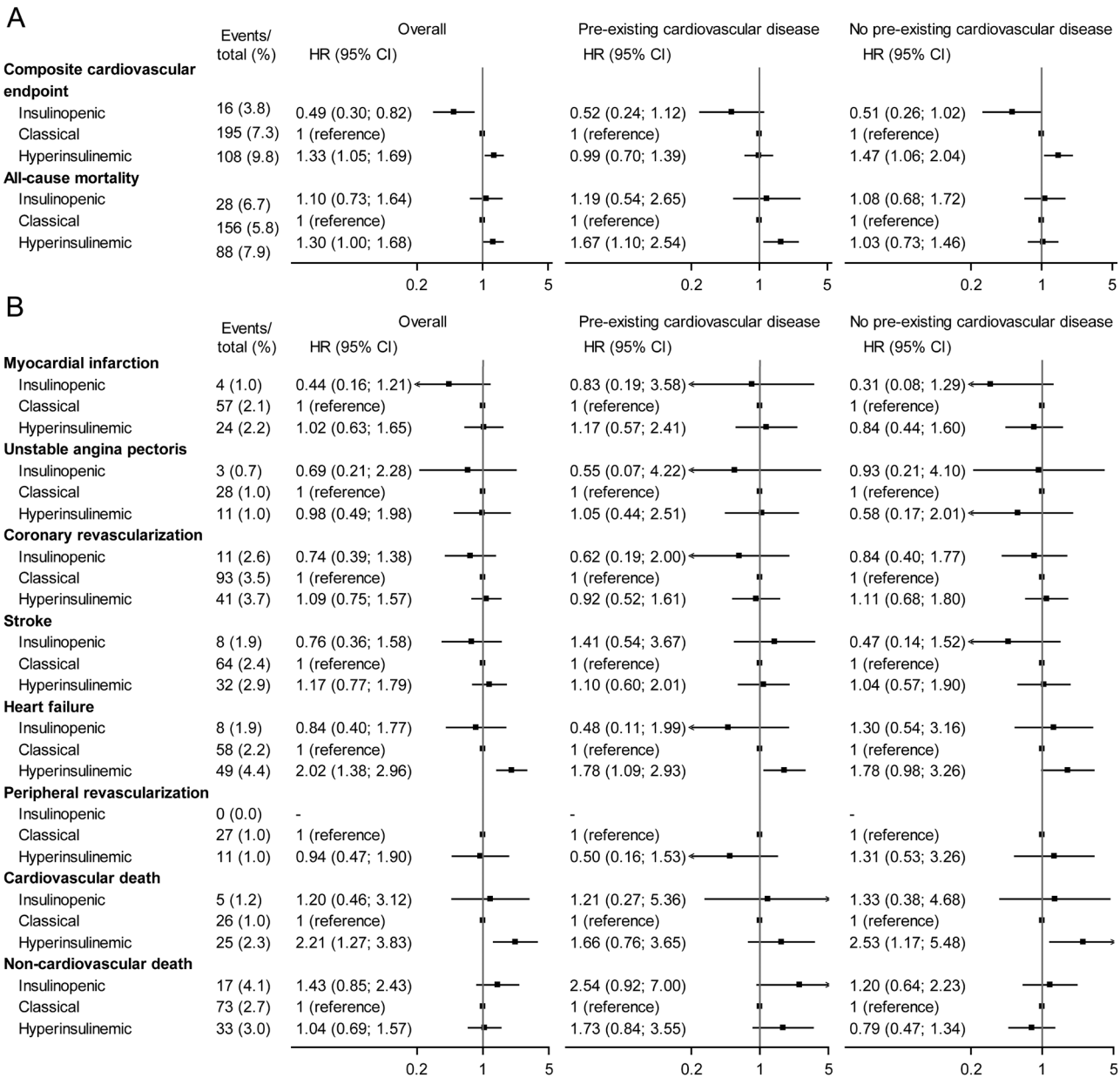

Figure 3

(A) Forest plot of hazard ratios for the composite cardiovascular endpoint and all-cause mortality. (B) Forest plot of hazard ratios for myocardial infarction, stroke, coronary revascularization, unstable angina pectoris, heart failure, peripheral revascularization, cardiovascular death, or non-cardiovascular death by phenotype. Age- and sex-adjusted hazard ratios are shown for the endpoints overall and stratified by pre-existing cardiovascular disease.

addition to age and sex in model 2, the association with the hyperinsulinaemic phenotype was weakened, from an age- and sex-adjusted aHR of 1.33 (95% CI: 1.05–1.69) to an aHR of 1.18 (95% CI: 0.93–1.51) with further weakening after adjustment for likely mediators in model 3 (aHR: 1.10; 95% CI: 0.82–1.47). Of the potential confounders, higher waist circumference, lower physical activity, and smoking moderated the risk association the most and importantly, adjustment for HbA_{1c} levels strengthened the association (Supplementary Table 9). However, heart failure and cardiovascular death retained a substantial association with the hyperinsulinaemic phenotype, even after adjustment for both potential confounders and likely mediators (Fig. 4B). For the insulinopenic phenotype, the almost neutral association with all-cause mortality increased after adjustment for potential confounders

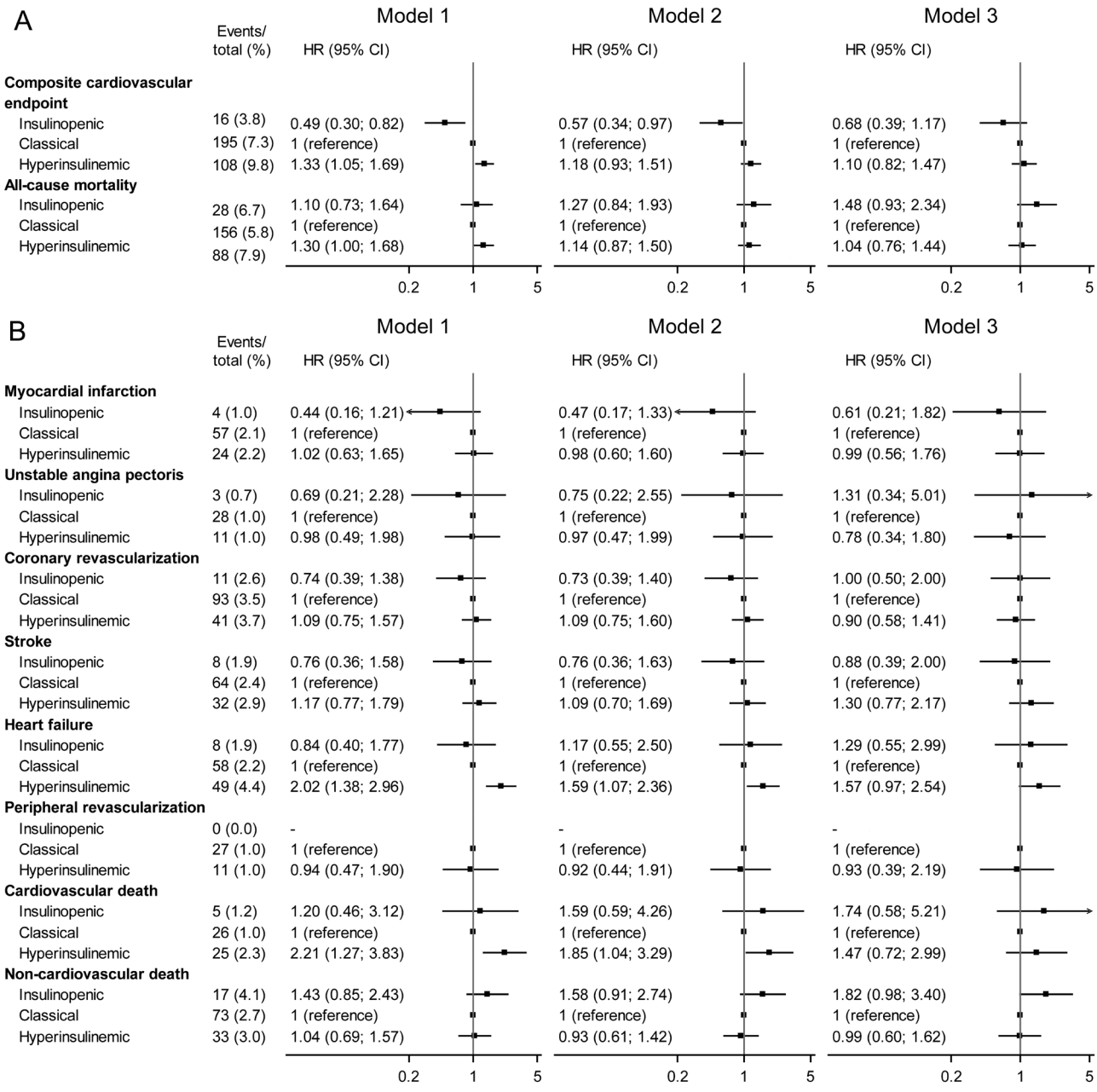

Figure 4

(A) Forest plot of hazard ratios for the composite cardiovascular endpoint and all-cause mortality. (B) Forest plot of hazard ratios for myocardial infarction, stroke, coronary revascularization, unstable angina pectoris, heart failure, peripheral revascularization, cardiovascular death, or non-cardiovascular death by phenotype. Adjusted hazard ratios are shown for the endpoints. Adjustment model 1: age and sex, model 2: age, sex, diabetes duration at index date, waist circumference, self-reported physical activity, family history of diabetes, smoking, and alcohol consumption, model 3: model 2 + systolic and diastolic blood pressure, FPG, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urine albumin-creatinine ratio, use of glucose-lowering, lipid-lowering, anti-hypertensive, or anti-thrombotic drugs, pre-existing kidney disease, and pre-existing cardiovascular disease.

(model 2- aHR: 1.27; 95% CI: 0.84–1.93), in particular, when adjusting for higher physical activity and lower waist circumference and even more when adjusting for likely mediators in model 3 (Fig. 4A and Supplementary Table 9). The increased all-cause mortality association with the hyperinsulinaemic phenotype was clearly attenuated after adjustment for potential confounders (model 2- aHR: 1.14; 95% CI: 0.86–1.50), with adjustment for obesity and physical inactivity reducing the association the most. Adjustment for likely mediators (model 3) reduced the estimate (Fig. 4A and Supplementary Table 9).

Stratification according to pre-existing cardiovascular disease

When associations were stratified according to pre-existing cardiovascular disease at enrollment, pre-existing cardiovascular disease status did not alter the robustly decreased risk estimates for the insulinopenic phenotype (with pre-existing cardiovascular disease, aHR: 0.52; 95% CI: 0.24–1.12; without pre-existing cardiovascular disease, aHR: 0.51; 95% CI: 0.26–1.02; Fig. 3A). Conversely, the increased risk of the composite cardiovascular endpoint associated with the hyperinsulinaemic phenotype was driven by individuals without pre-existing cardiovascular disease (aHR: 1.47; 95% CI: 1.06–2.04; Fig. 3A). In individuals who already had existing cardiovascular disease at baseline, the hyperinsulinaemic phenotype did not seem to confer any future increased cardiovascular risk (aHR: 0.99; 95% CI: 0.70–1.39; Fig. 3A). In contrast, for all-cause mortality, the increased risk with the hyperinsulinaemic phenotype was driven by individuals with pre-existing cardiovascular disease (aHR: 1.67; 95% CI: 1.10–2.54; Fig. 3A) and was not found in those without pre-existing cardiovascular disease (aHR: 1.03; 95% CI: 0.73–1.46; Fig. 3A); that is, the exact opposite of the findings for the cardiovascular endpoint. For heart failure, increased risk with the hyperinsulinaemic phenotype was seen in individuals both with and without pre-existing cardiovascular disease. This association was also observed for cardiovascular death, although the relative risk increase was most pronounced in individuals without pre-existing cardiovascular disease (Fig. 3B).

Sensitivity analyses

The characteristics of excluded individuals were comparable to those eligible to phenotyping (Supplementary Table 5). Restricting the analyses to individuals with a maximum of 1 year of confirmed duration of diabetes at the index date, to those without the use of glucocorticoids at the time of phenotype allocation, or to those without insulin use did not change the main associations materially (Supplementary Figs 5, 6, 7, 8 and 9).

When using a restricted cubic spline model, a gradual increase in the risk of the composite cardiovascular endpoint with lower insulin sensitivity regardless of pre-existing cardiovascular disease was observed (Supplementary Fig. 1). Beta-cell function showed a sigmoidal relationship with risk of the composite cardiovascular endpoint (Supplementary Fig. 2). All-cause mortality showed a U-shaped relationship with both insulin sensitivity and beta-cell function (Supplementary Figs 3 and 4).

Discussion

In this nationwide cohort study, we found that pathophysiological phenotyping of type 2 diabetes can identify individuals at high or low risk of cardiovascular events. The insulinopenic phenotype was associated with clearly lower cardiovascular risk, driven by atherosclerotic outcomes, compared with the classical type 2 diabetes phenotype. The hyperinsulinaemic phenotype was associated with higher cardiovascular risk, driven by a substantially increased risk of heart failure and cardiovascular death, whereas the hyperinsulinaemic phenotype also conferred a clearly higher mortality.

This simple phenotyping according to the basic aetiology of type 2 diabetes has not been investigated before and can be used directly in the clinic, as it is based on one fasting sample of plasma glucose and serum C-peptide. The associations with cardiovascular endpoints were not altered markedly after adjustment for readily observable clinical variables such as waist circumference, indicating that the pathophysiological phenotypes do provide information beyond these factors. Even with adjustment for likely mediators, the cardiovascular effect size associated with the phenotypes *per se* (direct effect) was still increased (albeit statistically imprecise) by a clinical important magnitude. The method may potentially improve the treatment and prognosis for the patients. It may protect patients with inherently low risk of cardiovascular disease against unnecessary treatment and may point to improved and more precise treatment of patients with hyperinsulinaemia, who we have shown to have a particularly high risk of heart failure and cardiovascular death.

HOMA2 aims to estimate beta-cell function and insulin sensitivity separately from each other; two measures that are otherwise entangled in fasting

insulin/C-peptide. However, the distribution of beta-cell function and insulin sensitivity clearly shows that a univariate analysis of either will still carry information on the other measure. The comparison of individuals with the insulinopenic phenotype against individuals with the classical phenotype is therefore a more accurate and unbiased description of the association between insulin sensitivity and cardiovascular events. Our results therefore qualify prior observational studies (22, 23), examining a potentially causal association between low insulin sensitivity and increased cardiovascular events, beyond beta-cell function, as illustrated in Fig. 1B. Similarly, the comparison of individuals with the hyperinsulinaemic phenotype against individuals with the classical phenotype is an unbiased description of the association of beta-cell function and atherosclerotic events, beyond insulin resistance. It has been proposed that hyperinsulinaemia independent of insulin resistance also drives atherosclerosis (12, 13, 14); however, our analysis for the first time brings human observational evidence to suggest that this proposed association is small or absent. Furthermore, our analysis suggests that high beta-cell function (hyperinsulinaemia), beyond low insulin sensitivity and other factors, directly increases the risk of heart failure and cardiovascular death. Prior studies on heart failure and the association with fasting insulin in individuals without diabetes (24, 25, 26) or insulin resistance in individuals with type 2 diabetes (27) have failed to separate the effect of beta-cell function and insulin resistance, making our results methodologically and clinically important and novel. Sodium retention in the kidneys is stimulated by insulin; this effect is preserved in people with low insulin sensitivity and may be a contributing underlying mechanism for our heart failure findings (28, 29, 30). Hypercoagulopathy could provide an explanation of the increased risk of cardiovascular death in the hyperinsulinaemic phenotype, as experimentally increased insulin levels induce a hypercoagulable state (31).

Our study has some limitations. First, enrollment into the DD2 – and thus blood sampling – at a median of 1.6 (IQR: 0.5–3.1) years after the onset of diabetes as well as treatment with insulin or glucocorticoids at the time of blood sampling could affect the phenotype allocation and the risk of cardiovascular events. However, sensitivity analyses restricted to individuals enrolled within 1 year of diagnosis or to those without insulin or glucocorticoid treatment at enrollment did not affect the results. Secondly, we did not have longitudinal measurements of insulin sensitivity and beta-cell function (23). As insulin sensitivity can change within short time (14), one measurement does not necessarily represent the integrated effect of insulin sensitivity and beta-cell function on the assessed risk during follow-up. Thirdly, some outcome misclassification may happen when using routine care data. However, we have complete and exact data on date of death, and the positive predictive values of the used cardiovascular diagnosis codes are high: 69–86% for stroke, 75–98% for myocardial infarction, and 81–100% for heart failure (32). Moreover, we expect any misclassification of outcomes to be non-differential, thus causing bias towards the null. Fourthly, although we had incomplete data for some variables in the most extensive adjustment model 3, we used multiple imputation as a valid approach to handle this (33, 34). We used waist circumference instead of BMI in our model, since waist circumference was both more completely measured and is a better predictor of cardiovascular disease than BMI (35). Fifthly, no official definition of insulin resistance exists and the third tertile (36, 37), fourth quartile (11, 38), or median (39) of insulin resistance in the background population have variably been used to define the condition. We chose the median as this enabled us to define three phenotypes formalizing WHO`s definition of type 2 diabetes (17). Sixthly, the cohort consisted of participants of Caucasian origin limiting generalizability. Seventhly, the cohort only covers 5–8% of individuals diagnosed with type 2 diabetes in Denmark in the period. However, the clinical profile of the DD2 cohort members is similar to average Danish type 2 diabetes patients diagnosed in routine clinical care (40). Eighthly, external validation of the phenotypes remains to be performed, including validation against other measures of insulin sensitivity and beta-cell function (41).

In conclusion, pathophysiological type 2 diabetes phenotypes, estimated by insulin sensitivity and beta-cell function and based on one simple fasting blood sample, identified individuals with high or low risks of future cardiovascular events and death. Despite the intensified, multifactorial treatment available in the recent decades, the risk of cardiovascular disease is still increased in individuals with type 2 diabetes (42, 43). The pathophysiology of the type 2 diabetes phenotypes may provide an individualized approach that enable targeted treatment of the pathophysiological defects, thereby closing this gap in cardiovascular disease risk in type 2 diabetes.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-22-0020.

Declaration of interest

J V S, D H C, K H, M H O, R W T, L B C, J S N, H B N, J E H, and T B O declare no personal duality of interest. J S N has received grants from the Novo Nordisk foundation to (and administered by) The Danish Centre for Strategic Research in Type 2 Diabetes study outside the submitted work. The Department of Clinical Epidemiology, Aarhus University Hospital receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. No other potential conflicts of interest relevant to this article were reported.

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Author contribution statement

H B N conceived the study. J V S, D H C, J E H, K H, M H O, R W T, T B O, and H B N designed the study. J S N was the principal manager of The Danish Center for Strategic Research in Type 2 Diabetes (DD2). L B C performed the statistical analysis. J V S prepared the first draft, and J V S, D H C, R W T, K H, and M H O revised the draft. All authors contributed to the interpretation of data and critically revised the content of the draft. R W T and H B N supervised the study. All authors gave final approval of the version to be published. J V S, D H C, L B C, and R W T are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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