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

Running title: T2D phenotypes and cardiovascular events

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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: Prospective cohort study.

Methods: We assessed estimates of insulin sensitivity and beta-cell function from the homeostasis model assessment-2 in 4,209 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: The 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% versus 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 hyperinsulinemic 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 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 individualised 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 hyperinsulinemic 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 hyperinsulinemic 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 hyperinsulinemia (7, 8) increases the risk of cardiovascular events, suggesting a causal relationship. This does not disentangle the coupling between hyperinsulinemia and insulin resistance, however (9, 10). Targeted treatment of insulin resistance with pioglitazone reduces risk of stroke in normoglycemic individuals (11), and insulin resistance and hyperinsulinemia may both independently cause atherosclerosis (12-14). 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.

Materials 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 until February 2015 (15). All persons with recently diagnosed type 2 diabetes in Denmark with diabetes debut after 2009 were eligible for enrolment 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 enrolment (a fasting sample in 80.9%), either at general practitioner 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. Data collected at DD2 enrolment 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 (eg, 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 1-4.

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Definition of type 2 diabetes phenotypes

Of the 5,988 participants, we excluded 1,447 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 enrolment were excluded (Fig. 1). Of the remaining 4,530 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 have been described in detail previously (4). Fasting serum C-peptide and plasma glucose levels measured at DD2 enrolment were used to estimate insulin sensitivity and beta-cell function by the homeostatic assessment model 2 (HOMA2) (18-20). 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 hyperinsulinemic 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 enrolment (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, enrolment 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 enrolment in the analyses terminated 31 December 2016, while 260 were censored in the analyses terminated 10 August 2018. We used Cox regression analysis to estimate adjusted hazard ratios (aHRs) of the endpoints comparing the insulinopenic and hyperinsulinemic 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,

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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 (FPG), 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 enrolment.

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.

Role of the funding source

None of the DD2 funding sources had a role in the study's design, conduct, or analysis, nor on the decision to submit the manuscript for publication.

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Results

Descriptive Data

Characteristics of individuals with the insulinopenic (n=417, 9.9%), classical (n=2,685, 63.8%), and hyperinsulinemic (n=1,107, 26.3%) type 2 diabetes phenotypes at enrolment 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 hyperinsulinemic 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 hyperinsulinemic 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 hyperinsulinemic 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 hyperinsulinemic 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 hyperinsulinemic 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-2J 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 hyperinsulinemic phenotype was associated with a substantially increased risk of cardiovascular death and heart failure (aHRs 2.21, 95% CI 1.27-3.83, and 2.02, 95% CI 1.38-2.96, respectively; Figures 2H, 2I and 3B). The hyperinsulinemic 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 hyperinsulinemic phenotype (Figures 2J and 3B).

Potential confounders and mediators

When we adjusted for additional potential confounders in addition to age and sex in model 2 (ie, physical activity, central obesity, and other lifestyle factors that 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; 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; Supplementary Table 9), such as those included in the metabolic syndrome. In contrast, after adjustment for potential confounders in addition to age and sex in model 2, the association with the hyperinsulinemic 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 hyperinsulinemic 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 (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

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3 (Fig. 4A; Supplementary Table 9). The increased all-cause mortality association with the hyperinsulinemic 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; Supplementary Table 9).

Stratification according to pre-existing cardiovascular disease

When associations were stratified according to pre-existing cardiovascular disease at enrolment, 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 hyperinsulinemic 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 hyperinsulinemic 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 hyperinsulinemic 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); i.e. the exact opposite of the findings for the cardiovascular endpoint. For heart failure, increased risk with the hyperinsulinemic 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 Figures 5-9).

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 Figures 3 and4).

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 hyperinsulinemic phenotype was associated with higher cardiovascular risk, driven by a substantially increased risk of heart failure and cardiovascular death, whereas the hyperinsulinemic phenotype also conferred a clearly higher mortality.

This simple phenotyping according to the basic etiology 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 hyperinsulinemia, 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

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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 hyperinsulinemic 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 hyperinsulinemia independent of insulin resistance also drives atherosclerosis (12-14), 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 (hyperinsulinemia), 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 (24-26) 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 (28-30). Hypercoagulopathy could provide an explanation of the increased risk of cardiovascular death in the hyperinsulinemic phenotype, as experimentally increased insulin levels induce a hypercoagulable state (31).

Our study has some limitations. First, enrolment 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 enrolment did not affect the results. Second, 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 represents the integrated effect of insulin sensitivity and beta-cell function on the assessed risk during follow-up. Third, 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. Fourth, 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). Fifth, 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). Sixth, the cohort consisted of participants of Caucasian origin limiting generalizability. Seventh, 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). Eighth, 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 individualised approach that enable targeted treatment of the pathophysiological defects, thereby closing this gap in cardiovascular disease risk in type 2 diabetes.

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Declaration of interest

JVS, DHC, KH, MHO, RWT, LBC, JSN, HBN, JEH, and TBO declare no personal duality of interest. J.S.N has received grants from the Novo Nordisk foundation to (and administered by) The Danish Center 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 Contributions

HBN conceived the study. JVS, DHC, JEH, KH, MHO, RWT, TBO, and HBN designed the study. JSN was the principal manager of The Danish Center for Strategic Research in Type 2 Diabetes (DD2). LBC performed the statistical analysis. JVS prepared the first draft, and JVS, DHC, RWT, KH, and MHO revised the draft. All authors contributed to the interpretation of data and critically revised the content of the draft. RWT and HBN supervised the study. All authors gave final approval of the version to be published. JVS, DHC, LBC and RWT 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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Legends

Figure 1. A) Flow diagram of the study population. DD2= The Danish Center 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 depicts the median of the insulin sensitivity and beta-cell function in a background population with normal glucose tolerance.

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-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.

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,

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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.

Table 1: Characteristics of the three type 2 diabetes phenotypes at enrolment. 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**	**Hyperinsulinemic phenotype**
n	417	2,685	1,107
Male sex, n (%)	242 (58.0%)	1,610 (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*= 4,204	92.0 (85.0-100.0)	105.0 (97.0-115.0)	112.0 (102.0-121.0)
Body mass index, kg/m^2, *n*= 1,942	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*= 2,269	6.6 (6.1-7.2)	6.7 (6.2-7.3)	6.4 (6.0-6.8)
LDL cholesterol, mmol/L, *n*= 2,186	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*= 2,083	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*= 2,098	7.6 (4.0-16.0)	10.0 (4.0-24.0)	10.0 (4.0-30.0)
Diastolic blood pressure, mmHg, *n*= 2,147	80.0 (72.0-85.0)	80.0 (75.0-85.0)	80.0 (72.0-85.0)
Systolic blood pressure, mmHg, *n*= 2,147	130.0 (125.0-137.0)	130.0 (124.0-140.0)	130.0 (120.0-140.0)
Smoking *n*= 3,866			
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%)	2,140 (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%)	1,892 (70.5%)	872 (78.8%)
Lipid-lowering drugs	268 (64.3%)	1,844 (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.

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A)

The first 5,988 consecutive individuals eligible in the DD2 study cohort enrolled by February 2015

→ 1,447 individuals without information on relevant variables:
253 without GADA
1,264 without data on fasting C-peptide
1,424 without data on fasting blood glucose
1,446 without data on fasting HOMA

11 individuals without residence in Denmark at least 1 year before enrolment

4,530 individuals with all required measurements for further phenotyping into WHO-defined type 2 diabetes or other specific forms of diabetes

→ 306 individuals with other specific forms of diabetes.

(n=4 for rare subtypes, n=127 for LADA, n=35 for secondary diabetes, n=140 for glucocorticoid-induced-diabetes)

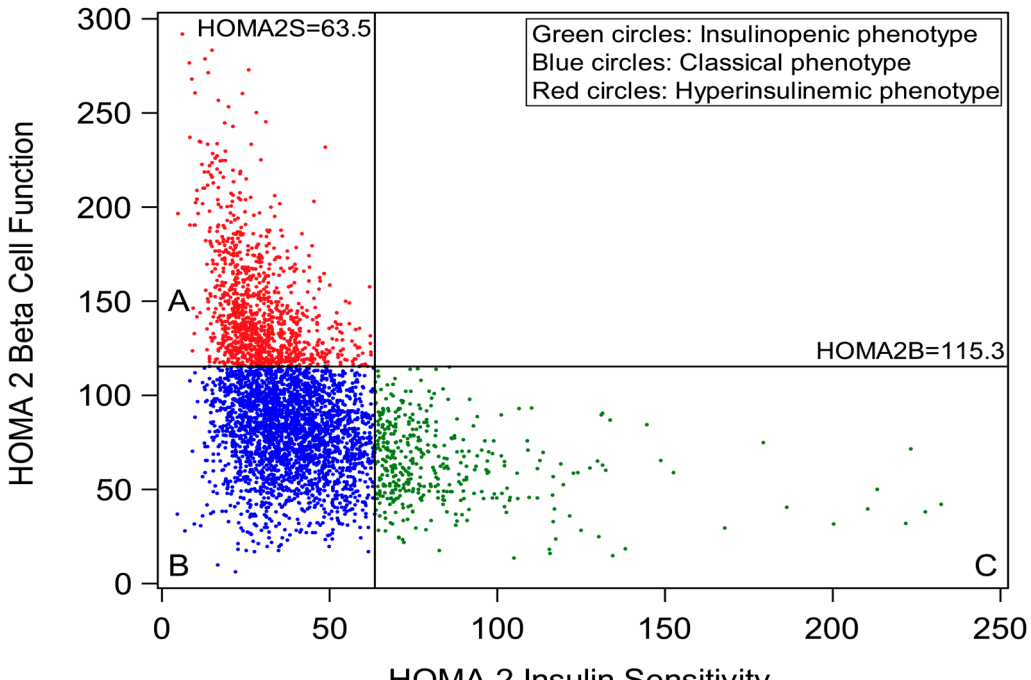
4,224 individuals with WHO-defined type 2 diabetes

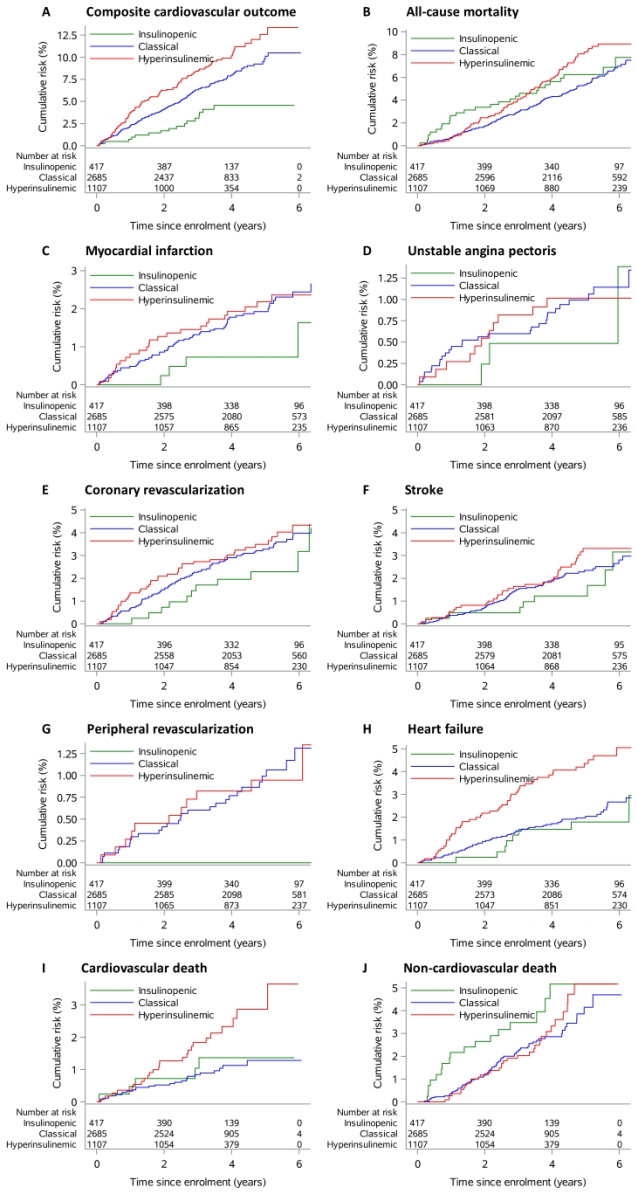
→ 15 individuals with high beta-cell function and high insulin sensitivity not considered for characterisation

4,209 indivduals with WHO-defined type 2 diabetes available for further subphenotyping

- Insulinopenic phenotype, n= 417
  -*High* insulin sensitivity
  -*Low* beta-cell function
- Classical phenotype, n= 2,685
  -*Low* insulin sensitivity
  -*Low* beta-cell function
- Hyperinsulinemic phenotype, n= 1,107
  -*Low* insulin sensitivity
  -*High* beta-cell function

B)





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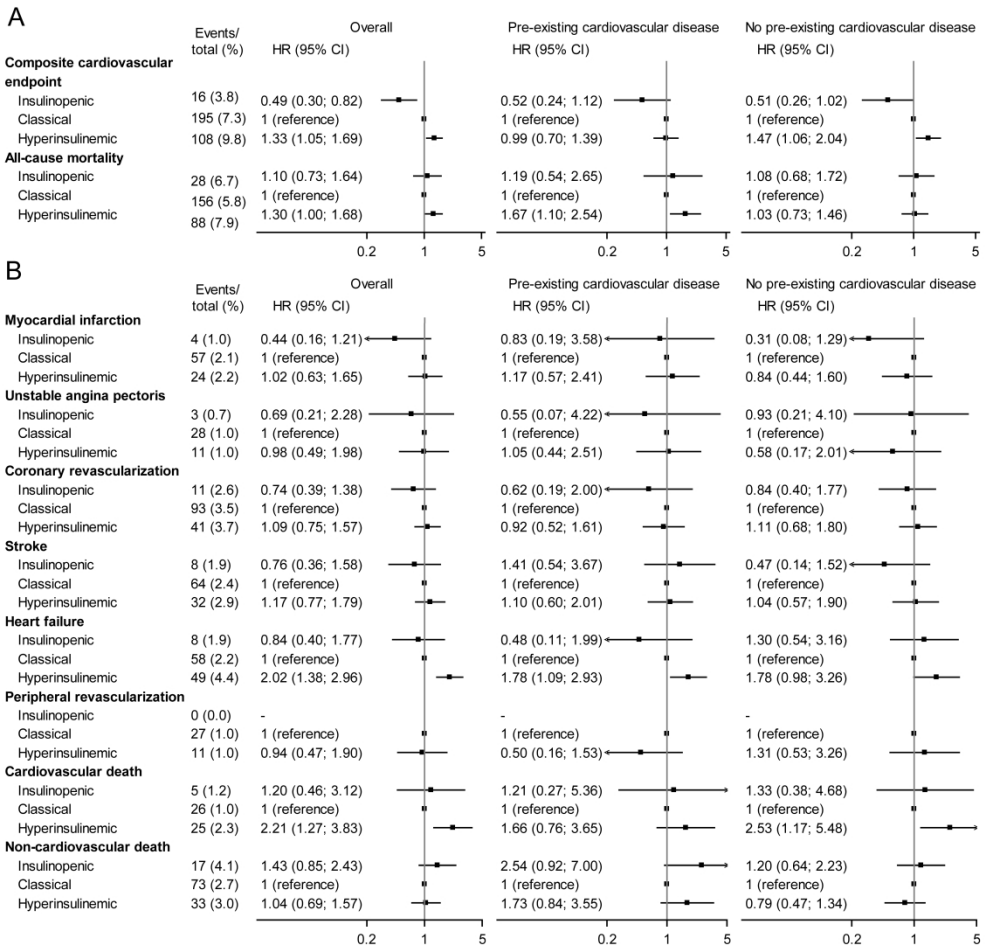

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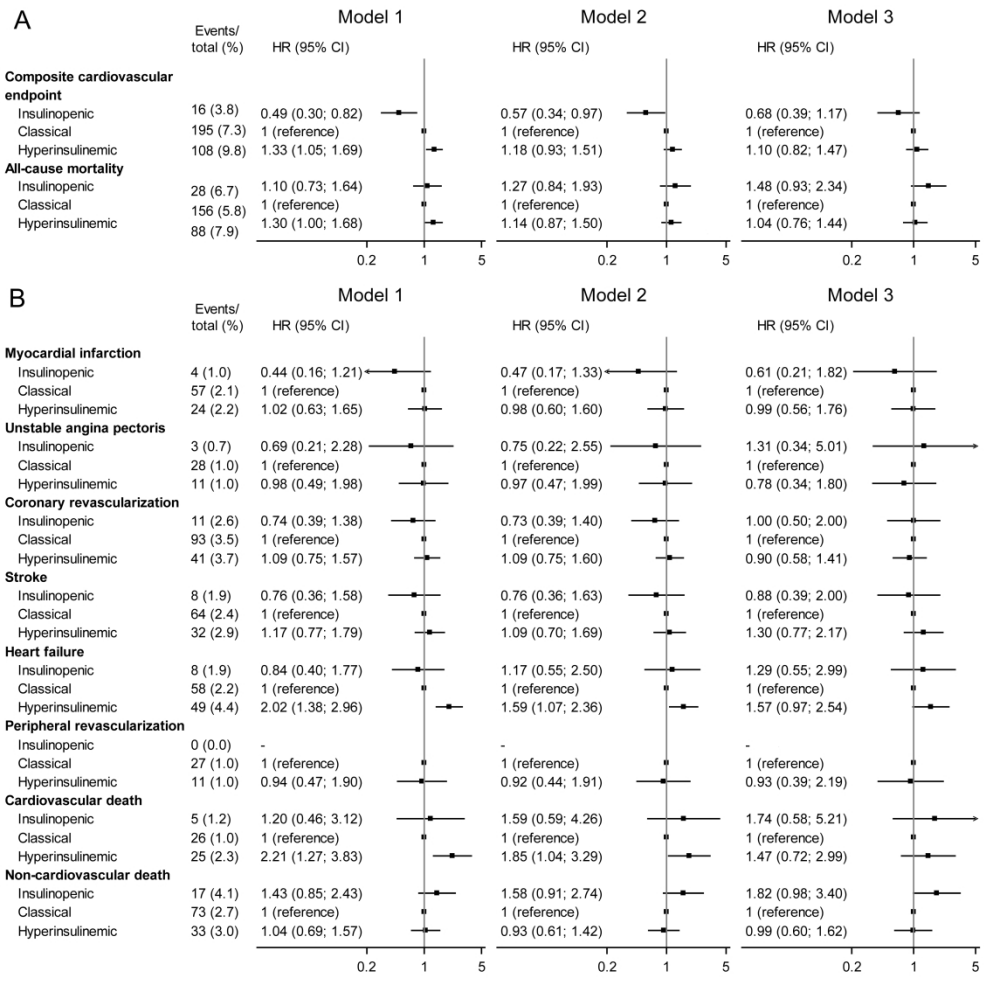

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133x133mm (1200 x 1200 DPI)

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Supplementary material

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

Contents

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Supplementary methods

The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort

Study participants and recruitment have been summarized thoroughly by Christensen et al (1): "Since 1 January 2009, all patients with newly or recently diagnosed T2D in Denmark have been eligible to participate in the DD2 cohort. The first patient was enrolled in November 2010, and the cohort now consists of 7011 patients. The DD2 project is ongoing, with continuous enrolment. The process of enrolling in the DD2 cohort has been described in detail elsewhere: (1) clinical providers (usually either the patient's GP or a hospital physician/ nurse) identify patients newly diagnosed with T2D in routine clinical practice. (2) Those patients are informed by the clinical provider about the existence of the DD2 project. (3) Patients interested in participating receive detailed oral and written information and are asked to sign a written informed consent document for enrolment. (4) Patient clinical information is then collected: GPs or hospital physicians/nurses complete an online questionnaire, including items requiring a physical examination. (5) Urine and fasting blood samples are collected for storage in a biobank.

Approximately 80% of patients with T2D in Denmark receive care at GPs' offices and the remainder at hospital specialist outpatient clinics. Enrolment into the DD2 cohort takes place in both settings (figure 1). From 2010 to 2012, most patients were enrolled at hospital outpatient clinics rather than at GP offices (1559 vs 739 patients). From 2013 on, the number of patients recruited by GPs increased rapidly, reaching 3688 in February 2016. As of that month, the corresponding number of patients recruited by outpatient specialist clinics was 3323 (table 1).

During the entire DD2 enrolment period, all diagnosing of T2D in routine clinical practice has been made according to WHO criteria, before 2012 primarily based on OGTT and after 2012 primarily based on glycosylated haemoglobin A (HbA1c) >48 mmol/mol (6.5%). No further diagnostic criteria for enrolment have been applied in the DD2 project. The DD2 project explicitly aims to comprehensively study T2D as diagnosed in everyday clinical care, as one of the project aims is to document pitfalls in initial T2D diagnosing, including investigation of subtypes and subphenotypes in the cohort, occurrence of secondary diabetes, autoimmune diabetes and so on.

While the DD2 cohort from the beginning aimed to focus on newly diagnosed T2D patients, in clinical practice, the referral to DD2 may not happen at first diabetes notice when other clinical activity may be more pertinent. Individuals who have had prevalent T2D for some time after 2009 are also accepted for participation. While we do not have complete data on exact date of diabetes diagnosis for all individuals, average time from first recorded glucose-lowering drug initiation to enrolment date in the DD2 cohort is 1–1.5 years.

The exact proportion of all patients with incident T2D in Denmark that is enrolled into the DD2 cohort is unknown. With an average enrolment in the order of 1000–1200 DD2 patients per year, the project enrols an estimated 5% of newly diagnosed patients with T2D nationwide.

The number of enrolled patients and recruitment sites vary across the five Danish healthcare regions. Currently, the largest proportion (35%) of the cohort patients has been recruited from the region of Southern Denmark, which comprises 21% of Denmark's population, followed by the Central Denmark Region (with 24% of cohort patients) and the Capital Region (with 19% of cohort patients), comprising 22% and 31% of Denmark's population, respectively.

Loss of patients from the DD2 cohort can occur due to emigration and death. These events are identified by linkage to the Danish Civil Registration System (CRS), which has recorded vital status for the entire Danish population since 1968, with daily electronic updates. Enrolled patients have the right to withdraw from the DD2 cohort, but only four individuals have done so thus far."

All patients in DD2 were by definition clinically perceived as having type 2 diabetes by their clinician. Patient recruitment was done at all hospital outpatient clinics in Denmark and at 462 out of 1853 general practitioner clinics throughout the country. Directly collected DD2 variables include waist–hip ratio, recalled body weight at age 20 years,

maximum lifetime body weight, alcohol consumption, family history of diabetes, resting heart rate, physical activity level and (added in 2015) self-reported date of first T2D diagnosis.

Imputation procedures

Missing values were sampled from the posterior predictive distribution of the covariate values using an imputation model that included all covariates from the survival analysis, the outcomes and the Nelson-Aalen estimator of the cumulative baseline hazard, as well as other variables. We used multiple imputation by chained equations employing imputation models for each missing variable, choosing model according to the type of variable being imputed. Fifty complete data sets were imputed using a Bayesian approach with a Markov chain Monte Carlo algorithm. Covariate variables from the survival analysis, outcomes, and the Nelson-Aalen estimator of the cumulative baseline hazard, were included in the imputation model to ensure maximum recovery of information about the association of interest (2, 3). Furthermore, the imputation model also included the variables: inclusion at general practitioner or at outpatient clinic, residence at DD2 enrolment, year of inclusion, weight, homeostatic assessment model 2 beta (HOMA2B), homeostatic assessment model 2 insulin sensitivity (HOMA2S), and glutamate decarboxylase antibodies (GADA). Continuous variables (fasting blood glucose (FPG), systolic and diastolic blood pressure, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, Hemoglobin A1c (HbA1c), and albumin/creatinine ratio) with clear non-normal (skewed) distributions were zero-skewness log-transformed, i.e., transformed to approximate normality before imputation. Then the imputed values were transformed back to the original scale before analysis. The imputation models were validated by comparing the mean, median, and inter-quartile range of the first and last imputed dataset with the complete dataset.

Each variable in the data set was characterized as being 'imputed' or 'regular'. Imputed variables contain missing values, and those values were imputed. Regular variables usually do not contain missing values, or if they do, the missing values were not imputed.

The following variables were characterized as 'imputed': HbA1c, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urine albumin/creatinine ratio and smoking.

The following variables were characterized as 'regular': all-cause mortality, cardiovascular events, age, sex, diabetes duration, waist circumference, anti-diabetic treatment, antihypertensive treatment, use of lipid-lowering drugs, anti-thrombotic treatment, self-reported physical activity, family history of diabetes, alcohol consumption, and pre-existing kidney disease. In a sensitivity analysis, we performed a complete case analysis restricted to only individuals with complete data on all variables included in model 2 and 3.

Additional statistical analyses

We performed separate cox regression analysis for each variable, adjusting for age, sex and the variable under investigation, to further explore the impact on the risk estimates of each variable in model 2 and 3.

The Cox proportional hazards assumption was tested by plotting the natural log of the cumulative hazard function against the natural log of time and was checked for parallelism. The Schoenfeld residuals for each continuous covariate were plotted against the natural log of time for each phenotype and were checked for non-random patterns.

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Data description

Supplementary Table 1: Data sources

Source	Description
DD2 biobank (4)	DD2 is a prospective, nationwide population-based cohort of newly diagnosed type 2 diabetes individuals, with collection of matching interview data and biological samples for a biobank at baseline. Enrolment started in November 2010 and is still ongoing.
DD2 questionnaire (5)	Ditto
The Danish Adult Diabetes Registry (6)	The database was established to assess quality in diabetes care on a national level in 2004. It only covers a subset of the diabetes population.
The Danish National Patient Registry (7)	Covers all inpatient (somatic) hospital contacts since 1977 and from 1995 all inpatient and outpatient hospital contacts in Denmark. Diagnostic information is coded according to the International Classification of Diseases, Tenth Revision (ICD-10) from 1994 onwards. We retrieved information from 1994 and onwards.
The Danish National Prescription Registry (8)	Covers all redeemed prescriptions at Danish pharmacies since 1995.
Civil Registration System (9)	All citizens of Denmark are registered in this system by a unique Civil Personal Register number linked to registrations of birth, address, marital status, kinship and migration among others. The Civil Personal Register number is used as linkage to other databases.
The Danish Registry of Causes of Death (10)	Death and cause of death among citizens in Denmark are recorded in this database since 1970. Both the immediately cause and the underlying cause of death are registered. Causes of death were coded according to the International Classification of Diseases, Tenth Revision (ICD-10) from 1994 onwards.

Supplementary Table 2: Endpoint definitions

Endpoint	Definition	Source
All-cause mortality	Death	The Civil Registration System
Composite cardiovascular endpoint	First occurrence of myocardial infarction, stroke, unstable angina, coronary revascularization, heart failure, peripheral revascularization or cardiovascular death. See definitions below	
Myocardial infarction	DI21	Primary or secondary inpatient discard ICD-10 diagnoses from the Danish National Patient Registry (date defined by d_inddto)
Unstable angina pectoris	DI200	Primary or secondary inpatient discard ICD-10 diagnoses from the Danish National Patient Registry (date defined by d_inddto)
Coronary revascularization	KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH20	ICD-10 procedure codes (regardless of hospitalization) from the Danish National Patient Registry (date defined by d_odto)
Stroke	DI61, DI63, DI64	Primary or secondary inpatient discard ICD-10 diagnoses from the Danish National Patient Registry (date defined by d_inddto)
Heart failure	DI50, DI110, DI130, DI132	Primary inpatient discarge ICD-10 diagnoses from the Danish National Patient Registry (date defined by d_inddto)
Peripheral revascularization (lower limb including infrarenale aorta and a.iliacae)	Thrombectomy or embolectomy: KPDE, KPEE, KPFE Thromboendarterectomy: KPDF, KPEF, KPFF, KPDU74. KPEU74, KPFU74 bypass-operations: KPDH, KPEH, KPFH, KPGH20+21+22+23+30+31+40+99 Angioplasty: KPDN, KPEN, KPFN KPDU82, KPEU82, KPFU82 Percutaneous angioplasty: KPDP, KPEP, KPFP, KPDU83, KPEU83, KPFU83 Unspecified: KPDW, KPEW, KPFW	ICD-10 procedure codes (regardless of hospitalization) from the Danish National Patient Registry (date defined by d_odto)
Cardiovascular death	DI00-DI99	Death was obtained from the Civil Registration System. The cause of death (either immediate or underlying causes) was obtained from the Danish Registry of Causes of Death.

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Supplementary Table 3: Phenotype definitions

Phenotype	Definition	Codes
Rare subtypes	One or more of the following: Cushing's disease, acromegaly, pheochromocytoma, glucagonoma, somatostatinoma, Down's syndrome, Friedreich's ataxia, Huntington's chorea, Klinefelter syndrome, Lawrence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome, or Turner syndrome	From the Danish National Patient Registry: DE24, DE220, DD350A, DD137B, DE168C, DQ90, DG111C, DG10, DQ980-DQ985, DQ878B, DG711A, DQ871E, DE800-DE802 or DQ96
Type 1 diabetes	GAD antibody titer≥20IU/ml, age< 30 years and fasting C-peptide<300 pmol/l (No patients fulfilled this criteria)	
Latent diabetes of the adult (LADA)	GAD antibody titer≥20IU/ml and not type 1 diabetes We chose to categorize all GADA positive patients as LADA, as the clinical diagnosis of type 2 diabetes would most likely characterize them as latent and not as type 1 diabetes.	
Secondary diabetes	History of pancreatitis, haemochromatosis, cystic fibrosis or pancreas resection prior to diabetes debut	From the Danish National Patient Registry: DK850, DK860-DK861, DE831A, DE84 or procedure code KJLC
Glucocorticoid induced diabetes	Prescription on oral glucocorticoids within 3 month of diabetes debut	ATC codes: H02AB
Classical phenotype	HOMA2-B<115.3% and HOMA2-S<63.5%	
Insulinopenic phenotype	HOMA2-B<115.3% and HOMA2-S≥63.5%	
Hyperinsulinemic phenotype	HOMA2-B≥115.3% and HOMA2-S<63.5%	
Non-diabetes phenotype	HOMA2-B≥115.3% and HOMA2-S≥63.5%	

HOMA2-B=homeostatic assessment model 2 beta. HOMA2-S=homeostatic assessment model 2 insulin sensitivity.

Supplementary Table 4: Variable definitions

Variable	Source	Remarks	
GADA	DD2 biobank	Analysed with the AESKULISA GAD65 kit (AESKU Diagnostics, Wendelsheim, Germany).	Continuous variable
Fasting serum C-peptide	DD2 biobank	Analysed with the Roche C-Peptide assay (Roche Diagnostics, Mannheim, Germany)	Continuous variable
Fasting plasma glucose	DD2 biobank	analysed using an enzymatic hexokinase method (Glucoquant Glucose/HK, Roche Diagnostics, Mannheim, Germany).	Continuous variable
Site of inclusion	DD2 registration form	The variable: ”MemberNavn-Amb”	Categorical variable
Fasting status	DD2 biobank and DD2 registration form		Categorical variable (Yes, No, Unknown)
HOMA2-B	Calculated by the HOMA2 calculator using fasting C-peptide and fasting plasma glucose	https://www.dtu.ox.ac.uk/homacalculator/download.php	Continuous variable
HOMA2-S	Calculated by the HOMA2 calculator using fasting C-peptide and fasting plasma glucose	https://www.dtu.ox.ac.uk/homacalculator/download.php	Continuous variable
Waist circumference	DD2 clinical examination		Continuous variable
Weight	DD2 clinical examination and Danish Adult Diabetes registry	Weight was obtained from the DD2 clinical examination if present. Otherwise the weight from Registration in The Danish Adult Diabetes registry closest to and within 1 year prior to the DD2 enrolment date was used.	Continuous variable
Height	DD2 clinical examination and Danish Adult Diabetes registry	We used available heights in the following hierarchical order: height obtained at DD2 enrolment, height obtained at Registration in The Danish Adult Diabetes registry enrolment, and questionnaire data (self-reported) obtained in 2016.	Continuous variable
Diabetes debut	DD2 interview, The Danish National Prescription Registry, The Danish National	The diabetes defining events were (whichever came first): 1) Diabetes debut obtained from the DD2 interview. If only a year was registered the debut was set to the first day of the 7th month of that year. 2) first prescription of glucose-lowering drugs, 3) first diabetes-related diagnosis in the Danish National Patient Registry, 4) Registration in The Danish Adult Diabetes registry, 5) DD2 enrolment	Continuous variable

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	Patient Registry, Danish Adult Diabetes registry		
Diabetes duration	DD2 interview, The, Danish National Prescription Registry, The Danish National Patient Registry, Danish Adult Diabetes registry	Time from *first* diabetes defining event to DD2 enrolment. The diabetes defining events were: 1) Diabetes debut obtained from the DD2 interview. If only a year was registered the debut was set to the first day of the 7th month of that year. 2) first prescription of glucose-lowering drugs, 3) first diabetes-related diagnosis in the Danish National Patient Registry, 4) Registration in The Danish Adult Diabetes registry, 5) DD2 enrolment	Continuous variable
Alcohol consumption	DD2 interview	>21 or 14 standard drinks (12 g alcohol) per week for men and women, respectively	Categorical variable (Yes/No)
Physical activity	DD2 interview	Physical activity was defined as "number of days per week with a minimum of 30 minutes of physical activity."	Categorical variable (0, 1–2, ≥3 days/week)
Family history of diabetes	DD2 interview	Number of relatives with a family history of diabetes	Categorical variable (0, 1–2, ≥3 relatives)
Smoking status	The Danish Adult Diabetes registry, questionnaire data (self-reported) obtained in 2016.	The date of smoking registration closest to DD2 enrolment was used. If smoking was measured exactly the same number of days before and after the DD2 enrolment date, we used the measure prior to DD2 enrolment.	Categorical variable: never, former, current (daily + occasionally)
Blood pressure	The Danish Adult Diabetes registry	As a covariate in Cox regression analysis the blood pressure closest to and within 1 year prior to the DD2 enrolment was used.	Continuous variable
Anti-hypertensive medication	The Danish National Prescription Registry	Number of redeemed drug classes 6 month prior to the index date. Classes and ATC codes: **ACE inhibitors or angiotensin II receptor antagonists:** C09A, C09B, C09C, C09D, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15, C10BX10 **Calcium channel antagonists:** C08, C09BB. C09DB, C09DX01, C09DX03, C09XA53, C09XA54, C07FB, C09BX01, C09BX03, C10BX07, C10BX09, C10BX11, C10BX14 **Low-ceiling diuretics:** C03A, C03B, C03EA, C07D, C09BA, C09DA, C09XA52, C09XA54, C08G, C07B, C09DX01, C09DX03, C09BX03	Categorical variable (0, 1–2, ≥3 drugclasses) or for rapporting as a (yes/no variable)

		Potassium-sparing diuretics: C03D, C03E **Beta-blockers:** C07 **Alpha-blockers:** C02CA04, C04CA03 **Central adrenerg inhibition:** C02AC05, C02AB **Renin-inhibitors:** C09XA, C09DX02	
Lipid-lowering medication	The Danish National Prescription Registry	Redemption of a drug prescription 6 month prior to the index date. ATC codes: C10	Categorical variable: Yes/No
Statins	The Danish National Prescription Registry	Redemption of a drug prescription 6 month prior to the index date. ATC codes: C10AA, C10BA, C10BX	Categorical variable: Yes/No
Glucose-lowering medication	The Danish National Prescription Registry	Redeemed glucose-lowering medication (GLM) 6 month prior to the index date defined as 3 separate variables: Variable 1: Insulin use Yes/No (A10) Variable 2: GLP1-analogue or SGLT2 inhibitor use Yes/No (A10) Variable 3: other glucose-lowering (metformin, **DPP-4 inhibitors, SU and Meglitinides, Thiazolidinediones and Alfa-glucosidase inhibitors)** yes/No (A10) Classes and ATC codes: **Metformin:** A10BA, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22 **DPP-4 inhibitors:** A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD19, A10BD21, A10BD22 **GLP-1 analogues:** A10BX04, A10BX07, A10BX10, A10BX13, A10BX14, A10BJ, A10AE54, A10AE56 **SGLT2-inhibitors:** A10BX09, A10BX11, A10BX12, A10BD15, A10BD16, ADBD19, A10BD20, ADBD21, A10BK, A10BD23, A10BD24 **SU and meglitinides:** A10BB, A10BD04, A10BD02, A10BD06, A10BD01, A10BC01. A10BX02, A10BX03, A10BX08, A10BD14 **Insulin:** A10A **Thiazolidinediones:** A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12 **Alfa-glucosidase inhibitors:** A10BF, A10BD17	categorical variables

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Anti-thrombotic medication	The Danish National Prescription Registry	Redemption of a drug prescription during the year prior to the index date. ATC codes: B01AC04, B01AC06, B01AC07, B01AC22, B01AC24, B01AC30, N02BA01	Categorical variable: Yes/No
Glucocorticoid treatment		Prescription on oral glucocorticoids within 3 month of enrolment in DD2. ATC codes: H02AB	Categorical variable: Yes/No
HbA1c	The Danish Adult Diabetes registry	As a covariate in Cox regression analysis the HbA1c closest to and within 1 year prior to the DD2 enrolment was used.	Continuous variable
Low-density lipoprotein cholesterol	The Danish Adult Diabetes registry	As a covariate in Cox regression analysis the LDL-C closest to and within 1 year prior to the DD2 enrolment was used.	Continuous variable
High-density lipoprotein cholesterol	The Danish Adult Diabetes registry	As a covariate in Cox regression analysis the HDL-C closest to and within 1 year prior to the DD2 enrolment was used.	Continuous variable
Triglycerides	The Danish Adult Diabetes registry	As a covariate in Cox regression analysis the triglycerides closest to and within 1 year prior to the DD2 enrolment was used.	Continuous variable
Urine albumin-creatinine ratio	The Danish Adult Diabetes registry	As a covariate in Cox regression analysis urine albumin-creatinine ratio closest to and within 1 year prior to the DD2 enrolment was used.	Continuous variable
Any cardiovascular complication prior to index date	The Danish National Patient Registry	Any registration of primary or secondary inpatient diagnoses or operation codes (regardless of hospitalization) prior to index date of the following: DI21, DI23, DI24, DT822A (ischemic heart disease); DT823 (acute ischemic heart disease with/without complications); DI20 (angina pectoris); DI25 (chronic ischemic heart disease); KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF (coronary bypass or percutaneous coronary intervention); DI500, DI501, DI502, DI503, DI508, DI509, DI110, DI130, DI132, DI420, DI426, DI427, DI428, DI429 (heart failure); DI61 (cerebral bleeding); DI63, DI64, DI65, DI66 (cerebrovascular infarct); DG45 (transient cerebrovascular disease); DI672, DI678, DI679 (unspecified cerebrovascular disease); DI691, DI693, DI694, DI698 (previous cerebrovascular disease); KAAL10, KAAL11 (cerebral thrombolysis or thromboendarterectomy) DE105, DE115, DE125, DE135, DE145 (diabetes with peripheral vascular complications); DI700, DI701, DI702, DI708, DI709, DI739, DI74, DN280, DK550, DK551, DH340, DH341, DH342 (peripheral/abdominal vascular disease); KNBQ, KNCQ, KNDQ, KNEQ, KNFQ, KNGQ, KNHQ, KPAE, KPAF, KPAH, KPAN, KPAP, KPAQ, KPAW99, KPAU74, KPBE, KPBF, KPBH, KPBN, KPBP, KPBQ, KPBW, KPGH10, KPCE, KPCF, KPCH, KPCN, KPCP, KPCQ, KPCW99, KPCW20, KPCU74, KPCU82, KPCU83, KPCU84, KPGE, KPGF, KPGH, KPGN, KPGP, KPGQ, KPGW99, KPGW20, KPEE, KPEF, KPEH, KPEN, KPEP, KPEQ, KPEW, KPFE, KPFH, KPFN, KPFP, KPFQ, KPFW, KPGH20, KPGH21, KPGH22, KPGH23, KPGH30,	Categorical variable: Yes/No

		KPGH31, KPGH40, KPGH99, KPDU74, KPDU82, KPDU83, KPDU84, KPEU74, KPEU82, KPEU83, KPEU84, KPFU74, KPFU82, KPFU83, KPFU84, KPGU74, KPGU83, KPGU84, KPGU99 (vascular surgery)	
Myocardial infarction prior to index date	The Danish National Patient Registry	Any primary or secondary inpatient diagnoses: DI21	Categorical variable: Yes/No
Stroke prior to index date	The Danish National Patient Registry	Any primary or secondary inpatient diagnoses: DI61, DI63, DI64	Categorical variable: Yes/No
Heart failure prior to index date	The Danish National Patient Registry	Any primary or secondary inpatient diagnoses: DI50, DI110, DI130, DI132	Categorical variable: Yes/No
Chronic renal disease prior to index date	The Danish National Patient Registry	Any primary or secondary inpatient or outpatient diagnoses: DN18, DE102, DE112, DE132, DE142	Categorical variable: Yes/No
cancer prior to index date	The Danish National Patient Registry	DC00-DC99 excluding DC44	Categorical variable: Yes/No
COPD prior to index date	The Danish National Patient Registry	DJ40-48, DJ60-68, DJ701, DJ703, DJ961, DJ982, DJ983	Categorical variable: Yes/No
Migration status	Civil Registration System		Categorical variable: Yes/No
Age	Civil Registration System		Continuous variable
Sex	Civil Registration System		Continuous variable
Municipality at inclusion	Civil Registration System		Categorical variable

COPD=Chronic obstructive pulmonary disease. CVD=cardiovascular disease. DDP4=Dipeptidyl peptidase 4. GLP-1=glucagon-like protein 1. GADA=glutamate decarboxylase antibody. HOMA2B=homeostatic assessment model 2 beta. HOMA2S=homeostatic assessment model 2 insulin sensitivity. SGLT2=sodium glucose transporter 2. SU=sulfonylurea.

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Supplementary Figures and Tables

Supplementary Table 5. Characteristics of individuals excluded from analysis and individuals eligible for phenotyping

	Excluded individuals	Individuals eligible for phenotyping
Total	1458	4530
Male sex, n (%)	862 (59.1)	2625 (57.9)
Age, years	61.4 (52.3; 67.7)	62.4 (53.8; 69.1)
Diabetes duration, years	0.9 (0.2; 2.9)	1.6 (0.5; 3.1)
Waist circumference, cm, n= 5981	106.0 (98.0; 117.0)	106.0 (97.0; 116.0)
Body mass index, kg/m2, n= 2567	30.9 (27.6; 34.5)	30.4 (26.8; 34.5)
Diastolic blood pressure, mmHg, , n= 2988	80.0 (75.0; 89.0)	80.0 (75.0; 85.0)
Systolic blood pressure, mmHg, n= 2988	132.0 (125.0; 144.0)	130.0 (124.0; 140.0)
Smoking, n (%), n= 5495		
Never	569 (42.5)	1898 (45.7)
Former	501 (37.4)	1468 (35.3)
Current	268 (20.0)	791 (19.0)
Excess alcohol intake, n (%)	101 (6.9)	303 (6.7)
Family history of diabetes, number of relatives, n (%)		
0	704 (48.3)	2144 (47.3)
1-2	648 (44.4)	2055 (45.4)
≥ 3	106 (7.3)	331 (7.3)
Self-reported physical activity, days/week, n (%)		
0	247 (16.9)	748 (16.5)
1-2	275 (18.9)	900 (19.9)
≥ 3	936 (64.2)	2882 (63.6)
Hemoglobin A1c, %, n= 3105	6.7 (6.3; 7.5)	6.6 (6.1; 7.2)
Low-density lipoprotein cholesterol, mmol/L, n= 2976	2.2 (1.7; 2.9)	2.2 (1.7; 2.9)
High-density lipoprotein cholesterol, mmol/L, n= 1440	1.2 (1.0; 1.4)	1.2 (1.0; 1.4)
Total cholesterol, mmol/L, n= 1440	4.5 (3.8; 5.2)	4.4 (3.7; 5.1)
Triglycerides, mmol/L, n= 2851	1.7 (1.2; 2.5)	1.7 (1.2; 2.4)
Urine Albumin-creatinine ratio, mg/g, n= 2890	9.0 (4.0; 25.0)	9.0 (4.0; 25.0)
Prior cardiovascular disease, n (%)	314 (21.5)	857 (18.9)
Prior acute myocardial infarction, n (%)	100 (6.9)	294 (6.5)
Prior stroke, n (%)	78 (5.3)	184 (4.1)
Prior heart failure, n (%)	61 (4.2)	129 (2.8)
Prior COPD, n (%)	129 (8.8)	395 (8.7)
Prior cancer, n (%)	104 (7.1)	350 (7.7)
Chronic renal disease, n (%)	41 (2.8)	100 (2.2)
Glucose-lowering drug-naive	270 (18.5)	769 (17.0)
Metformin, n (%)	1120 (76.8)	3589 (79.2)
DPP-4 inhibitors, n (%)	126 (8.6)	354 (7.8)
GLP-1 analogues, n (%)	71 (4.9)	228 (5.0)

SGLT2-inhibitors, n (%)	12 (0.8)	18 (0.4)
SU and meglitinides, n (%)	91 (6.2)	280 (6.2)
Insulin, n (%)	115 (7.9)	264 (5.8)
Anti-hypertensive drugs, n (%)	1019 (69.9)	3215 (71.0)
Lipid-lowering drugs, n (%)	963 (66.0)	3101 (68.5)
Anti-thrombotic drugs, n (%)	443 (30.4)	1381 (30.5)

All continuous variables are reported as median (IQR). For variables with missing data the number with non-missing values is given. Excess alcohol intake was defined as more than 21 or 14 standard drinks (12 g alcohol) per week for men and women, respectively. Abbreviations: 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.

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Supplementary Table 6. Characteristics of the three type 2 diabetes phenotypes at enrolment, stratified by no pre-existing cardiovascular disease

	Insulinopenic phenotype	Classical phenotype	Hyperinsulinemic phenotype
Total	356	2219	844
Male sex, n (%)	195 (54.8)	1258 (56.7)	427 (50.6)
Age, years	63.3 (54.6-69.2)	61.2 (52.6-67.8)	61.4 (51.6-68.1)
Diabetes duration, years	1.6 (0.6-3.0)	1.7 (0.5-3.2)	1.3 (0.4-2.5)
Waist circumference, cm, n= 4204	92.0 (85.0-100.0)	105.0 (97.0-115.0)	112.0 (102.0-121.0)
Body mass index, kg/m^2, n= 1942	25.6 (23.0-28.7)	30.1 (27.1-34.0)	33.4 (29.7-37.0)
Diastolic blood pressure, mmHg, , n= 2147	80.0 (74.0-85.0)	80.0 (75.0-86.0)	80.0 (74.0-86.0)
Systolic blood pressure, mmHg, n= 2147	130.0 (125.0-137.0)	130.0 (124.0-140.0)	130.0 (124.0-140.0)
Smoking, n (%), n= 3866			
Never	176 (53.8)	976 (47.7)	348 (45.5)
Former	99 (30.3)	697 (34.0)	262 (34.2)
Current	52 (15.9)	374 (18.3)	155 (20.3)
Excess alcohol intake, n (%)	17 (4.8)	169 (7.6)	46 (5.5)
Family history of diabetes, number of relatives, n (%)			
0	161 (45.2)	974 (43.9)	425 (50.4)
1-2	169 (47.5)	1058 (47.7)	360 (42.7)
≥ 3	26 (7.3)	187 (8.4)	59 (7.0)
Self-reported physical activity, days/week, n (%)			
0	28 (7.9)	318 (14.3)	181 (21.4)
1-2	49 (13.8)	449 (20.2)	191 (22.6)
≥ 3	279 (78.4)	1452 (65.4)	472 (55.9)
HOMA2B, %	62.2 (48.3-77.6)	81.9 (65.5-97.1)	136.1 (124.5-157.7)
HOMA2S, %	74.4 (68.4-87.6)	37.7 (29.7-47.2)	27.8 (22.2-35.4)
Fasting blood glucose, mmol/L	6.5 (5.9-7.4)	7.6 (6.9-8.8)	6.4 (5.8-6.9)
Fasting C-peptide pmol/L	554.9 (471.5-602.8)	1045 (847.6-1287)	1527 (1213-1870)
Hemoglobin A1c, %, n= 2269	6.5 (6.1-7.2)	6.7 (6.2-7.3)	6.4 (6.0-6.8)
Low-density lipoprotein cholesterol, mmol/L, n= 2186	2.3 (1.8-2.9)	2.3 (1.8-3.0)	2.3 (1.8-2.9)
High-density lipoprotein cholesterol, mmol/L, n= 984	1.4 (1.2-1.8)	1.2 (1.0-1.4)	1.1 (0.9-1.4)
Total cholesterol, mmol/L, n= 987	4.4 (3.8-5.3)	4.5 (3.9-5.2)	4.6 (3.8-5.3)
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 (4.0-14.0)	9.0 (4.0-21.0)	10.0 (4.0-28.0)
Pre-existing acute myocardial infarction, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pre-existing stroke, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pre-existing heart failure, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pre-existing COPD, n (%)	18 (5.1)	144 (6.5)	74 (8.8)
Pre-existing cancer, n (%)	29 (8.1)	168 (7.6)	66 (7.8)
Chronic renal disease, n (%)	1 (0.3)	26 (1.2)	24 (2.8)
Glucose-lowering drug-naïve, n (%)	72 (20.2)	379 (17.1)	150 (17.8)
Metformin, n (%)	267 (75.0)	1774 (79.9)	668 (79.1)
DPP-4 inhibitors, n (%)	28 (7.9)	186 (8.4)	45 (5.3)
GLP-1 analogues, n (%)	10 (2.8)	120 (5.4)	55 (6.5)

SGLT2-inhibitors, n (%)	1 (0.3)	9 (0.4)	4 (0.5)
SU and meglitinides, n (%)	22 (6.2)	154 (6.9)	33 (3.9)
Insulin, n (%)	45 (12.6)	96 (4.3)	26 (3.1)
Anti-hypertensive drugs, n (%)	196 (55.1)	1472 (66.3)	628 (74.4)
Lipid-lowering drugs, n (%)	220 (61.8)	1441 (64.9)	551 (65.3)
Anti-thrombotic drugs, n (%)	60 (16.9)	417 (18.8)	199 (23.6)

All continuous variables are reported as median (IQR). For variables with missing data the number with non-missing values is given. Excess alcohol intake was defined as more than 21 or 14 standard drinks (12 g alcohol) per week for men and women, respectively. Abbreviations: 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.

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Supplementary Table 7. Characteristics of the three type 2 diabetes phenotypes at enrolment, stratified by pre-existing cardiovascular disease

	Insulinopenic phenotype	Classical phenotype	Hyperinsulinemic phenotype
Total	61	466	263
Male sex, n (%)	47 (77.0)	352 (75.5)	187 (71.1)
Age, years	67.3 (60.0-71.6)	66.3 (60.0-72.5)	68.6 (60.5-74.3)
Diabetes duration, years	1.4 (0.4-3.0)	2.2 (0.6-3.6)	1.6 (0.5-3.0)
Waist circumference, cm, n= 4204	95.0 (90.0-100.0)	106.0 (98.0-116.0)	111.0 (102.0-121.0)
Body mass index, kg/m^2, n= 1942	26.3 (24.3-29.5)	30.1 (27.3-34.2)	32.6 (28.6-35.9)
Diastolic blood pressure, mmHg, , n= 2147	76.0 (70.0-85.0)	80.0 (71.5-85.0)	78.0 (70.0-83.0)
Systolic blood pressure, mmHg, n= 2147	135.0 (128.0-141.0)	130.0 (122.0-140.0)	130.0 (120.0-140.0)
Smoking, n (%), n= 3866			
Never	19 (33.9)	165 (37.8)	74 (31.5)
Former	22 (39.3)	190 (43.6)	116 (49.4)
Current	15 (26.8)	81 (18.6)	45 (19.1)
Excess alcohol intake, n (%)	7 (11.5)	28 (6.0)	23 (8.7)
Family history of diabetes, number of relatives, n (%)			
0	30 (49.2)	234 (50.2)	158 (60.1)
1-2	27 (44.3)	203 (43.6)	96 (36.5)
≥ 3	4 (6.6)	29 (6.2)	9 (3.4)
Self-reported physical activity, days/week, n (%)			
0	6 (9.8)	82 (17.6)	71 (27.0)
1-2	12 (19.7)	95 (20.4)	50 (19.0)
≥ 3	43 (70.5)	289 (62.0)	142 (54.0)
HOMA2B, %	64.3 (52.5-84.3)	83.9 (70.0-98.0)	138.5 (126.3-167.5)
HOMA2S, %	74.7 (68.7-91.9)	35.2 (28.3-44.9)	25.4 (19.8-31.8)
Fasting plasma glucose, mmol/L	6.3 (5.7-7.1)	7.7 (6.9-8.6)	6.5 (6.0-7.1)
Fasting C-peptide pmol/L	539.3 (475.4-605.4)	1114 (899.3-1393)	1656 (1337-2096)
Hemoglobin A1c, %, n= 2269	6.7 (6.0-7.1)	6.7 (6.2-7.3)	6.4 (6.0-6.7)
Low-density lipoprotein cholesterol, mmol/L, n= 2186	2.2 (1.6-3.1)	2.0 (1.6-2.4)	1.9 (1.5-2.5)
High-density lipoprotein cholesterol, mmol/L, n= 984	1.3 (1.0-1.5)	1.1 (0.9-1.3)	1.1 (1.0-1.3)
Total cholesterol, mmol/L, n= 987	4.5 (3.7-5.3)	4.0 (3.4-4.6)	3.9 (3.4-4.7)
Triglycerides, mmol/L, n= 2083	1.0 (0.8-1.6)	1.7 (1.2-2.6)	1.8 (1.4-2.5)
Urine Albumin-creatinine ratio, mg/g, n= 2098	9.4 (6.0-24.6)	11.0 (4.0-41.0)	10.0 (3.0-39.0)
Pre-existing acute myocardial infarction, n (%)	24 (39.3)	150 (32.2)	98 (37.3)
Pre-existing stroke, n (%)	8 (13.1)	117 (25.1)	48 (18.3)
Pre-existing heart failure, n (%)	5 (8.2)	63 (13.5)	51 (19.4)
Pre-existing COPD, n (%)	7 (11.5)	52 (11.2)	42 (16.0)
Pre-existing cancer, n (%)	8 (13.1)	37 (7.9)	15 (5.7)
Chronic renal disease, n (%)	2 (3.3)	18 (3.9)	20 (7.6)
Glucose-lowering drug-naive	6 (9.8)	76 (16.3)	53 (20.2)
Metformin, n (%)	53 (86.9)	366 (78.5)	202 (76.8)
DPP-4 inhibitors, n (%)	1 (1.6)	50 (10.7)	9 (3.4)
GLP-1 analogues, n (%)	0 (0.0)	22 (4.7)	6 (2.3)

SGLT2-inhibitors, n (%)	0 (0.0)	2 (0.4)	0 (0.0)
SU and meglitinides, n (%)	3 (4.9)	36 (7.7)	11 (4.2)
Insulin, n (%)	8 (13.1)	25 (5.4)	7 (2.7)
Anti-hypertensive drugs, n (%)	46 (75.4)	420 (90.1)	244 (92.8)
Lipid-lowering drugs, n (%)	48 (78.7)	403 (86.5)	228 (86.7)
Anti-thrombotic drugs, n (%)	46 (75.4)	369 (79.2)	210 (79.8)

All continuous variables are reported as median (IQR). For variables with missing data the number with non-missing values is given. Excess alcohol intake was defined as more than 21 or 14 standard drinks (12 g alcohol) per week for men and women, respectively. Abbreviations: 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.

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Supplementary Table 8: 3- and 5-year cumulative incidences of all endpoints

For the secondary endpoints the cumulative incidence was estimated taking all-cause mortality into account, except for cardiovascular death and non-cardiovascular death where non-cardiovascular death and cardiovascular death were taken into account, respectively. For the composite cardiovascular endpoint, non-cardiovascular death was taken into account. All-cause mortality was estimated by the Kaplan-Meier method.

	3-year cumulative incidence (95% CI)	5-year cumulative incidence (95% CI)
Composite cardiovascular endpoint		
Insulinopenic phenotype	3.10 (1.69-5.20)	4.55 (2.68-7.17)
Classical phenotype	6.31 (5.40-7.31)	10.12 (8.48-11.93)
Hyperinsulinemic phenotype	8.42 (6.83-10.20)	12.56 (10.06-15.36)
All-cause mortality		
Insulinopenic phenotype	4.35 (2.67-6.63)	6.24 (4.15-8.91)
Classical phenotype	2·95 (2.35-3.64)	5.34 (4.49-6.30)
Hyperinsulinemic phenotype	4.11 (3.04-5.40)	8.23 (6.62-10.05)
Myocardial infarction		
Insulinopenic phenotype	0.73 (0.20-2.00)	0.73 (0.20-2.00)
Classical phenotype	1.32 (0.94-1.81)	1.93 (1.44-2.52)
Hyperinsulinemic phenotype	1.45 (0.87-2.30)	2.19 (1.42-3.22)
Unstable angina pectoris		
Insulinopenic phenotype	0.48 (0.10-1.64)	0.48 (0.10-1.64)
Classical phenotype	0.60 (0.36-0.95)	0.99 (0.66-1.44)
Hyperinsulinemic phenotype	0.82 (0.41-1.51)	1.01 (0.54-1.76)
Coronary revascularization		
Insulinopenic phenotype	1.70 (0.76-3.34)	2.29 (1.12-4.16)
Classical phenotype	2.26 (1.75-2.88)	3.28 (2.63-4.03)
Hyperinsulinemic phenotype	2.73 (1.88-3.82)	3.49 (2.50-4.73)
Stroke		
Insulinopenic phenotype	0.48 (0.10-1.63)	1.22 (0.47-2.70)
Classical phenotype	1.52 (1.10-2.04)	2.35 (1.80-3.01)
Hyperinsulinemic phenotype	1.64 (1.01-2.53)	3.31 (2.30-4.60)
Heart failure		
Insulinopenic phenotype	1.22 (0.46-2.68)	1.79 (0.79-3.52)
Classical phenotype	1.40 (1.00-1.90)	2.04 (1.54-2.66)
Hyperinsulinemic phenotype	3.19 (2.26-4.35)	4.35 (3.23-5.72)
Peripheral revascularization		
Insulinopenic phenotype	0.00 (.-.)	0.00 (.-.)
Classical phenotype	0.60 (0.36-0.96)	0.99 (0.65-1.46)
Hyperinsulinemic phenotype	0.82 (0.41-1.51)	0.95 (0.49-1.69)
Cardiovascular death		
Insulinopenic phenotype	1.04 (0.35-2.52)	1.37 (0.51-3.03)
Classical phenotype	0.84 (0.54-1.27)	1.28 (0.82-1.93)
Hyperinsulinemic phenotype	1.84 (1.14-2.81)	2.87 (1.81-4.30)
Non-cardiovascular death		
Insulinopenic phenotype	3.47 (1.99-5.61)	5.16 (2.98-8.21)
Classical phenotype	2.21 (1.68-2.84)	4.14 (3.06-5.47)
Hyperinsulinemic phenotype	2.03 (1.30-3.04)	5.17 (3.38-7.51)

Supplementary Table 9: Hazard ratios for the composite cardiovascular endpoint and all-cause mortality with adjustment for the individual covariates of model 2 and 3 in addition to age and sex.

	Composite cardiovascular endpoint, aHR (95% CI)		All-cause mortality, aHR (95% CI)	
	Insulinopenic vs classical phenotype	Hyperinsulinemic vs classical phenotype	Insulinopenic vs classical phenotype	Hyperinsulinemic vs classical phenotype
Age + sex	0.49 (0.30-0.82)	1.33 (1.05-1.69)	1.10 (0.73-1.64)	1.30 (1.00-1.68)
Confounders:				
+ waist circumference	0.56 (0.33-0.94)	1.25 (0.98-1.59)	1.22 (0.80-1.85)	1.22 (0.93-1.59)
+ physical activity	0.52 (0.31-0.87)	1.26 (0.99-1.60)	1.15 (0.77-1.73)	1.20 (0.92-1.56)
+ family history of diabetes	0.49 (0.30-0.82)	1.31 (1.03-1.66)	1.10 (0.73-1.64)	1.29 (0.99-1.67)
+ smoking	0.50 (0.29-0.86)	1.27 (0.98-1.64)	0.96 (0.60-1.53)	1.22 (0.91-1.63)
+ excess alcohol intake	0.49 (0.30-0.82)	1.33 (1.05-1.69)	1.10 (0.73-1.64)	1.30 (1.00-1.69)
+ diabetes duration	0.49 (0.30-0.82)	1.35 (1.07-1.71)	1.10 (0.73-1.64)	1.30 (1.00-1.69)
Mediators:				
+ systolic blood pressure	0.49 (0.29-0.81)	1.32 (1.04-1.67)	1.10 (0.73-1.64)	1.30 (1.00-1.69)
+ diastolic blood pressure	0.48 (0.29-0.81)	1.31 (1.03-1.66)	1.10 (0.73-1.64)	1.30 (1.00-1.69)
+ fasting glucose	0.56 (0.33-0.94)	1.54 (1.19-1.99)	1.18 (0.78-1.78)	1.41 (1.06-1.87)
+ HbA1c	0.50 (0.30-0.83)	1.41 (1.11-1.79)	1.10 (0.73-1.64)	1.32 (1.01-1.72)
+ Total cholesterol	0.49 (0.30-0.82)	1.32 (1.04-1.68)	1.10 (0.73-1.64)	1.29 (0.99-1.68)
+ LDL-C	0.49 (0.30-0.82)	1.33 (1.05-1.68)	1.09 (0.73-1.63)	1.30 (1.00-1.69)
+ HDL-C	0.58 (0.34-0.98)	1.20 (0.93-1.54)	1.30 (0.85-1.98)	1.16 (0.88-1.52)
+ Triglycerid	0.53 (0.32-0.89)	1.30 (1.03-1.65)	1.14 (0.76-1.72)	1.27 (0.98-1.66)
+ Urine Albumin-creatinine ratio	0.50 (0.30-0.83)	1.32 (1.05-1.68)	1.11 (0.74-1.67)	1.28 (0.98-1.66)
+ insulin use	0.47 (0.28-0.78)	1.34 (1.06-1.70)	1.06 (0.71-1.59)	1.30 (1.00-1.69)
+ GLP1-analogue or SGLT2i use	0.49 (0.30-0.82)	1.33 (1.05-1.69)	1.10 (0.73-1.64)	1.30 (1.00-1.69)
+ Metformin, DPP-4i, SU and meglitinides, Thiazolid inediones or Alfa-glucosidase inhibitor use	0.49 (0.30-0.82)	1.33 (1.05-1.68)	1.10 (0.73-1.64)	1.30 (1.00-1.69)
+ Use of lipid-lowering drugs	0.50 (0.30-0.83)	1.33 (1.05-1.68)	1.07 (0.72-1.61)	1.31 (1.01-1.70)
+ Use of anti-hypertensive drugs	0.54 (0.33-0.91)	1.26 (1.00-1.60)	1.12 (0.75-1.68)	1.28 (0.98-1.66)
+ use of anti-thrombotic drugs	0.52 (0.31-0.86)	1.24 (0.98-1.57)	1.11 (0.74-1.66)	1.27 (0.98-1.66)
+ chronic renal disease	0.50 (0.30-0.83)	1.31 (1.03-1.65)	1.10 (0.74-1.65)	1.25 (0.96-1.63)
+ pre-existing CVD	0.51 (0.31-0.86)	1.19 (0.94-1.51)	1.12 (0.75-1.67)	1.25 (0.96-1.63)

Excess alcohol intake was defined as more than 21 or 14 standard drinks (12 g alcohol) per week for men and women, respectively. HbA1c: Hemoglobin A1c, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, GLP1: glucagon-like protein 1, SGLT2i: sodium glucose co-transporter 2 inhibitor, DPP4i: Dipeptidyl peptidase-4 inhibitor, CVD: cardiovascular disease, SU: sulfonylurea

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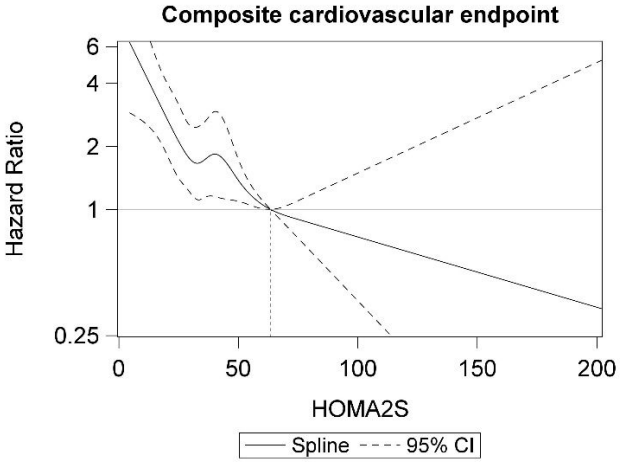
Primary endpoints according to continuous measures of insulin sensitivity and beta cell function

Supplementary Figure 1: Hazard ratio of the composite cardiovascular endpoint by continuous HOMA2S.
A restricted cubic spline model, adjusted for age and sex, with six knots was used to examine the association between HOMA2S levels, as a continuous variable, and the risk of the composite cardiovascular endpoint for A) all individuals, B) individuals with pre-existing cardiovascular disease, C) individuals without pre-existing cardiovascular disease.

A



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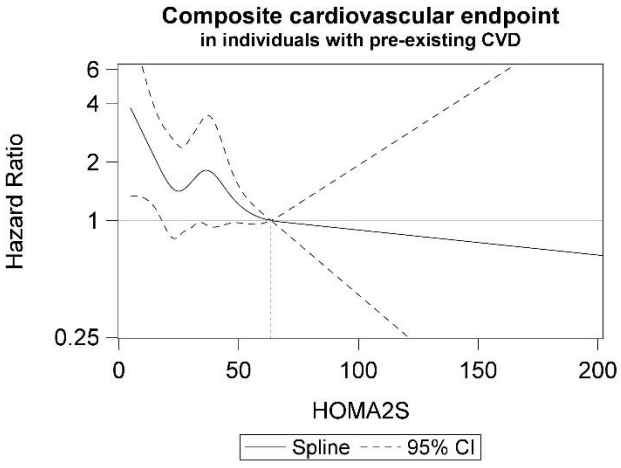

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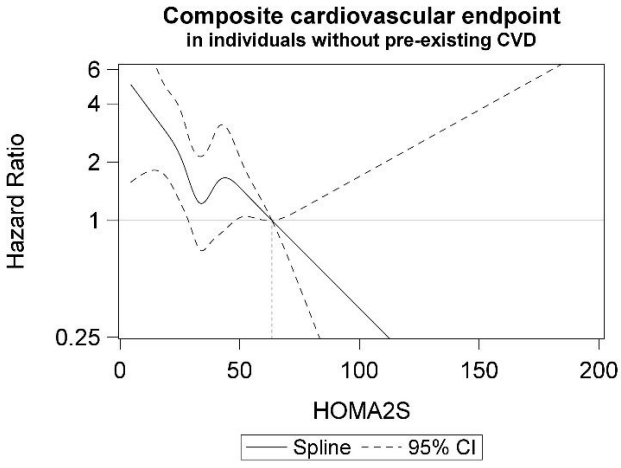
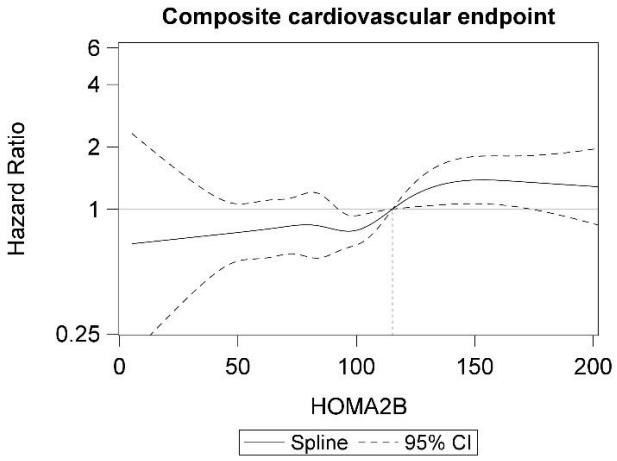


Supplementary Figure 2: Hazard ratio of the composite cardiovascular endpoint by continuous HOMA2B.
A restricted cubic spline model, adjusted for age and sex, with six knots was used to examine the association between HOMA2B levels, as a continuous variable, and the risk of the composite cardiovascular endpoint for A) all individuals, B) individuals with pre-existing cardiovascular disease (CVD), C) individuals without pre-existing cardiovascular disease (CVD)

A



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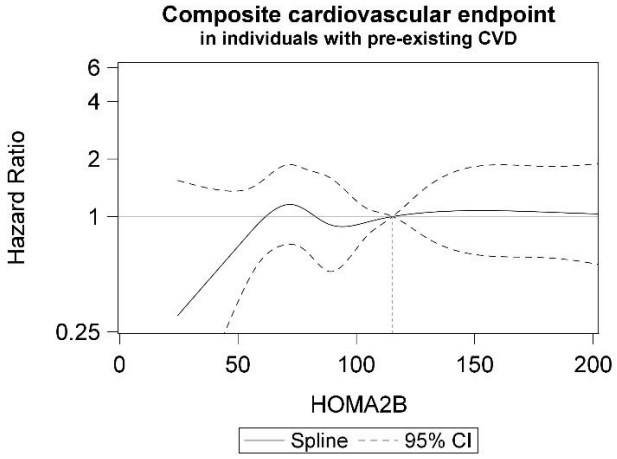

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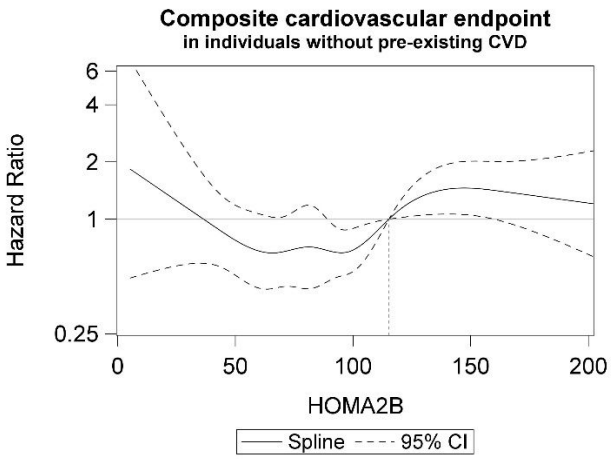

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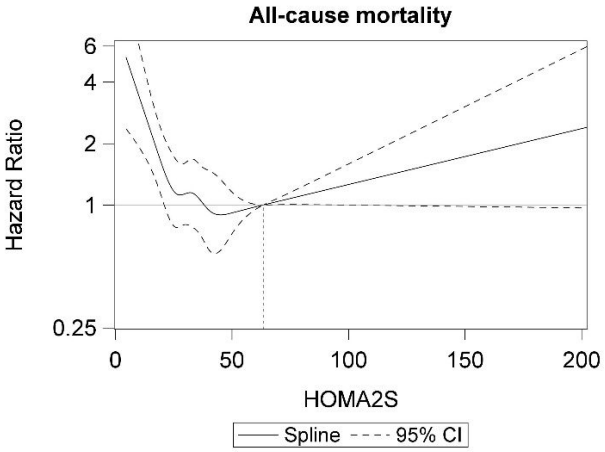
Supplementary Figure 3: Hazard ratio of all-cause mortality by continuous HOMA2S.

A restricted cubic spline model, adjusted for age and sex, with six knots was used to examine the association between HOMA2S levels, as a continuous variable, and the risk of the composite cardiovascular endpoint for A) all individuals, B) individuals with pre-existing cardiovascular disease, C) individuals without pre-existing cardiovascular disease.

A



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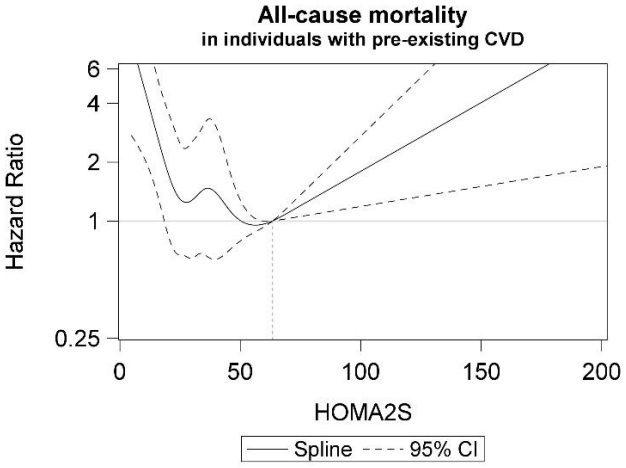

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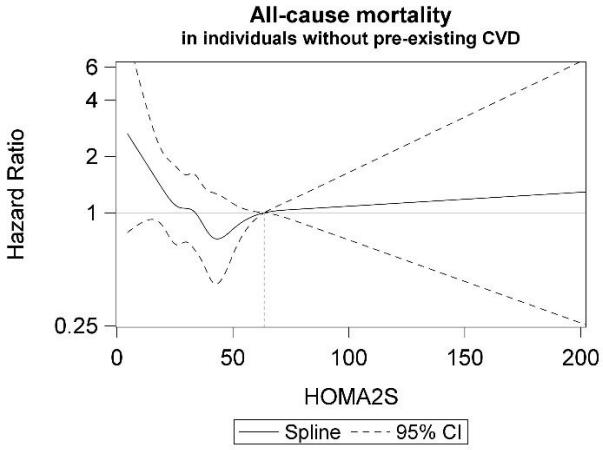
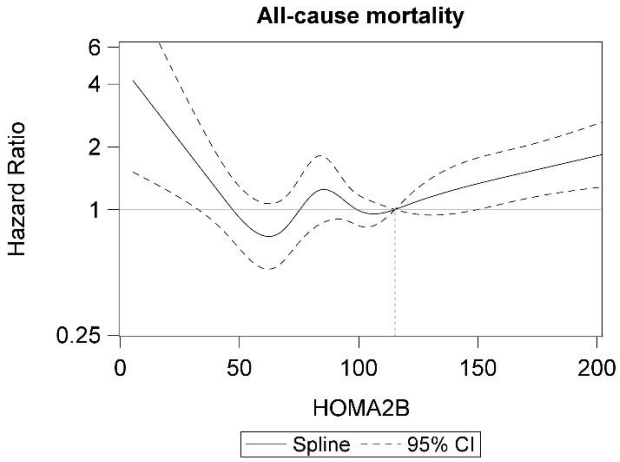


Supplementary Figure 4: Hazard ratio of all-cause mortality by continuous HOMA2B.

A restricted cubic spline model, adjusted for age and sex, with six knots was used to examine the association between HOMA2B levels, as a continuous variable, and the risk of the composite cardiovascular endpoint for A) all individuals, B) individuals with pre-existing cardiovascular disease, C) individuals without pre-existing cardiovascular disease.

A



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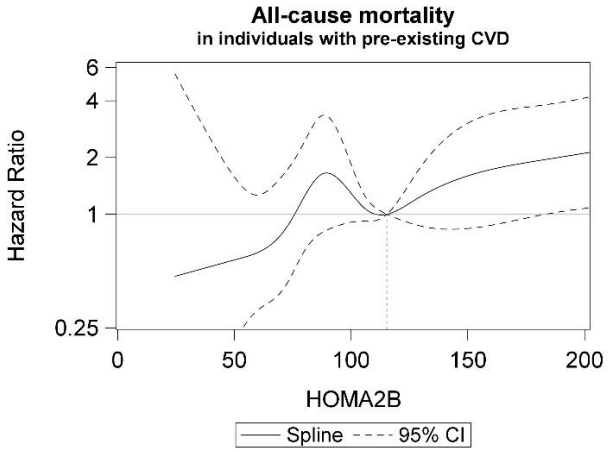

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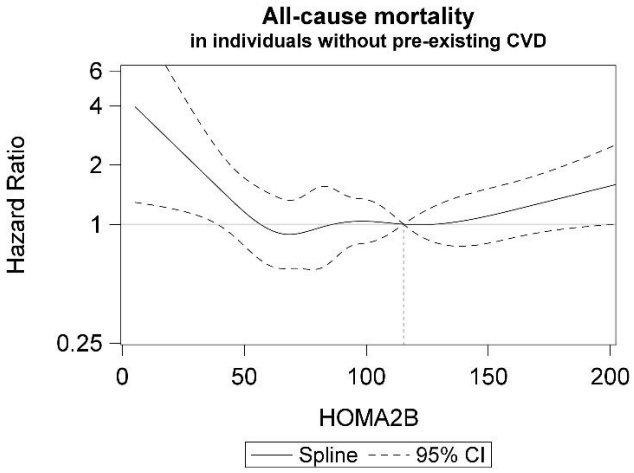

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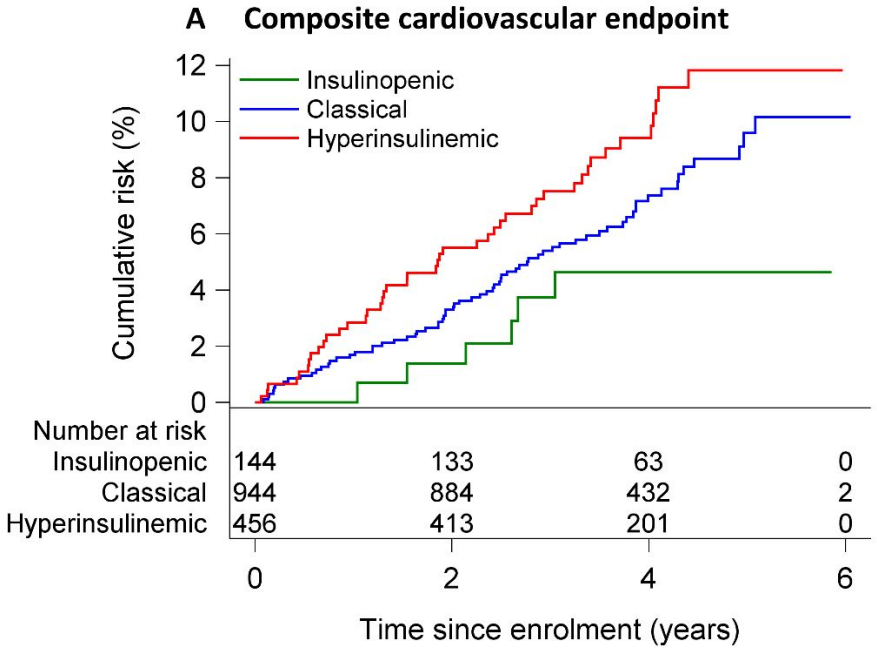
Sensitivity analyses

Supplementary Figure 5: Crude cumulative incidence of the composite cardiovascular endpoint (A) and all-cause mortality (B) by phenotypes in individuals with diabetes debut within 1 year of enrolment in the cohort. Competeting risk from non-cardiovascular death was taken into account in the analysis of the composite cardiovascular endpoint. All-cause mortality was estimated by the Kaplan-Meier method.

A



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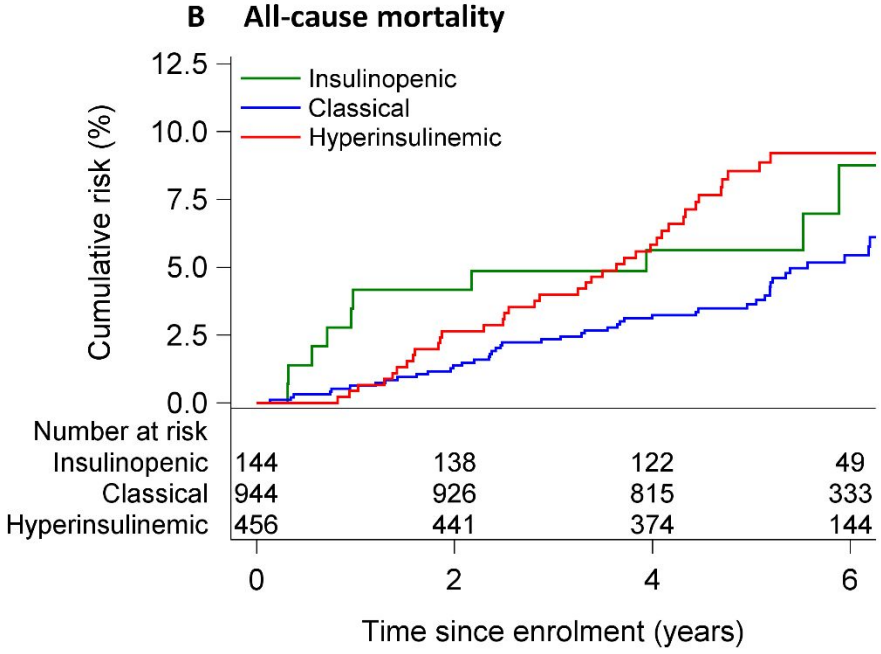
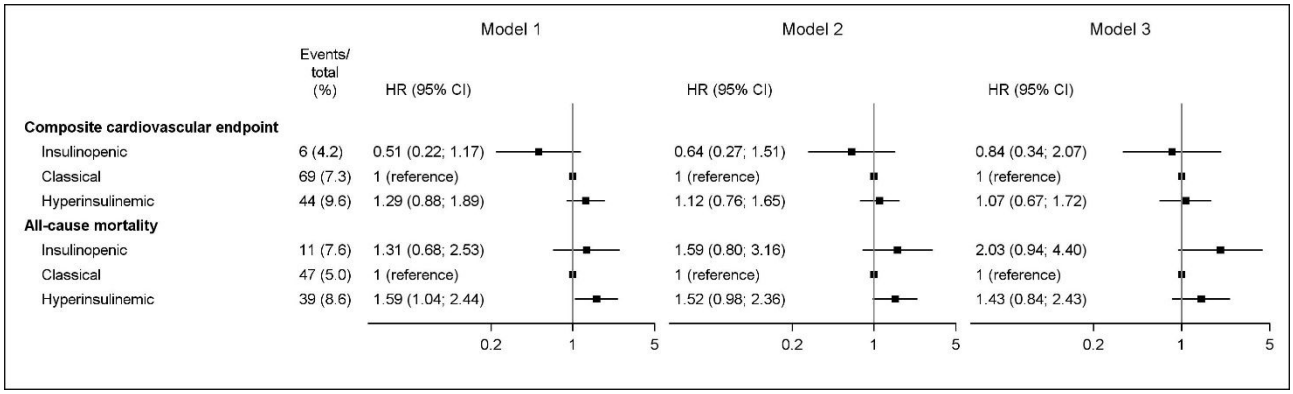


Supplementary Figure 6: Forest plot of hazard ratios for the composite cardiovascular endpoint and all-cause mortality in individuals with diabetes debut within 1 year of enrolment in the cohort.



Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, diabetes duration at index date, self-reported physical activity, family history of diabetes, waist circumference, smoking, and alcohol consumption. Model 3: adjusted for model 2 + systolic and diastolic blood pressure, fasting plasma glucose, Hemoglobin A1c, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein 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.

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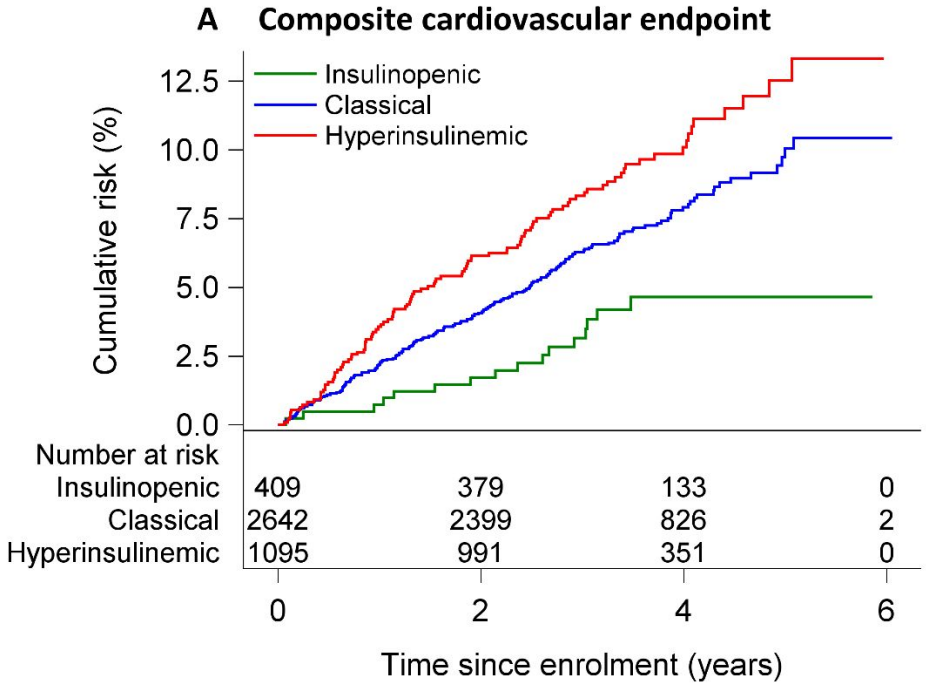
Supplementary Figure 7: Crude cumulative incidence of the composite cardiovascular endpoint (A) and all-cause mortality (B) by phenotypes in individuals without redemption of glucocorticoids within 3 month of enrolment. Competeting risk from non-cardiovascular death was taken into account in the analysis of the composite cardiovascular endpoint

A



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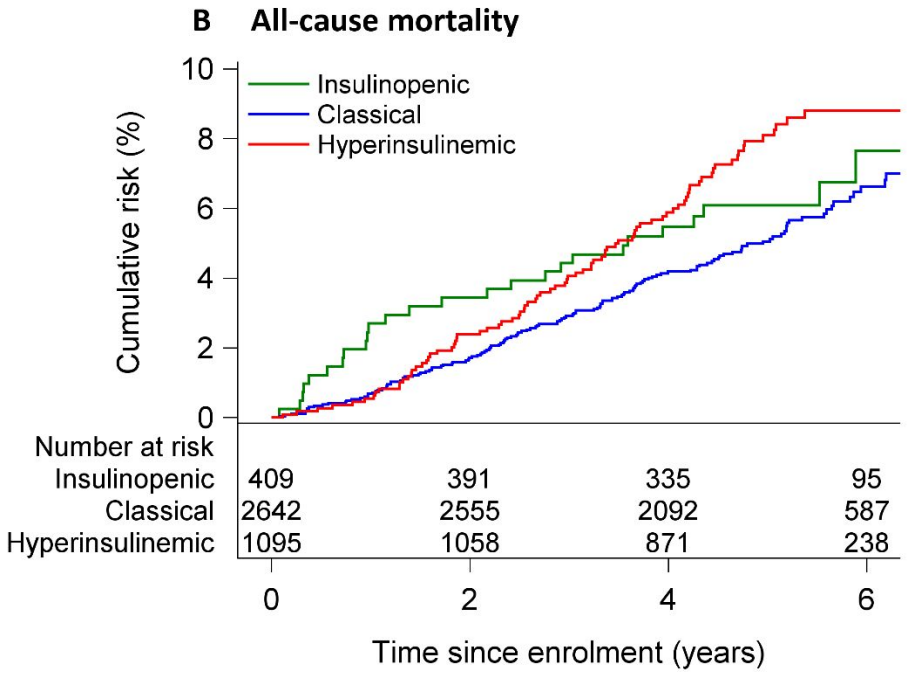
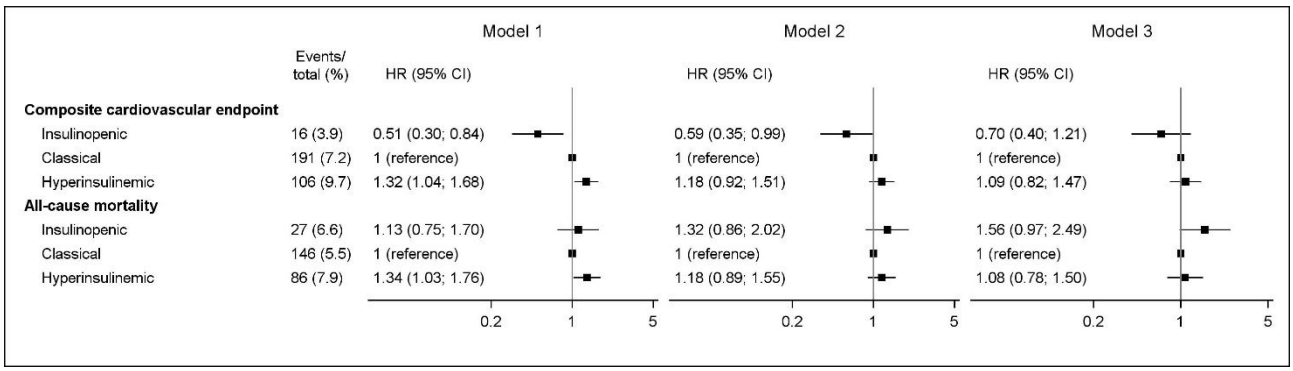


Supplementary Figure 8: Forest plot for hazard ratios for the composite cardiovascular endpoint and all-cause mortality in individuals without redemption of glucocorticoids within 3 month of enrolment.



Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, diabetes duration at index date, self-reported physical activity, family history of diabetes, waist circumference, smoking and alcohol consumption. Model 3: adjusted for model 2 + systolic and diastolic blood pressure, fasting plasma glucose, Hemoglobin A1c, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein 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.

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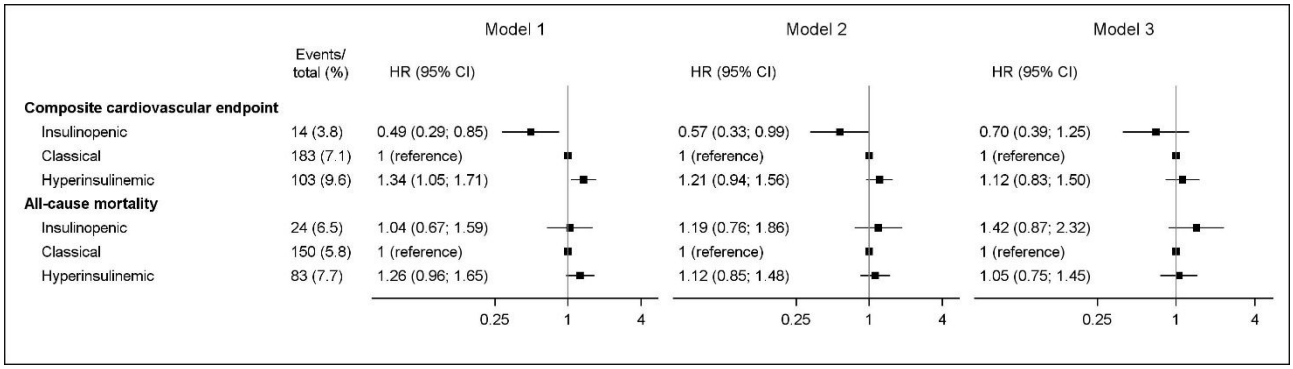
Supplementary Figure 9: Forest plot of hazard ratios for the composite cardiovascular endpoint and all-cause mortality in individuals without redemption of insulin within 3 month of enrolment.

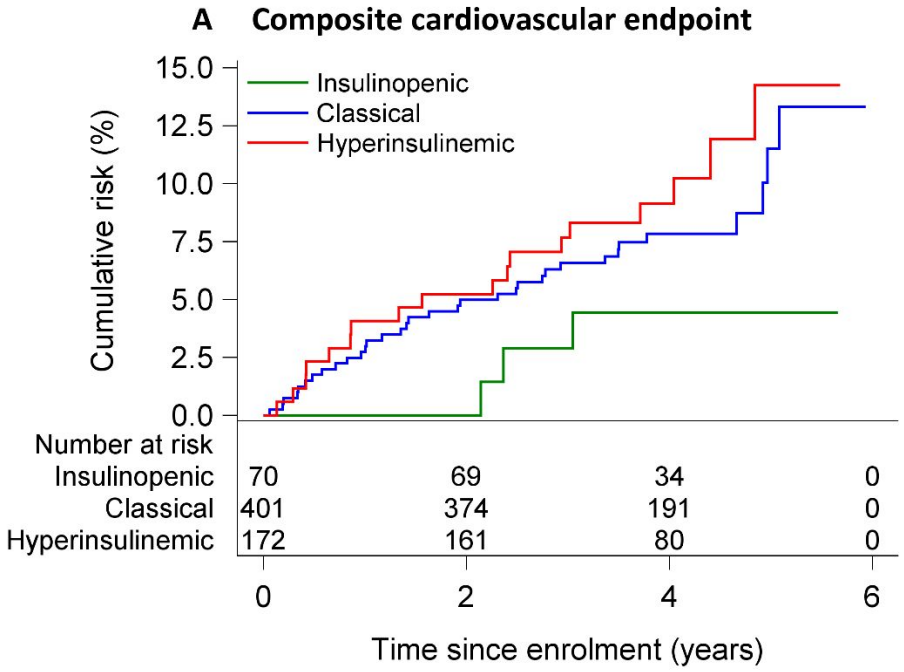


Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, diabetes duration at index date, self-reported physical activity, family history of diabetes, waist circumference, smoking and alcohol consumption. Model 3: adjusted for model 2 + systolic and diastolic blood pressure, fasting plasma glucose, Hemoglobin A1c, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein 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.

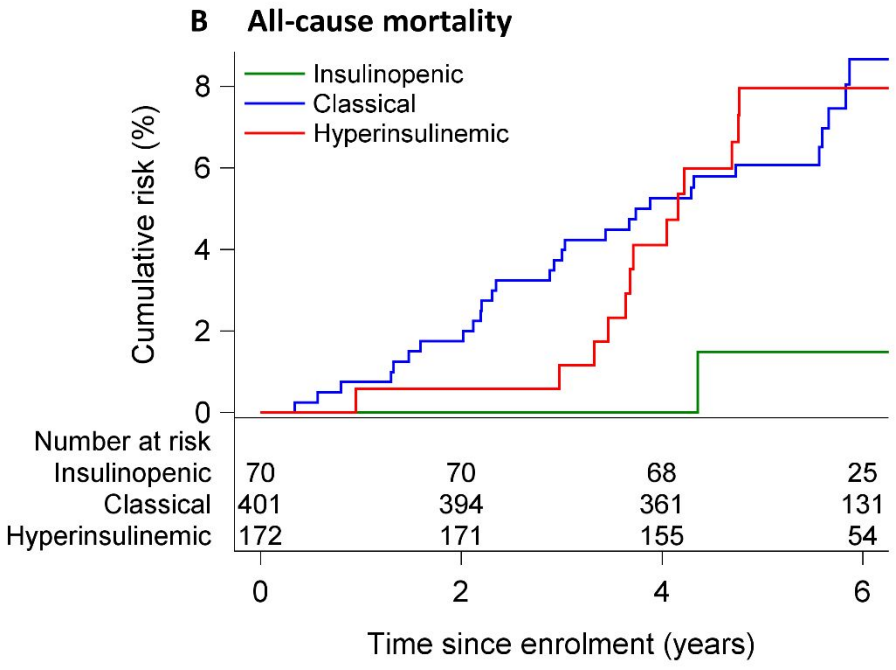
Supplementary Figure 10: Crude cumulative incidence of the composite cardiovascular endpoint and all-cause mortality by phenotype in individuals with a complete covariate case

Cumulative incidence of the composite cardiovascular endpoint (A) and all-cause mortality (B) for individuals with a complete covariate case (N=699). For the composite cardiovascular endpoint competing risk from non-cardiovascular death was taken into account.

A



B



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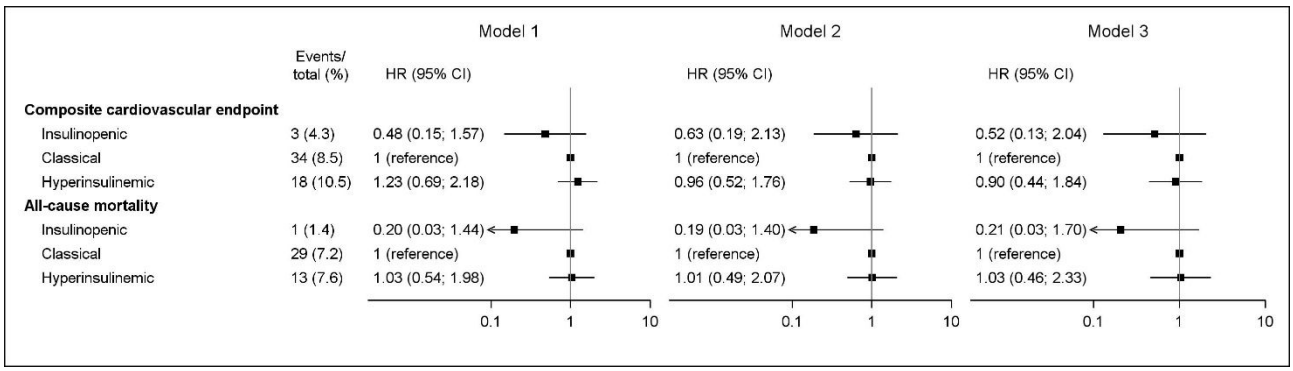
Supplementary Figure 11: Forest plot of hazard ratios for the composite cardiovascular endpoint and all-cause mortality in individuals with a complete covariate case.



Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, diabetes duration at index date, self-reported physical activity, family history of diabetes, waist circumference, smoking and alcohol consumption. Model 3: adjusted for model 2 + systolic and diastolic blood pressure, fasting plasma glucose, Hemoglobin A1c, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein 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.

Missing data

Supplementary Table 10: Number of missing values of the covariates and characteristics at enrolment of complete cases and non-complete cases according to model 2 and 3.

	Number of missing values N=4209	Complete cases N=643	Non-complete cases N=3566
Male sex, n (%)	0 (0.0)	369 (57.4)	2097 (58.8)
Age, years	0 (0.0)	62.0 (53.3-68.5)	62.5 (54.0-69.3)
Diabetes duration, years	0 (0.0)	1.3 (0.5-2.5)	1.7 (0.5-3.2)
Waist circumference, cm, n= 4204	5 (0.1)	106.0 (96.0-116.0)	105.0 (97.0-116.0)
Body mass index, kg/m^2, n= 1942	2267 (53.8)	30.5 (26.8-34.4)	30.3 (27.0-34.6)
Diastolic blood pressure, mmHg, , n= 2147	2063 (49.0)	80.0 (75.0-87.0)	80.0 (74.0-85.0)
Systolic blood pressure, mmHg, n= 2147	2063 (49.0)	131.0 (123.0-142.0)	130.0 (124.0-140.0)
Smoking, n (%), n=3866	344 (8.2)		
Never		310 (48.2)	1448 (44.9)
Former		220 (34.2)	1166 (36.2)
Current		113 (17.6)	609 (18.9)
Excess alcohol intake, n (%)	0 (0.0)	44 (6.8)	246 (6.9)
Family history of diabetes, number of relatives, n (%n)	0 (0.0)		
0		303 (47.1)	1679 (47.1)
1-2		279 (43.4)	1634 (45.8)
≥ 3		61 (9.5)	253 (7.1)
Self-reported physical activity, days/week, n (%)	0 (0.0)		
0		94 (14.6)	592 (16.6)
1-2		139 (21.6)	707 (19.8)
≥ 3		410 (63.8)	2267 (63.6)
HOMA2B, %	0 (0.0)	91.3 (69.8-117.6)	90.9 (69.3-117.4)
HOMA2S, %	0 (0.0)	35.8 (26.7-48.0)	35.8 (26.9-48.6)
Fasting plasma glucose, mmol/L	0 (0.0)	7.2 (6.4-8.2)	7.1 (6.4-8.2)
Fasting C-peptide, pmol/L	0 (0.0)	1120 (849.6-1464)	1114 (838.0-1479)
Hemoglobin A1c, %, n= 2269	1941 (46.1)	6.5 (6.1-7.3)	6.6 (6.1-7.1)
Low-density lipoprotein cholesterol, mmol/L, n= 2186	2024 (48.1)	2.2 (1.8-2.9)	2.2 (1.7-2.9)
High-density lipoprotein cholesterol, mmol/L, n= 984	3226 (76.6)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
Total cholesterol, mmol/L, n= 987	3223 (76.6)	4.3 (3.7-5.1)	4.5 (3.8-5.3)
Triglycerides, mmol/L, n= 2083	2127 (50.5)	1.7 (1.2-2.4)	1.7 (1.2-2.4)
Urine Albumin-creatinine ratio, mg/g, n= 2098	2112 (50.2)	9.0 (4.0-35.4)	9.0 (4.0-20.0)
Pre-existing cardiovascular disease, n (%)	0 (0.0)	137 (21.3)	653 (18.3)
Pre-existing acute myocardial infarction, n (%)	0 (0.0)	50 (7.8)	222 (6.2)
Pre-existing stroke, n (%)	0 (0.0)	34 (5.3)	139 (3.9)
Pre-existing heart failure, n (%)	0 (0.0)	23 (3.6)	96 (2.7)
Pre-existing COPD, n (%)	0 (0.0)	59 (9.2)	278 (7.8)
Pre-existing cancer, n (%)	0 (0.0)	39 (6.1)	284 (8.0)
Chronic renal disease, n (%)	0 (0.0)	9 (1.4)	82 (2.3)
Glucose-lowering drug-naive	0 (0.0)	84 (13.1)	652 (18.3)
Metformin, n (%)	0 (0.0)	541 (84.1)	2789 (78.2)
DPP-4 inhibitors, n (%)	0 (0.0)	41 (6.4)	278 (7.8)

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GLP-1 analogues, n (%)	0 (0.0)	48 (7.5)	165 (4.6)
SGLT2-inhibitors, n (%)	0 (0.0)	1 (0.2)	15 (0.4)
SU and meglitinides, n (%)	0 (0.0)	40 (6.2)	219 (6.1)
Insulin, n (%)	0 (0.0)	45 (7.0)	162 (4.5)
Anti-hypertensive drugs, n (%)	0 (0.0)	474 (73.7)	2532 (71.0)
Lipid-lowering drugs, n (%)	0 (0.0)	472 (73.4)	2419 (67.8)
Anti-thrombotic drugs, n (%)	0 (0.0)	217 (33.7)	1084 (30.4)

All continuous variables are reported as median (IQR). For variables with missing variables the number with non-missing values is given. Excess alcohol intake was defined as more than 21 or 14 standard drinks (12 g alcohol) per week for men and women, respectively. Abbreviations: 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.

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