# Risk of Diabetic Retinopathy According to Subtype of Type 2 Diabetes

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**Type 2 diabetes is a heterogeneous disease that can be subdivided on the basis of β-cell function and insulin sensitivity. We investigated the presence, incidence, and progression of diabetic retinopathy (DR) according to subtypes of type 2 diabetes. In a national cohort, we identified three subtypes of type 2 diabetes: classical, hyperinsulinemic, and insulinopenic type 2 diabetes, based on HOMA2 measurements. From the Danish Registry of Diabetic Retinopathy we extracted information on level of DR. We used several national health registries to link information on comorbidity, medications, and laboratory tests. We found individuals with hyperinsulinemic type 2 diabetes were less likely to have DR at entry date compared with those with classical type 2 diabetes, whereas individuals with insulinopenic type 2 diabetes were more likely to have DR. In multivariable Cox regression analysis, individuals with hyperinsulinemic type 2 diabetes had a decreased risk of both incidence and progression of DR compared to those with classical type 2 diabetes. We did not find any clear difference in risk of incident or progression of DR in individuals with insulinopenic compared to classical type 2 diabetes. These findings indicate that subcategorization of type 2 diabetes is important in evaluating the risk of DR.**

## ARTICLE HIGHLIGHTS

- Type 2 diabetes can be subcategorized on the basis of β-cell function and insulin sensitivity, but little is known about the association of subtypes of type 2 diabetes with risk of diabetic retinopathy (DR).
- Do individuals with hyperinsulinemic or insulinopenic type 2 diabetes have an increased risk of DR compared with individuals with classical type 2 diabetes?
- Individuals with hyperinsulinemic type 2 diabetes had almost half the risk of prevalent or incident DR or progression of DR compared with individuals with classical type 2 diabetes.
- These results suggest that more individualized screening intervals for DR may be possible within subgroups of type 2 diabetes.

Diabetic retinopathy (DR) is a common complication in type 2 diabetes that affects 25% of individuals globally (1). Early detection is crucial to optimize treatment and prevent progression to sight-threatening DR. Important risk factors of DR include type of diabetes, diabetes duration,

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and glycemic control (1). Type 2 diabetes is a heterogeneous disease, which can be further categorized into subtypes based on the relative contribution of the two main pathophysiological defects: deterioration in β-cell function and insulin sensitivity. The subtypes are classical, hyperinsulinemic, and insulinopenic type 2 diabetes (2). Studies suggest that impaired β-cell function measured by reduced fasting or stimulated C-peptide levels in patients with type 2 diabetes is associated with higher presence and elevated risk of incident and progression of DR. These findings imply that the hyperinsulinemic phenotype may be less prone to develop DR (3–7). However the role of insulin resistance in DR development remains poorly understood, with limited data available (8). Although the existing data within this area indicate that preserved β-cell function is a protective factor of DR, earlier studies were limited primarily by cross-sectional design or small samples. Thus, in this study, we investigated the risk of presence, incidence, and progression of DR according to pathophysiological subtypes of type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Main Data Sources, Design, and Study Population

In general, the Danish health care system is tax-funded and provides free access to general practitioners and hospitals, and partial reimbursement for the cost of prescribed medication. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) has enrolled, since 2010, individuals with newly diagnosed type 2 diabetes (9). The median time of diabetes diagnosis to enrollment in the DD2 cohort is 1.3 (interquartile range [IQR], 0.3; 2.9] years (10). Since 2013, the Danish Registry for Diabetic Retinopathy (DiaBase) has been collecting information about individuals aged 18 years or older who participate in Denmark's DR screening program (11). The screening examination is performed by practicing ophthalmologists or at designated hospitals, and it is mandatory for the reporting physician to report findings to DiaBase. The screening procedure primarily relies on retinal fundus images, in accordance with national guidelines (12). The severity of DR is categorized using the International Clinical Diabetic Retinopathy Disease Severity Scale, which consists of five stages: level 0 (no DR), levels 1–3 (mild, moderate, and severe DR, respectively), and level 4 (proliferative DR) (13). DiaBase has recently been validated with high agreement between graders according to the severity of DR (14).

We performed a nationwide cohort study of individuals included in the DD2 cohort who had at least one screening episode for DR registered in DiaBase. The entry date was defined as the first registered screening episode in DiaBase between 1 January 2013 and 1 June 2022. The level of DR was defined according to level of DR in the worse eye. The HOMA2 computational model (University of Oxford, Oxford, U.K.) was used to estimate β-cell function (HOMA2-B) and insulin sensitivity (HOMA2-S) (2,15). Measurements were based on fasting serum C-peptide and plasma glucose values measured at DD2 enrollment. We classified individuals into three subtypes, with high/low HOMA2-B defined as $\geq$115.3/$<$115.3% and high/low HOMA2-S defined as $\geq$63.5/$<$63.5%, based on median HOMA2-B and HOMA2-S values for a healthy control group with normal fasting plasma glucose levels (2). Individuals categorized as having hyperinsulinemic type 2 diabetes had high HOMA2-B and low HOMA2-S, those with insulinopenic type 2 diabetes had low HOMA2-B and high HOMA2-S, and individuals with classical type 2 diabetes had low HOMA2-B and low HOMA2-S.

### Outcome

We estimated odds ratios (ORs) of DR presence at entry date by type 2 diabetes subtype and calculated risk of incident DR during follow-up. Incident DR was defined as absence of DR at entry date, followed by its registration at a later examination. Time of risk was from entry to outcome, or last registered screening episode in DiaBase. Last, we estimated progression risk by comparing the last registered screening episode for DR with baseline severity, with progression defined as at least a one-step worsening.

### Covariates

The Danish National Patient Registry, which includes ICD-10 codes for diseases, was used to evaluate comorbidities using a modified Charlson Comorbidity Index (CCI) score excluding diabetes. The CCI score was calculated following the methodology described by Quan et al. (16). Medication use was assessed using Anatomical Therapeutic Chemical codes provided by the Danish National Prescription Registry, specifically for insulin (A10A*), noninsulin glucose-lowering medications (A10B*), antihypertensive treatments (C03*, C07*, C08*, C09*), or lipid-lowering therapy (C10*), provided they were prescribed at least twice within 1 year of the entry date. Diabetes duration was calculated as the time elapsed between the diagnosis date of diabetes registered in DD2 and the entry date. BMI was calculated at the date of DD2 enrollment. Date of birth, sex, marital, and vital status were obtained from the Danish Civil Registration System. From the Register of Laboratory Results for Research, we extracted information on mean laboratory values for measurements of $HbA_{1c}$, estimated glomerular filtration rate, LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides based on the measurement within 1 year before and after entry date.

### Statistics

Continuous variables are presented as median with IQR and categorical variables as counts and proportions. We applied Pearson $\chi^2$ test to investigate differences between groups. We estimated ORs with 95% CIs for presence of DR at entry date (yes/no), using logistic regression. We applied a crude model, an age- and sex-adjusted model, and multivariable models that were first adjusted for age; sex;

marital status; glucose-, lipid-, or blood pressure–lowering medication; $HbA_{1c}$; a modified CCI; and, finally, for BMI.

We estimated hazard ratios (HRs) for risk of incidence and progression of DR in a crude, age- and sex-adjusted, and multivariable Cox regression models that met the proportional hazard assumption (using the same stepwise adjustment models as for the multivariable logistic regression model). We performed a sensitivity analysis excluding individuals using insulin therapy (Supplementary Table 1). We also examined the dose–response association among β-cell function, insulin sensitivity and incidence, and progression of DR. We stratified the HOMA2-B model according to levels of HOMA-S values (HOMA-S $<$ 63.5%) in that analysis. When investigating the HOMA2-S model, we stratified according to levels of HOMA-B $<$115.3%. Both models were adjusted for the same covariates as the fully adjusted multivariable model and adjusted for HOMA2-B when investigating HOMA2-S and vice versa. The use of medication and the CCI were handled as time-varying covariates. CIs that did not include 1.0 and $P < 0.05$ were considered statistically significant. All statistics were performed using Stata, version 18.0 (StataCorp LLC, College Station, TX).

### Ethics Statement

The study was performed according to the tenets of the Declaration of Helsinki, and permissions were obtained from relevant health authorities (17,18).

### Data and Resource Availability

Data are available from the Danish Health Data Authority, but restrictions apply to these data.

## RESULTS

Among 10,209 individuals enrolled in the DD2, 4,373 were subcategorized, with 3,672 individuals having at least one screening episode in DiaBase (Fig. 1). In short, individuals with hyperinsulinemic type 2 diabetes had higher CCI, BMI, and triglyceride values, but lower level

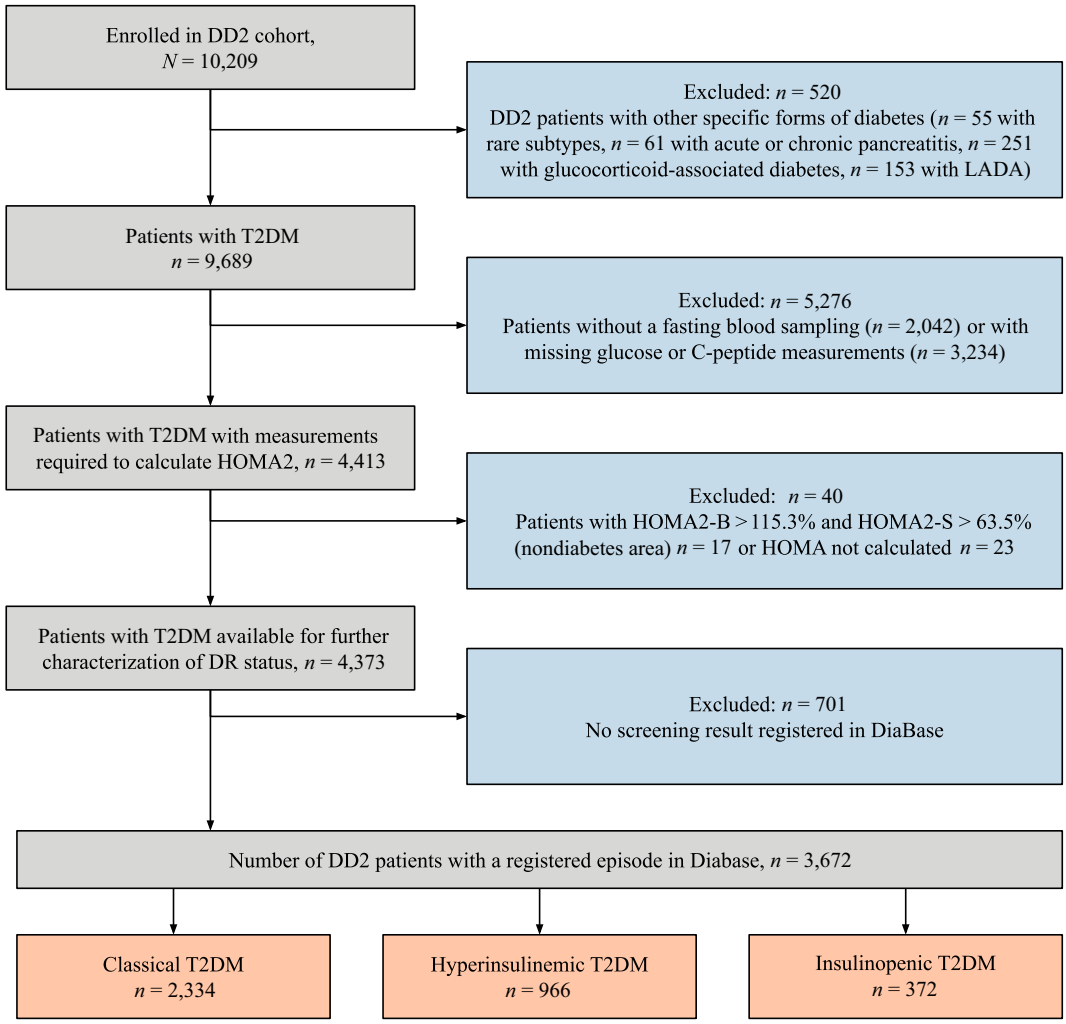


**Figure 1**—Flowchart of study cohort. LADA, latent autoimmune diabetes in adults; T2DM, type 2 diabetes mellitus.

of HDL cholesterol and lower $HbA_{1c}$ compared with the other subtypes (Table 1).

Individuals with hyperinsulinemic type 2 diabetes were less likely to have DR at the entry date compared with those with classical type 2 diabetes (age- and sex-adjusted OR 0.46; 95% CI 0.30–0.72), although the association weakened in the fully multivariable adjusted model (OR 0.69; 95% CI 0.42–1.14) (Table 2). In contrast, individuals with insulinopenic type 2 diabetes were more likely to have prevalent DR (multivariable adjusted OR 1.52; 95% CI 1.23–1.89, before adjustment for BMI) with the risk estimate declining in the fully adjusted model (multivariable adjusted OR 1.30; 95% CI 1.02–1.65) (Table 2).

Individuals with hyperinsulinemic type 2 diabetes had a lower risk of incident and progression of DR compared with individuals with classical type 2 diabetes (incident: multivariable adjusted HR 0.60; 95% CI 0.45–0.80; DR progression: multivariable adjusted HR 0.53; 95% CI 0.37–0.77) (Table 3). There was no clear difference between insulinopenic and classical type 2 diabetes (incident: multivariable adjusted HR 1.01; 95% CI 0.70–1.45; DR progression: multivariable adjusted HR 1.12; 95% CI 0.74–1.68). The results for both hyperinsulinemic and insulinopenic type 2 diabetes did not change in the sensitivity analysis in which we excluded individuals using insulin at cohort entry (Supplementary Table 1).

**Table 1—Characteristics of type 2 diabetes stratified by subtype**

| Characteristic | Overall | Classical | Hyperinsulinemic | Insulinopenic |
|---|---|---|---|---|
| Patients, *n* | 3,672 | 2,334 | 966 | 372 |
| Male sex, *n* (%) | 2,130 (58.0) | 1,383 (59.3) | 534 (55.3) | 213 (57.3) |
| Age, years (IQR) | 64.3 (55.7; 70.8) | 63.8 (55.4; 70.5) | 64.7 (56.0; 71.7) | 66.0 (56.9; 71.1) |
| Duration of diabetes, years (IQR) | 3.7 (2.3; 5.5) | 3.7 (2.3; 5.6) | 3.5 (2.2; 5.5) | 3.8 (2.4; 5.2) |
| Marital status, *n* (%) | | | | |
| Never married | 473 (12.9) | 305 (13.1) | 122 (12.6) | 46 (12.4) |
| Married | 2,263 (61.6) | 1,474 (63.2) | 556 (57.6) | 233 (62.6) |
| Widowed or divorced | 936 (25.5) | 555 (23.8) | 288 (29.8) | 93 (25.0) |
| CCI score, *n* (%) | | | | |
| 0 (low) | 2,699 (73.5) | 1,741 (74.6) | 668 (69.2) | 290 (78.0) |
| 1 (moderately low) | 452 (12.3) | 284 (12.2) | 128 (13.3) | 40 (10.8) |
| 2 (moderately high) | 337 (9.2) | 202 (8.7) | 106 (11.0) | 29 (7.8) |
| ≥3 (high) | 184 (5.0) | 107 (4.6) | 64 (6.6) | 13 (3.5) |
| Use of medication, *n* (%) | | | | |
| Insulin | 306 (8.3) | 201 (8.6) | 48 (5.0) | 57 (15.3) |
| Glucose-lowering treatment, excluding insulins | 3,190 (86.9) | 2,054 (88.0) | 820 (84.9) | 316 (84.9) |
| Antihypertensive drugs | 2,804 (76.4) | 1,742 (74.6) | 815 (84.4) | 247 (66.4) |
| Cholesterol-lowering drugs | 2,845 (77.5) | 1,794 (76.9) | 778 (80.5) | 273 (73.4) |
| Level of DR, *n* (%) | | | | |
| 0 (no DR) | 3,484 (94.9) | 2,208 (94.6) | 942 (97.5) | 334 (89.8) |
| 1 (mild DR) | 144 (3.9) | 96 (4.3) | 19 (2.0) | 29 (7.8) |
| 2 (moderate DR) | 33 (0.9) | 22 (0.9) | <5 | 7 (1.9) |
| 3 (severe DR) | 5 (0.1) | <5 | <5 | <5 |
| 4 (proliferative DR) | 6 (0.2) | <5 | <5 | <5 |
| Screening facility, *n* (%) | | | | |
| Private practice | 3,177 (86.5) | 1,995 (85.5) | 862 (89.2) | 320 (86.0) |
| Hospital | 495 (13.5) | 339 (14.5) | 104 (10.8) | 52 (14.0) |
| Laboratory results, median (IQR) | | | | |
| $HbA_{1c}$, mmol/mol | 48.5 (44.0; 55.3) | 50.0 (45.2; 57.0) | 46.0 (42.5; 51.1) | 48.0 (43.0; 54.1) |
| $HbA_{1c}$, % | 6.6 (6.2; 7.2) | 6.7 (6.3; 7.4) | 6.4 (6.0; 6.8) | 6.5 (6.1; 7.1) |
| eGFR, mmol/mol | 82.7 (70.1; 90.0) | 83.9 (71.6; 90.0) | 77.2 (64.0; 88.9) | 86.0 (77.0; 90.0) |
| Cholesterol, mmol/mol | 4.2 (3.6; 4.8) | 4.2 (3.7; 4.8) | 4.2 (3.6; 4.7) | 4.2 (3.7; 4.7) |
| HDL, mmol/mol | 1.2 (1.0; 1.5) | 1.2 (1.0; 1.4) | 1.1 (0.9; 1.4) | 1.5 (1.2; 1.8) |
| LDL, mmol/mol | 2.0 (1.6; 2.6) | 2.1 (1.6; 2.6) | 2.0 (1.5; 2.5) | 2.1 (1.6; 2.5) |
| Triglycerides, mmol/mol | 1.8 (1.3; 2.4) | 1.8 (1.3; 2.5) | 2.0 (1.5; 2.7) | 1.2 (0.9; 1.5) |
| uACR | 12.0 (6.0; 28.0) | 12.0 (6.1; 27.2) | 12.1 (6.5; 36.0) | 8.8 (5.2; 18.4) |
| HOMA2-B, % | 90.0 (68.5; 117.4) | 81.2 (65.6; 96.7) | 137.2 (124.8; 159.9) | 61.4 (48.0; 77.8) |
| HOMA2-S, % | 35.7 (26.9; 48.5) | 37.0 (29.3; 46.7) | 27.2 (21.9; 34.7) | 74.6 (68.6; 87.2) |
| BMI | 30.2 (26.9; 34.2) | 29.9 (26.9; 33.6) | 32.8 (29.4; 36.9) | 25.7 (23.4; 28.7) |

According to Danish legislation, we are not permitted to present data for fewer than five cases. eGFR, estimated glomerular filtration rate; uACR, urine albumin-to-creatinine ratio.

**Table 2—Data on presence of prevalent DR according to type 2 diabetes subtype**

| Subtype | DR no | DR yes | OR (95% CI) Crude | Age and sex adjusted | Multivariable model excluding BMI | Multivariable model |
|---|---|---|---|---|---|---|
| Classical | 2,208 | 126 | Reference | Reference | Reference | Reference |
| Hyperinsulinemic | 942 | 24 | 0.45 (0.29, 0.70) | 0.46 (0.30, 0.72) | 0.57 (0.36, 0.92) | 0.69 (0.42, 1.14) |
| Insulinopenic | 334 | 38 | 1.41 (1.17, 1.71) | 1.45 (1.20, 1.76) | 1.52 (1.23, 1.89) | 1.30 (1.02, 1.65) |

Multivariable logistic regression model adjusted for sex; age; civil status; diabetes duration; glucose-, lipid-, or blood pressure–lowering medication; BMI; $HbA_{1c}$; and a modified CCI.

We found a linear relationship between HOMA levels and increased risk of DR incidence and progression. HOMA2-B levels <100% correlated with higher risk, whereas for HOMA2-S, risk of DR incidence and progression started to increase at 50% (Supplementary Fig. 1).

## DISCUSSION

In this Danish cohort study involving 3,672 individuals with biochemically classified subtypes of type 2 diabetes, those with hyperinsulinemic type 2 diabetes had a 31% lower risk for present DR, 40% for upcoming DR, and 47% for worsening of DR. Individuals with insulinopenic type 2 diabetes had 30% higher risk of present DR at cohort entry, but there were no clear differences in DR incidence or progression between insulinopenic and classical type 2 diabetes. We also found that lower HOMA2-B values were associated linearly with an increasing incidence and progression of DR.

Duration of diabetes and degree of hyperglycemia are strong risk factors for developing DR in type 2 diabetes (1), but it is not fully understood how impaired β-cell function and insulin sensitivity associate with DR. Most studies have investigated the association of β-cell function and DR in people with a long duration of diabetes (3–7,19). The findings from the present study confirm the association found in previous studies in people with a short duration of type 2 diabetes. In addition, most studies did not take into consideration the intricate correlation between β-cell function and insulin sensitivity. Our results indicate that β-cell function is associated with DR independently of insulin resistance.

Suzuki et al. (19) reported low pancreatic β-cell insulin secretory capacity as a risk of proliferative DR, based on 10-year follow-up of 160 patients. Another 5-year prospective study of 233 individuals newly diagnosed with type 2 diabetes found that reduced β-cell function at baseline was associated with incident DR, also after adjustment for insulin sensitivity (20), which is in line with our findings. Likewise, Ahlqvist et al. (21) found that their severe insulin-deficient subtype, characterized by being GAD antibody negative, younger age at onset, relatively low BMI, low insulin secretion, and poor metabolic control, had the highest risk of DR. On the contrary, their severe insulin-resistant diabetes subtype, characterized by high BMI and insulin resistance, had the highest risk of kidney disease (21). A previous analysis demonstrated a 70% similarity between our hyperinsulinemic subtype and the severe insulin resistance diabetes identified by Ahlqvist et al. (21). Conversely, the similarity between the severe insulin deficient subtype and our insulinopenic subtype was limited (10). Studies outside Europe have reported the same results as Ahlqvist et al. (22,23). Of interest, we found that BMI had

**Table 3—Data on risk of incident and progression of DR according to subtype of type 2 diabetes**

| Subtype | Events, *n* | Person-years at risk | HR (95% CI) Crude | Age and sex adjusted | Multivariable model excluding BMI | Multivariable model |
|---|---|---|---|---|---|---|
| Risk of incidence | | | | | | |
| Classical | 259 | 11,136.4 | Reference | Reference | Reference | Reference |
| Hyperinsulinemic | 67 | 4,378.9 | 0.75 (0.58, 0.99) | 0.76 (0.58, 1.00) | 0.62 (0.47, 0.82) | 0.60 (0.45, 0.80) |
| Insulinopenic | 38 | 1,824.3 | 0.87 (0.62, 1.23) | 0.87 (0.62, 1.22) | 0.92 (0.65, 1.30) | 1.01 (0.70, 1.45) |
| Risk of progression | | | | | | |
| Classical | 186 | 11,383.1 | Reference | Reference | Reference | Reference |
| Hyperinsulinemic | 37 | 4,396.0 | 0.63 (0.44, 0.90) | 0.63 (0.44, 0.90) | 0.53 (0.37, 0.76) | 0.53 (0.37, 0.77) |
| Insulinopenic | 32 | 1,849.1 | 1.06 (0.73, 1.55) | 1.07 (0.74, 1.56) | 1.02 (0.69, 1.51) | 1.12 (0.74, 1.68) |

Multivariable logistic regression model adjusted for sex; age; civil status; diabetes duration; glucose-, lipid-, or blood pressure–lowering medication; BMI; $HbA_{1c}$; and a modified CCI (excluding diabetes).

a substantial effect on the DR risk estimate in our logistic regression model in the insulinopenic (and slimmer) subtype versus classical type 2 diabetes, in which we saw a clear reduction in the elevated relative risk estimate when adjusting for BMI. This suggests that obesity may be an important confounder or mediator of the diabetes phenotype associations with DR.

This study benefits from a longitudinal design and a large well-defined cohort, as well as the use of national registries with valid, accurate, and high completeness in combination with biochemical data. The limitations are also important to acknowledge. We were unable to investigate the risk of progression to proliferative DR, because there were few events. Furthermore, the study lacks information on socioeconomic characteristics, smoking status, and blood pressure. In addition, insulin use might have influenced HOMA values; however, excluding insulin users in a sensitivity analysis did not alter our findings. Last, a subsample of individuals did not have a screening episode registered in DiaBase, which might cause a selection bias.

In summary, the results from this study indicate that subcategorization of type 2 diabetes may be important to tailor individualized diabetes treatment and screen for diabetic complications in individuals with type 2 diabetes.

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**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** F.N.P. and J.G. designed the study. F.N.P., L.S., and S.M. performed the data and statistical analyses. F.N.P. drafted the manuscript with input from all authors. F.N.P. is the guarantor 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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