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Dementia Risk According to Indices of Insulin Sensitivity and Beta-Cell Function in Individuals With Newly Diagnosed Type 2 Diabetes: A Cohort Study

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ABSTRACT

Background: Insulin resistance and impaired insulin secretion are hallmarks of type 2 diabetes (T2D) and may influence risks of complications including dementia. We investigated dementia risk across T2D subgroups defined by beta-cell function and insulin sensitivity.

Methods: We used Homeostasis Model Assessment-2 indices of beta-cell function (HOMA2-B) and insulin sensitivity (HOMA2-S) to classify 7221 individuals with recently diagnosed T2D into insulinopenic (low HOMA2-B, high HOMA2-S), classical (low HOMA2-B, low HOMA2-S), and hyperinsulinemic (high HOMA2-B, low HOMA2-S) subgroups. Incident dementia was ascertained by validated hospital diagnosis codes and dementia-specific medication over 13 years. Absolute risks were estimated using the Aalen-Johansen estimator and adjusted hazard ratios (aHRs) using Cox regression.

Results: Over a median follow-up of 9 years, 179 (2.5%) developed dementia. The 10-year risk (95% CI) was 3.8% (2.4%–5.8%) in the insulinopenic subgroup versus 2.8% in both classical (2.3%–3.5%) and hyperinsulinemic (2.0%–3.8%) subgroups. Compared with classical T2D, aHRs (95% CI) were 1.31 (0.83–2.09) for insulinopenic and 1.10 (0.78–1.54) for hyperinsulinemic T2D. No robust associations with dementia were observed with insulin resistance (HOMA-IR) or C-peptide levels, although compared to the lowest C-peptide levels (quartile 1), aHRs (95% CI) were decreased at 0.67 (0.45–1.01) in quartile 2, 0.73 (0.48–1.09) in quartile 3, and 0.89 (0.59–1.33) in quartile 4.

Conclusions: We found no clear associations between T2D subgroup, insulin resistance, or C-peptide level at T2D diagnosis and dementia risk. The numerically higher risk in those with lower insulin secretion was statistically imprecise and warrants further study.

1 | Introduction

Type 2 diabetes (T2D) is a recognized risk factor for dementia [1]. Despite strong evidence of 1.5- to twofold higher risk of Alzheimer's disease (AD) and vascular dementia (VaD) in individuals with T2D compared with the general population [2, 3], the mechanisms linking T2D to dementia remain incompletely understood. Atherosclerosis-driven cerebrovascular disease and chronic hyperglycemia are known to contribute to the association; however, impaired insulin signaling has recently been identified as an additional possible pathophysiological pathway [4].

Insulin plays a critical role in the central nervous system, potentially influencing memory formation by modulating brain glucose metabolism, synaptic plasticity, and neurotransmission [5–7]. Intranasal insulin administration, which delivers insulin directly to the brain, has been shown to enhance cognitive performance in individuals with and without memory impairment [8]. In postmortem brain tissue from individuals with AD, impaired brain insulin signaling has been observed and linked to disease severity [9]. This suggests that both reduced brain insulin availability and sensitivity may contribute to neurodegeneration. As brain insulin primarily originates from peripheral circulation [7], systemic insulin levels may serve as an indicator of dementia risk. Furthermore, peripheral insulin resistance has been associated with a reduced cerebrospinal fluid to serum insulin ratio, suggesting impaired transport of insulin into the brain, as well as with brain insulin resistance [10, 11]. Consequently, insulin resistance and/or impaired insulin secretion could be important predictors of dementia.

In newly diagnosed T2D, individuals can be classified into three pathophysiological subgroups—insulinopenic, classical, and hyperinsulinemic—using the Homeostasis Model Assessment-2 (HOMA2) indices of beta-cell function and insulin sensitivity [12]. The insulinopenic subgroup is characterized by preserved insulin sensitivity but substantial beta-cell dysfunction, reflected in low C-peptide levels. The classical subgroup, which is most prevalent, exhibits both insulin resistance and beta-cell dysfunction. The hyperinsulinemic subgroup displays pronounced insulin resistance with compensatory high beta-cell function, severe obesity, and extensive metabolic derangement. These metabolic traits might lead to different dementia risks.

Observational studies have demonstrated that pronounced peripheral insulin resistance and hyperinsulinemia accelerate cognitive decline and increase the risk of dementia [13–21]. Yet the impact of low beta-cell function/insulin secretion on dementia incidence has been less extensively investigated but may be equally, if not more, consequential [22, 23]. Prior studies excluded individuals with diabetes or did not stratify participants by diabetes status, leaving the specific contributions of insulin resistance and secretion in T2D unclear. This question is especially relevant in newly diagnosed T2D, where targeted preventive interventions could yield the greatest benefit.

To address this knowledge gap, we analyzed data from a large, national cohort of individuals with newly diagnosed T2D to test the hypothesis that the hyperinsulinemic and/or insulinopenic subgroups had a higher risk of incident dementia than the classical subgroup. We further examined how quartiles of insulin resistance (HOMA2-IR) and fasting C-peptide (a marker of insulin secretion) were associated with subsequent dementia risk.

2 | Method

2.1 | Study Cohort, Setting, and Ethics

We conducted a cohort study using data from the nationwide Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort [24, 25]. The DD2 cohort has since 2010 enrolled individuals with newly diagnosed T2D from general practitioners and hospital outpatient clinics across Denmark [26]. All Danish citizens aged 18 years or older with recently diagnosed T2D (diagnosed according to the Danish and international guidelines, adhering to WHO criteria [27]) are eligible for participation. At enrollment, participants undergo an interview, clinical examination, and collection of blood and urine samples. Data and samples are then stored in a research database and biobank [28]. All participants in the DD2 study have provided written informed consent, and the DD2 study has been approved by the Danish Data Protection Agency (record numbers 2008-58-0035 and 2016–051-000001/2514) and the Regional Committees on Health Research Ethics for Southern Denmark (record number S-20100082) and is carried out in accordance with the Declaration of Helsinki.

The tax-supported Danish National Health Service provides universal healthcare and partial reimbursement for prescribed medications for all Danish residents [29]. The unique civil personal registration number assigned at birth or upon immigration enables linkage of DD2 data to ongoing national health registries and databases for ascertainment of additional participant characteristics and prospective follow-up [30]. The linked registries and databases used in this study were: The Danish Civil Registration System [30] for data on demographics and vital status; the Register of Laboratory Results for Research [31] for biomarkers assessed during routine clinical care in primary and secondary care; the Danish Diabetes Database for Adults [32] for data on clinical and lifestyle factors; the Danish National Patient Registry [33] for nationwide data on hospital diagnosis and procedure codes; and the Danish National Prescription Registry [29] for data on redeemed drug prescriptions from local Danish pharmacies. A detailed description of the registries is provided in Table S1 and Figure S1.

This study is reported in accordance with the STROBE statement and the STROND recommendations (see Files S1 and S2).

2.2 | Study Cohort

We included participants that were enrolled in the DD2 cohort between November 2010 and March 31, 2022 ($n = 10{,}013$) unless they met the following exclusion criteria: (1) residence in Denmark for <1 year prior to enrollment; (2) diagnosed with other specific forms of diabetes (Table S1); (3) pre-existing dementia diagnosis or redeemed prescription for dementia-specific medication; or (4) absence of a fasting blood sample in the DD2 biobank analyzed for plasma glucose and serum C-peptide (Figure 1).

2.3 | T2D Subgroups, Insulin Resistance, and C-Peptide Levels

We used fasting glucose and C-peptide measurements in the HOMA2 computational model (University of Oxford, Oxford, UK) to estimate beta-cell function (HOMA2-B), insulin sensitivity (HOMA2-S), and insulin resistance (HOMA2-IR) [34, 35]. Details on sample preparation and analysis are provided in Table S1.

Our primary exposure was T2D subgroups defined following previous descriptions [12, 36–38]. Participants with insulinopenic

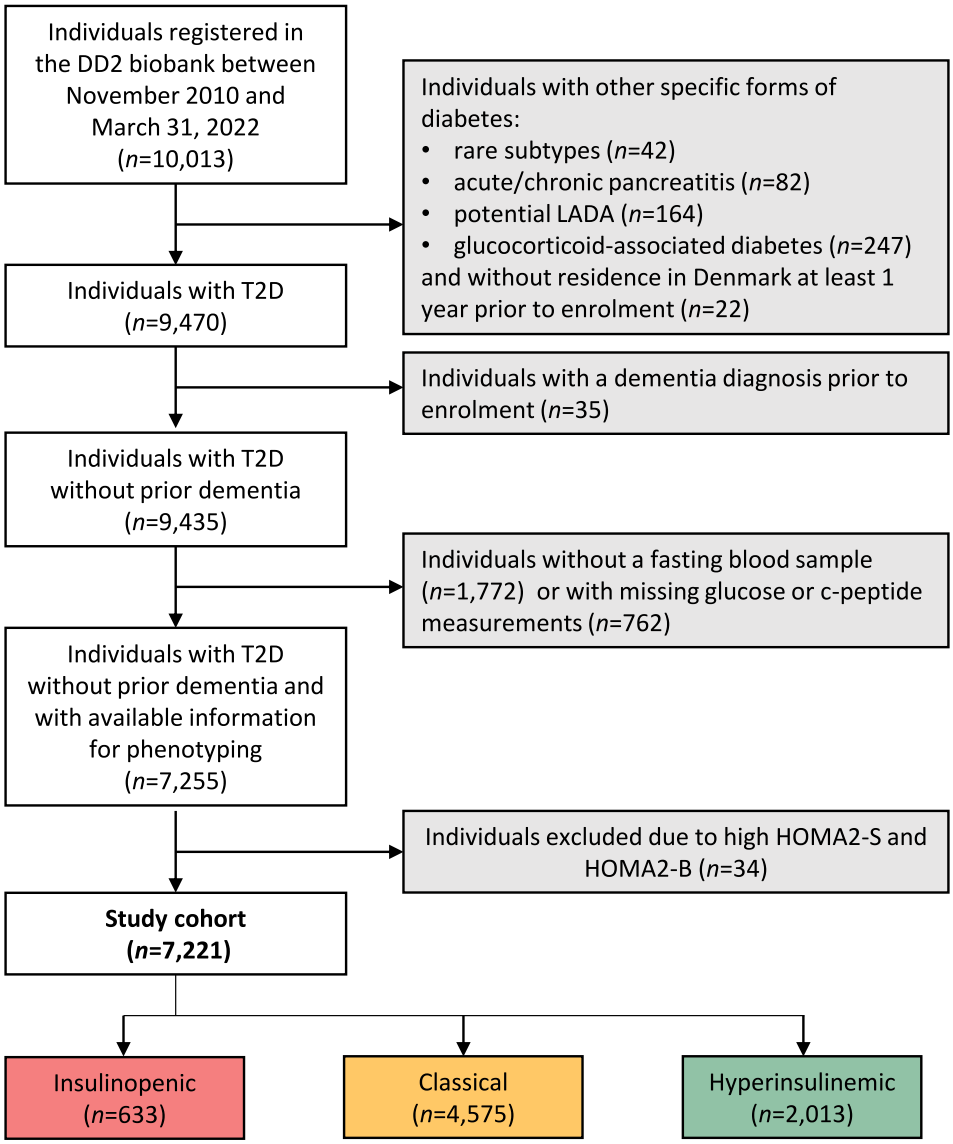

FIGURE 1 | Flow chart of the study cohort. Enrolled participants were grouped by insulin sensitivity (HOMA2-S) and beta-cell function (HOMA2-B) into insulinopenic (high HOMA2-S, low HOMA2-B), classical (low HOMA2-S, low HOMA2-B), or hyperinsulinemic (low HOMA2-S, high HOMA2-B) type 2 diabetes using the cut-off values 63.5% for HOMA2-S and 115.3% for HOMA2. Individuals with high HOMA2-S and high HOMA2-B were excluded from the analysis because of the small number of individuals ($n = 34$). Details on data sources and codes used for defining variables are provided in Table S1. Abbreviations: DD2, Danish Centre for Strategic Research in Type 2 Diabetes; HOMA2, homeostasis model assessment-2; LADA, latent autoimmune diabetes of adults; T2D, type 2 diabetes.

T2D had high HOMA2-S and low HOMA2-B, classical T2D had low HOMA2-S and low HOMA2-B, and hyperinsulinemic T2D had low HOMA2-S and high HOMA2-B. Cut-offs for high and low values were 63.5% for HOMA2-S and 115.3% for HOMA2-B, which were derived from the median values in a cohort with normal fasting glucose levels ($n = 483$) [12]. Participants with high HOMA2-S and high HOMA2-B were excluded due to the small sample size ($n = 34$). Quartiles of HOMA2-IR and fasting serum C-peptide levels were used as secondary exposures.

2.4 | Dementia and All-Cause Mortality

Our primary endpoint was any dementia, identified by the first occurrence of either: (1) a hospital-based inpatient, emergency, or outpatient record of a dementia diagnosis in the Danish National Patient Registry [33] using International Classification of Diseases 10th revision codes, or (2) a redeemed prescription for dementia specific medication in the Danish National Prescription Registry [29] (Table S1). This definition reflects established dementia rather than prodromal stages. The validity of registry-based dementia diagnoses is high, with a positive predictive value (PPV) of 86% for any dementia. The PPV for AD is 81% and 52% for non-AD dementias (combined VaD and other/unspecified dementia) [39].

Given the competing risk of death in dementia research [40], we included all-cause mortality as a secondary endpoint. The date of death was procured from the Danish Civil Registration System [30].

2.5 | Covariates

Participant characteristics and potentially important dementia risk factors were assessed at DD2 enrollment and extracted from linked registries. We obtained key variables from the DD2 cohort and the Danish Diabetes Database for Adults [32], including anthropometric (waist circumference and BMI), clinical (blood pressure), lifestyle (physical activity level, alcohol consumption, and smoking status), and biomarker (high-sensitivity C-reactive protein [hs-CRP]) measures. Additional routine care laboratory biomarkers were obtained from the Register of Laboratory Results for Research [31]. Comorbidities and medication use were extracted from the Danish National Patient Registry [33] and the Danish National Prescription Registry, respectively [29]. All definitions and operationalizations are provided in Table S1.

2.6 | Statistical Analyses

Baseline characteristics by T2D subgroup were summarized as medians and interquartile ranges (IQR) for continuous variables and percentages for categorical variables. We also assessed potential selection bias by summarizing baseline characteristics of individuals excluded due to missing fasting glucose or C-peptide.

Participants were followed from the date of DD2 enrollment until the first occurrence of dementia, death, emigration, or study end (November 30, 2023), whichever occurred first. The Aalen-Johansen estimator was used to compute the 10-year cumulative incidence of dementia with death as a competing risk. We used the complement of the Kaplan–Meier estimator (1-KM) to plot all-cause mortality curves by T2D subgroup. Incidence rates (IR) of dementia and all-cause mortality were calculated as the number of events divided by 1000 person-years and 95% confidence intervals (CI) of IR were estimated by exact Poisson confidence limits.

A Cox proportional hazards regression model was used to calculate crude and adjusted hazard ratios (HRs) with 95% CIs. Model adjustments (main model) were based on known confounders in dementia research and a prespecified Direct Acyclic Graph (DAG) (Figure S2), and included the following adjustments: age (continuous variable), sex (male or female), diabetes duration (years since T2D diagnosis; continuous variable), alcohol consumption (fewer or more than 14 drinks/week for women and 21 drinks/week for men), physical activity level (categorized as 0–1, 2–4, or ≥5 days per week with ≥30 min physical activity), history of depression (dichotomized), previous stroke events (dichotomized), and insulin use (dichotomized). Continuous variables were modeled as a linear function. Similar analyses were performed using quartiles of HOMA2-IR and fasting serum C-peptide levels as exposures and with dementia subtypes (AD and non-AD) as outcomes. In our DAG we defined obesity as a mediator, but because obesity also may act as a confounder in the T2D-dementia pathway [1], we performed an exploratory analysis with waist circumference added to the model as a natural cubic spline with three knots. Complete case analyses were performed because the proportions of missing data in the covariates included in the adjustment models were low (<0.5%; Table S2). The proportional hazards assumption and functional forms of continuous covariates were verified by visual inspection of score processes and cumulative martingale residuals, and no violations were found. Data management and statistical analyses were performed in SAS software, version 9.4 (Cary, NC, USA).

3 | Results

3.1 | Cohort Characteristics

Among the 10,013 enrolled in the DD2 cohort, few with T2D had a dementia diagnosis upon enrollment ($n=35$; <0.5%). In total, 7221 (72%) participants had fasting glucose and C-peptide measurements and could be categorized into the three T2D subgroups: insulinopenic (9%), classical (63%), and hyperinsulinemic (28%). Participants without fasting glucose or C-peptide measurements ($n=2180$; 22%) had similar baseline characteristics to those included (Table S3).

Compared to the classical T2D subgroup, the insulinopenic subgroup exhibited the lowest values for BMI, waist circumference, *hs*-CRP, triglycerides, and these individuals had a lower frequency of depression and previous stroke events at baseline. Conversely, the hyperinsulinemic subgroup showed the highest values for these characteristics and individuals had the shortest diabetes duration at enrollment. The insulinopenic subgroup was also more frequently treated with insulin at enrollment than the other subgroups (Table 1).

3.2 | T2D Subgroups and Risk of Dementia

Over a median follow-up of 9.0 years (IQR: 5.4 to 10.5 years), 179 participants (2.5%) developed dementia. This included 69 cases of AD, 12 cases of VaD, 67 cases of other/unspecified dementia, and 31 cases with more than one subtype. In the follow-up period, 929 individuals died.

The overall 10-year cumulative incidence of dementia in the cohort was 2.9% (95% CI: 2.5–3.4). The insulinopenic subgroup had the highest risk of 3.8% (95% CI: 2.4–5.8) compared to 2.8% for both the classical (95% CI: 2.3–3.5) and the hyperinsulinemic (95% CI: 2.0–3.8) subgroups (Figure 2A). Corresponding incidence rates per 1000 person-years were 4.2 (95% CI: 2.6–6.3) in the insulinopenic subgroup, 2.9 (95% CI: 2.3–3.5) in the classical subgroup, and 3.4 (95% CI: 2.5–4.4) in the hyperinsulinemic subgroup. Compared to the classical subgroup, the aHRs in the main model showed a modest (but statistically imprecise) increased risk at 1.31 (95% CI: 0.83–2.09) for the insulinopenic subgroup. In comparison, no clear difference was shown for the hyperinsulinemic subgroup with an aHR of 1.10 (95% CI: 0.78–1.54) (Table 2). Additional adjustment for waist circumference attenuated the HR for the insulinopenic subgroup to 1.14 (95% CI: 0.70–1.84) but left the HR unchanged for the hyperinsulinemic subgroup at 1.16 (95% CI: 0.82–1.64) (Table S4).

Across dementia subtypes, the insulinopenic subgroup showed the highest 10-year cumulative incidence of AD, whereas the classical and hyperinsulinemic subgroups had similar risks (Figure S3). Compared with the classical group, the aHRs for AD were 1.55 (95% CI: 0.84–2.84) in the insulinopenic

TABLE 1 | Baseline characteristics of the study cohort of 7221 individuals with newly diagnosed T2D, by pathophysiological subgroup.

	Insulinopenic	Classical	Hyperinsulinemic	All
No. of participants, *n* (%)	633 (8.8)	4575 (63.4)	2013 (27.9)	7221 (100.0)
Year of enrollment, *n* (%)				
2010–2013	314 (49.6)	2023 (44.2)	857 (42.6)	3194 (44.2)
2014–2017	221 (34.9)	1626 (35.5)	626 (31.1)	2473 (34.2)
2018–2022	98 (15.5)	926 (20.2)	530 (26.3)	1554 (21.5)
Age, years	63 (55; 70)	61 (53; 68)	62 (52; 69)	62 (53; 69)
Males, *n* (%)	376 (59.4)	2781 (60.8)	1107 (55.0)	4264 (59.0)
Marital status, *n* (%)				
Married	393 (62.1)	2820 (61.6)	1157 (57.5)	4370 (60.5)
Unmarried	88 (13.9)	722 (15.8)	333 (16.5)	1143 (15.8)
Divorced	93 (14.7)	715 (15.6)	346 (17.2)	1154 (16.0)
Widowed	59 (9.3)	318 (7.0)	177 (8.8)	554 (7.7)
Diabetes duration, years	1.5 (0.5; 3.2)	1.5 (0.5; 3.1)	1.1 (0.4; 2.5)	1.4 (0.5; 3.0)
BMI, kg/m^2	26 (23; 29)	30 (27; 34)	34 (30; 38)	31 (27; 35)
BMI, kg/m^2, *n* (%)				
<25	189 (41.1)	311 (9.7)	69 (4.7)	569 (11.1)
25–<30	188 (40.9)	1148 (35.8)	336 (22.8)	1672 (32.6)
30–<35	68 (14.8)	1018 (31.8)	469 (31.9)	1555 (30.3)
≥ 35	15 (3.3)	727 (22.7)	598 (40.6)	1340 (26.1)
Waist circumference, cm	94 (86; 101)	106 (98; 116)	113 (103; 123)	107 (98; 117)
Waist: hip ratio	0.9 (0.9; 1.0)	1.0 (0.9; 1.0)	1.0 (0.9; 1.1)	1.0 (0.9; 1.0)
Excessive alcohol consumption*, *n* (%)	36 (5.7)	305 (6.7)	93 (4.6)	434 (6.0)
Days/week with ≥ 30 min physical activity, %				
0–1 days per week	12	21	28	22
2–4 days per week	35	38	36	37
5–7 days per week	53	42	36	41
Smoking status, *n* (%)				
Never	218 (53.6)	1269 (47.6)	508 (44.1)	1995 (47.2)
Former	124 (30.5)	911 (34.2)	425 (36.9)	1460 (34.6)
Current	65 (16.0)	485 (18.2)	218 (18.9)	768 (18.2)
HOMA2-IR	1.3 (1.1; 1.5)	2.8 (2.2; 3.5)	3.7 (2.9; 4.6)	2.9 (2.1; 3.8)
HOMA2-S, %	75 (69; 88)	36 (29; 46)	27 (22; 35)	35 (26; 47)
HOMA2-B, %	63 (48; 78)	82 (65; 97)	138 (125; 161)	92 (69; 119)
Fasting C-peptide, pmol/L	550 (470; 600)	1080 (880; 1340)	1580 (1260; 1920)	1150 (870; 1520)
Fasting plasma glucose, mmol/L	6.5 (5.9; 7.5)	7.8 (7.0; 8.9)	6.4 (5.9; 7.0)	7.2 (6.4; 8.3)
hsCRP, mg/L	0.8 (0.4; 2.0)	1.9 (0.8; 4.1)	2.6 (1.1; 5.3)	2.0 (0.8; 4.4)
HbA1C, mmol/mol	46 (42; 52)	49 (44; 55)	45 (41; 49)	47 (43; 53)
Systolic blood pressure, mmHg	130 (124; 138)	131 (125; 140)	130 (121; 140)	130 (124; 140)

(Continues)

TABLE 1 | (Continued)

	Insulinopenic	Classical	Hyperinsulinemic	All
Diastolic blood pressure, mmHg	80 (73; 85)	80 (75; 86)	80 (73; 85)	80 (75; 86)
Total cholesterol, mmol/L	4.2 (3.6; 4.9)	4.3 (3.7; 5.0)	4.2 (3.5; 4.9)	4.2 (3.6; 5.0)
HDL cholesterol, mmol/L	1.4 (1.2; 1.7)	1.2 (1.0; 1.4)	1.1 (0.9; 1.3)	1.2 (1.0; 1.4)
LDL cholesterol, mmol/L	2.1 (1.7; 2.8)	2.2 (1.7; 2.9)	2.1 (1.6; 2.7)	2.2 (1.7; 2.8)
Triglycerides, mmol/L	1.1 (0.8; 1.5)	1.7 (1.2; 2.4)	1.8 (1.3; 2.6)	1.7 (1.2; 2.4)
Albumin-creatinine ratio, *n* (%)				
Normal/no albuminuria (< 30 mg/g)	395 (84.2)	2623 (79.5)	1162 (77.6)	4180 (79.4)
Microalbuminuria (30–300 mg/g)	69 (14.7)	613 (18.6)	294 (19.6)	976 (18.5)
Macroalbuminuria (> 300 mg/g)	5 (1.1)	64 (1.9)	42 (2.8)	111 (2.1)
Modified Charlson Comorbidity Index, *n* (%)				
0	509 (80.4)	3415 (74.6)	1307 (64.9)	5231 (72.4)
1–2	102 (16.1)	1001 (21.9)	578 (28.7)	1681 (23.3)
≥ 3	22 (3.5)	159 (3.5)	128 (6.4)	309 (4.3)
Depression, *n* (%)	68 (10.7)	621 (13.6)	384 (19.1)	1073 (14.9)
Stroke, *n* (%)	23 (3.6)	255 (5.6)	131 (6.5)	409 (5.7)
Medication, *n* (%)				
No glucose-lowering drug use	90 (14.2)	668 (14.6)	300 (14.9)	1058 (14.7)
Metformin	518 (81.8)	3795 (83.0)	1654 (82.2)	5967 (82.6)
DPP-4 inhibitors	60 (9.5)	454 (9.9)	108 (5.4)	622 (8.6)
GLP-1 RA	26 (4.1)	257 (5.6)	147 (7.3)	430 (6.0)
SGLT2 inhibitors	19 (3.0)	168 (3.7)	35 (1.7)	222 (3.1)
SU and meglitinides	41 (6.5)	278 (6.1)	69 (3.4)	388 (5.4)
Insulin	83 (13.1)	223 (4.9)	77 (3.8)	383 (5.3)
Lipid-lowering drugs	421 (66.5)	3159 (69.0)	1438 (71.4)	5018 (69.5)
Anti-hypertensive drugs	353 (55.8)	3165 (69.2)	1590 (79.0)	5108 (70.7)
Anti-thrombotic drugs	136 (21.5)	1171 (25.6)	654 (32.5)	1961 (27.2)

Note: Data are presented as median (interquartile range) unless otherwise specified. Definitions of covariates are provided in Table S1, and an overview of missing values is provided in Table S2. C-peptide is rounded to the nearest 10 pmol/L for masking purposes.
Abbreviations: BMI, body mass index; DPP-4, dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide 1; HbA1c, Glycated hemoglobin; *HDL*, High-density lipoprotein; *HOMA2*, homeostasis model assessment-2; *hs*-CRP, high-sensitivity C-reactive protein; *LDL*, Low-density lipoprotein; SGLT2, sodium–glucose cotransporter 2; SU, sulfonylureas.
*More than 14/21 units/week (female/male).

subgroup and 1.05 (95% CI: 0.66–1.69) in the hyperinsulinemic subgroup. For non-AD dementia, the insulinopenic subgroup showed no clear association (aHR 0.97; 95% CI: 0.48–1.97), while the hyperinsulinemic subgroup had a modest but imprecise elevation in risk (aHR 1.25; 95% CI: 0.80–1.94) (Table S5).

3.3 | C-Peptide, Insulin Resistance, and Risk of Dementia

Across C-peptide quartiles, the crude 10-year cumulative incidence curves suggested a higher dementia risk in the group with lowest C-peptide levels (Figure 2B). Compared with the 1st C-peptide quartile, the aHRs were 0.67 (95% CI: 0.45–1.01) in quartile 2, 0.73 (95% CI: 0.48–1.09) in quartile 3, and 0.89 (95% CI: 0.59–1.33) in quartile 4 (Table 2). Similarly, the crude 10-year cumulative incidence curves showed the numerically highest dementia risk in the group with lowest HOMA2-IR (Figure 2C). The aHRs for dementia among the more insulin resistant, compared to those with less insulin resistance (HOMA2-IR quartile 1) were 0.79 (95% CI: 0.54–1.17) in quartile 2, 0.82 (95% CI: 0.55–1.24) in quartile 3, and 0.90 (95% CI: 0.59–1.37) in quartile 4 (Table 2). Across dementia subtypes, we found no trend toward higher HOMA2-IR or C-peptide values in AD versus non-AD (Table S5).

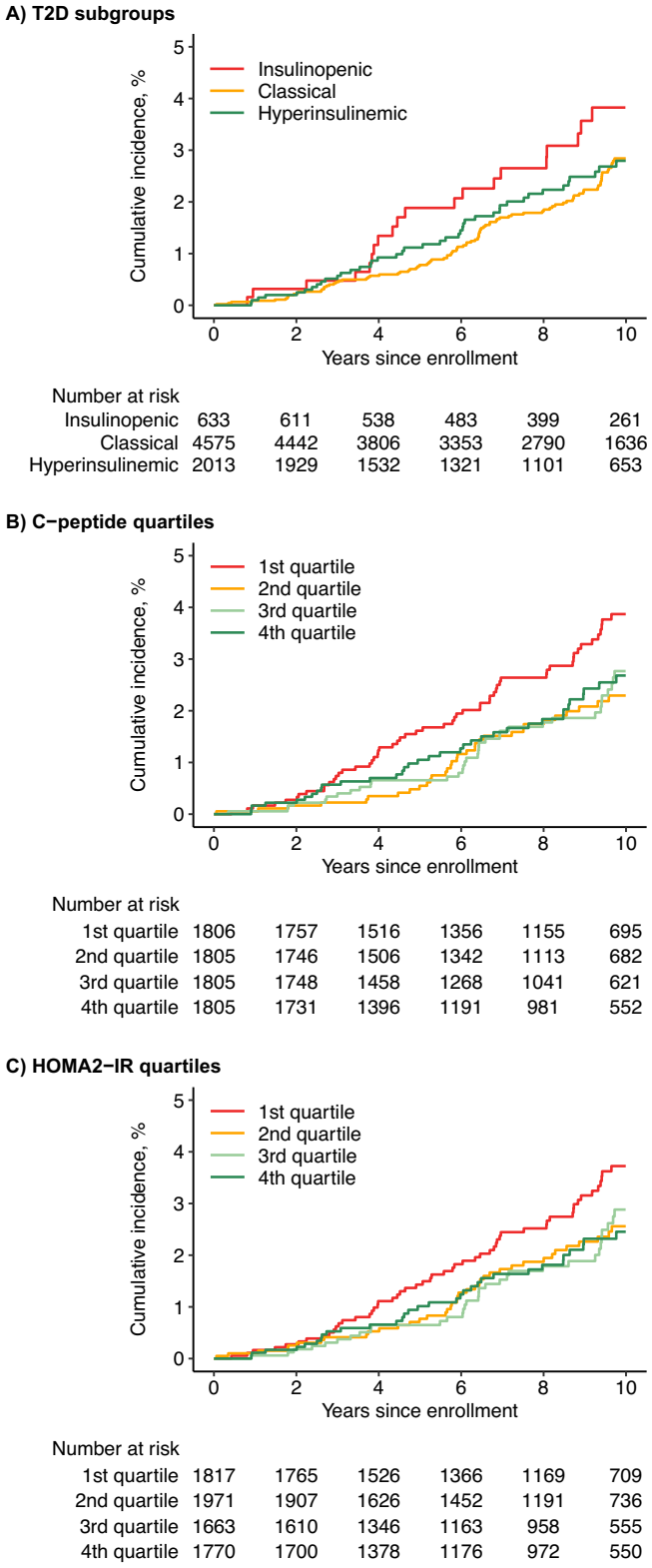

FIGURE 2 | Cumulative incidence of dementia by type 2 diabetes subgroup (A), C-peptide quartile (B), and HOMA2-IR quartile (C). Estimates are based on the method of Aalen-Johansen, taking the competing risk of death into account.

3.4 | All-Cause Mortality

The 10-year mortality risk was 15.6% (95% CI: 14.6–16.7) in the cohort. The hyperinsulinemic subgroup had the highest mortality at 18.9% (95% CI: 16.9–21.1), followed by the insulinopenic subgroup at 15.6% (95% CI: 12.6–18.9), and the classical subgroup at 14.3% (95% CI: 13.1–15.5) (Figure S4). Accordingly, the aHRs for mortality were 1.04 (95% CI: 0.83–1.30) in the insulinopenic and 1.29 (95% CI: 1.12–1.49) in the hyperinsulinemic compared with the classical subgroup (Table S6).

The highest C-peptide and HOMA2-IR levels showed increased mortality compared to the lowest levels. Compared with the 1st C-peptide quartile, the aHRs were 0.95 (95% CI: 0.79–1.15) in quartile 2, 1.12 (95% CI: 0.93–1.34) in quartile 3, and 1.37 (95% CI: 1.14–1.64) in quartile 4. Similar associations were found based on HOMA2-IR levels (Table S6).

4 | Discussion

In this nationwide cohort study of individuals with newly diagnosed T2D recruited from routine clinical care settings, we found no robust association between T2D subgroups and risk of incident dementia. The risk of dementia was 30% higher in the insulinopenic subgroup versus the classical subgroup, yet this finding lacked statistical precision related to relatively few dementia events over 13 years of follow-up. Also, the association between elevated levels of C-peptide and HOMA2-IR was consistently below 1, compared to lower levels. These findings suggest the possibility that impaired beta-cell function and low C-peptide levels might contribute to dementia risk. Finally, we found a higher mortality in the hyperinsulinemic T2D subgroup and in those with elevated C-peptide and HOMA2-IR levels, consistent with prior studies [41].

Classifying T2D into pathophysiological subgroups has been proposed as a step toward more tailored diabetes management and has proven effective in assessing risks for micro- and macrovascular complications [36–38]. However, in our study, we did not find a strong association between T2D subgroups and risk of developing dementia. While the limited number of dementia cases restricted our ability to draw strong conclusions, the observed trend of increased dementia risk among individuals with lower C-peptide levels aligns with existing literature. Prior studies have found non-linear associations between insulin levels and dementia risk suggesting that those with low insulin levels have an elevated risk of developing dementia [22, 23]. Furthermore, polygenic risk scores for fasting insulin have shown negative associations with dementia risk, and both reduced insulin responses and genetically predicted lower HOMA-beta-cell function have been associated with an increased risk of AD [21, 42, 43]. Collectively, this points toward beta-cell dysfunction and low insulin levels as possible predictors of dementia.

Unlike our findings for the hyperinsulinemic subgroup of T2D, earlier cohort studies without or with few diabetes cases at baseline have reported an association between insulin resistance and compensatory hyperinsulinemia—key traits of the hyperinsulinemic subgroup—and increased dementia risk [20, 21]. A possible explanation for this discrepancy is that the adverse effects of hyperinsulinemia may diminish or become less pronounced after diabetes onset, with other factors emerging as primary contributors to dementia risk. Supporting this

TABLE 2 | Incidence rates and HRs for dementia by T2D subgroup, HOMA2-IR quartile, and C-peptide quartile.

Exposure	Events	Person-years	Incidence rate (95% CI)	Crude model HR (95% CI)	Main model aHR (95% CI)
Subgroup					
Classical	106	36,963	2.9 (2.3; 3.5)	1 (reference)	1 (reference)
Insulinopenic	22	5262	4.2 (2.6; 6.3)	1.44 (0.91; 2.27)	1.31 (0.83; 2.09)
Hyperinsulinemic	51	15,190	3.4 (2.5; 4.4)	1.19 (0.85; 1.67)	1.10 (0.78; 1.54)
HOMA2-IR					
HOMA2-IR 1st quartile	58	15,023	3.9 (2.9; 5.0)	1 (reference)	1 (reference)
HOMA2-IR 2nd quartile	46	15,943	2.9 (2.1; 3.8)	0.75 (0.51; 1.11)	0.79 (0.54; 1.17)
HOMA2-IR 3rd quartile	38	13,007	2.9 (2.1; 4.0)	0.78 (0.52; 1.17)	0.82 (0.55; 1.24)
HOMA2-IR 4th quartile	37	13,443	2.8 (1.9; 3.8)	0.74 (0.49; 1.12)	0.90 (0.59; 1.37)
C-peptide					
C-peptide 1st quartile	60	14,910	4.0 (3.1; 5.2)	1 (reference)	1 (reference)
C-peptide 2nd quartile	38	14,703	2.6 (1.8; 3.5)	0.64 (0.43; 0.97)	0.67 (0.45; 1.01)
C-peptide 3rd quartile	40	14,175	2.8 (2.0; 3.8)	0.72 (0.48; 1.07)	0.73 (0.48; 1.09)
C-peptide 4th quartile	41	13,627	3.0 (2.2; 4.1)	0.78 (0.52; 1.15)	0.89 (0.59; 1.33)

Note: Crude incidence rates are per 1000 person-years with exact 95% Poisson confidence intervals. Hazard ratios (HR) for the main model were adjusted for sex, age, diabetes duration, alcohol consumption, physical activity level, depression, stroke, and insulin use.

hypothesis, a US cohort study of 683 individuals found a link between hyperinsulinemia and dementia risk, with a HR of 2.1 (95% CI: 1.5–2.9). When stratified by diabetes status, a strong association was observed in those without diabetes (HR of 2.3 [95% CI: 1.5–3.6]), while the association was weaker in those with diabetes (HR of 1.5 [95% CI: 0.8–2.9]) [19]. Additionally, the fact that the hyperinsulinemic subgroup exhibited the highest mortality rate may relate to a lower probability of developing dementia if otherwise dementia-prone individuals died early from other reasons.

The insulinopenic subgroup exhibited characteristics such as less abdominal obesity, lower inflammation, a more favorable lipid profile, and fewer comorbidities—including depression and stroke—suggesting a possible distinct pathway to dementia that diverges from the traditional metabolic and vascular mechanisms [44]. The attenuation of risk estimates after adjusting for waist circumference suggests that body composition may influence this association, either through confounding or mediation. This aligns with the subgroup's lower adiposity and leaves open the possibility that inherent physiology or early frailty-related weight loss could contribute to the observed pattern. In contrast, the hyperinsulinemic subgroup's greater vascular burden is more consistent with mechanisms typically implicated in vascular dementia. The insulinopenic subgroup showed numerically higher rates of AD, and the hyperinsulinemic subgroup slightly higher estimates for non-AD dementia, but these differences were highly uncertain due to the small number of subtype-specific cases. Interpretation of non-AD outcomes is further limited by the comparatively poor diagnostic validity of this category [39]. Further studies are needed to clarify these potential subgroup-specific pathways.

This study has several strengths. First, the cohort consisted of individuals with recent-onset T2D, enabling the identification of potential early markers of dementia risk. Second, the use of register-based data limited selection bias during follow-up. However, several limitations must be acknowledged. First, the small number of dementia events, even after 13 years of follow-up, limited the statistical precision of our findings, necessitating further research to confirm observed associations. Most dementia events ($n = 149$; $> 80\%$) occurred at least 3 years after cohort enrollment, and although dementia develops over a long time, this does not suggest a major risk of reverse causality with incubating dementia symptoms having led to T2D diagnosis in our study. Not all dementia cases may have been captured in hospital records or through dementia medication prescriptions, though this limitation likely applies uniformly across T2D subgroups. Furthermore, we lacked genetic data to identify carriers of the apolipoprotein E ε4 allele (*APOE* ε4), the strongest genetic risk factor for AD. While some studies suggest that *APOE* ε4 carriage is more prevalent among individuals with low insulin levels [22], others report a heightened dementia risk among *APOE* ε4 carriers with hyperinsulinemia [21]. Thus, we cannot exclude the possibility that *APOE* ε4 stratification could have influenced our results. The absence of these data therefore adds to the overall uncertainty of our findings and limits the ability to fully assess potential interactions between T2D subgroups and genetic risk. Another limitation is the use of the HOMA2 calculator, which provides only steady-state estimates of insulin sensitivity, beta-cell function, and insulin resistance. Dynamic measures could potentially offer greater insight into the mechanisms linking T2D subgroup to dementia risk. Moreover, blood samples were collected only at enrollment, limiting our ability to account for changes in subgroup classification over time due

to disease progression, lifestyle changes, or initiation of new glucose-lowering medications. Most participants had already initiated treatment at enrollment, and although only minor differences, except for insulin use, were found between subgroups, potential confounding by indication cannot be entirely ruled out, as the likelihood of receiving glucose-lowering medication with potential for decreasing dementia risk may differ among T2D subgroups over the course of disease. Residual confounding may also affect our study due to missing or partially missing data for variables such as educational level, socioeconomic status, smoking habits, blood pressure, and BMI. Finally, while the DD2 cohort is broadly representative of individuals with T2D treated in routine clinical care in Denmark [26], results may not be generalizable to all settings.

In conclusion, our findings do not suggest any strong effect of insulin resistance or beta-cell function on dementia risk in individuals with newly diagnosed T2D. Given the limited number of dementia events and thus statistical uncertainty, the study was underpowered to detect modest associations between T2D subgroups or C-peptide levels and dementia risk. Accordingly, the observed numerical differences should be interpreted with caution, as they may reflect random variation. Further investigation in large T2D cohorts with extended follow-up and dementia assessment is needed to more reliably evaluate potential subgroup differences in T2D.

Author Contributions

Nicole Jacqueline Jensen, Allan Vaag, Reimar Wernich Thomsen, and Jørgen Rungby participated in the conceptualization of the overarching DD2 project, for which Nicole Jacqueline Jensen is the principal manager. Nicole Jacqueline Jensen, Reimar Wernich Thomsen, and Jørgen Rungby took initiative in planning the present study, and Frederik Pagh Bredahl Kristensen and Jens Steen Nielsen contributed to the study design. Nicole Jacqueline Jensen formulated the statistical analysis plan under the supervision of Astrid Kousholt, Frederik Pagh Bredahl Kristensen, Reimar Wernich Thomsen, and Jørgen Rungby; Astrid Kousholt performed the statistical analyses. Nicole Jacqueline Jensen drafted the initial manuscript, and all other authors critically revised the manuscript for important intellectual content. All authors approved the final version for publication. Reimar Wernich Thomsen is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosure

Prior presentation. Parts of this study were presented in abstract form at the European Association for the Study of Diabetes 58th annual meeting, Stockholm, 2022.

Conflicts of Interest

The Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of those studies have any relation to the present study. No other potential conflicts of interest relevant to this article are reported.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Description of the data sources and codes used for defining variables. **Table S2:** Overview of missing values. **Table S3:** Characteristics of participants excluded due to missing fasting glucose or C-peptide measurement. **Table S4:** Stepwise-adjusted HRs for dementia in type 2 diabetes subgroups, HOMA-IR quartiles, and c-peptide quartiles. **Table S5:** Stepwise-adjusted HRs for dementia subtype in type 2 diabetes subgroups, HOMA-IR quartiles, and c-peptide quartiles. **Table S6:** Incidence rates and HRs for all-cause mortality in type 2 diabetes subgroups, HOMA-IR quartiles, and c-peptide quartiles. **Figure S1:** Overview of the study design and linking registries. **Figure S2:** Directed acyclic graph of the association between type 2 diabetes subgroup and dementia. **Figure S3:** Cumulative incidence curves of dementia subtype in type 2 diabetes subgroups, HOMA-IR quartiles, and c-peptide quartiles. **Figure S4:** Cumulative incidence curves of all-cause mortality in type 2 diabetes subgroups, HOMA-IR quartiles, and c-peptide quartiles. **File S1:** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. **File S2:** The Standards of Reporting of Neurological Disorders (STROND) recommendations.