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For the German translation of the abstract see Online for appendix 1

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Summary

Background The subjective experiences of individuals living with diabetes is commonly assessed with patient-reported outcomes (PROs; eg, depression symptoms, wellbeing, health-related quality of life [HRQOL], and diabetes-related distress). Cluster analyses have identified novel diabetes subtypes differing in phenotypic and metabolic characteristics. We aimed to investigate associations between these subtypes and PROs and whether subtype predicted PROs 5 years later.

Methods Baseline (<12 months after a diabetes diagnosis) and 5-year follow-up data were collected from German Diabetes Study (GDS) participants. Multiple regressions were applied to analyse associations between diabetes subtypes and depression symptoms (Center for Epidemiologic Studies Depression Scale), wellbeing (WHO-5), HRQOL (SF-36), and diabetes-related distress (Problem Areas in Diabetes Scale).

Findings Cluster analyses at baseline (n=1391) identified participants with severe autoimmune diabetes (SAID, 417 [30%]), severe insulin-deficient diabetes (SIDD, 33 [2%]), severe insulin-resistant diabetes (SIRD, 150 [11%]), mild obesity-related diabetes (MOD, 354 [25%]), and mild age-related diabetes (MARD, 437 [31%]). At baseline, multiple regression analyses showed that participants with SIRD had higher depression symptoms than participants with MARD and lower physical HRQOL than all other subtypes. Participants with SAID reported higher depression symptoms and lower mental HRQOL than participants with MARD, higher physical HRQOL than participants with MARD and MOD, and higher diabetes-related distress than most other subtypes. At the 5-year follow-up, clustering predicted no statistically significant changes in PROs after adjustment for multiple testing, whereas descriptive analyses demonstrated that individuals with SIRD were more likely to experience clinically relevant depression symptoms (16% *vs* 6%) and low wellbeing (31% *vs* 14%), respectively, than individuals with MARD.

Interpretation Diabetes subtypes already differ in PROs at diabetes diagnosis. Our analyses had limited predictive power during follow-up. However, our findings suggest that clustering could predict future changes in depression symptoms.

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Introduction

Individuals with diabetes have a higher prevalence of depression and report lower health-related quality of life (HRQOL) than people without diabetes.[1–4] In clinical practice, patient-reported outcomes (PROs) such as depression symptoms, wellbeing, HRQOL, and diabetes-related distress are commonly used to screen for depressive disorders.[5] The presence or absence of depression symptoms can affect patients' compliance and adherence to diabetes therapy[6,7] and thus influence the development of adverse health outcomes and the risk of diabetes-related complications,[2,7–9] mortality,[9,10] health-care resource use, and health-care costs.[11]

As the overall goal of diabetes treatment is to prevent acute and long-term complications while maintaining a good quality of life,[2,12] identifying the subtypes at higher risk for diabetic complications could help develop tailored treatment in the context of precision medicine. Recent studies have subdivided the common classifications of type 1 and type 2 adult-onset diabetes and allocated patients to subtypes using cluster analysis as a data-driven approach.[13,14] Based on age at diagnosis, BMI,

Research in context

Evidence before this study

Based on the initial work of Ahlqvist and colleagues (2018), who used cluster analysis methodology to identify five subtypes of adult-onset diabetes, based on phenotypic and laboratory parameters. We did backward and forward citation searching in Google Scholar in English without date restrictions. We found that further analyses identified subtype-specific differences in risk for prevalence and progression of certain diabetes-related comorbidities, such as cardiovascular, renal, and hepatic diseases within 5 years after diagnosis. We found no evidence for patient-reported outcomes (PROs) such as depression symptoms, wellbeing, health-related quality of life (HRQOL), and diabetes-related distress, which might affect compliance and adherence to diabetes therapy and thus influence the development of adverse health outcomes and the risk of diabetes-related complications.

Added value of this study

This study investigated PROs across the five diabetes subtypes (SAID, SIDD, SIRD, MOD, and MARD). At the time of diabetes diagnosis, the subtypes showed variations in depression symptoms, wellbeing, HRQOL, and diabetes-related distress. The increased risk of developing diabetes-related complications for individuals with the SIRD subtype could also apply to depression symptoms.

Implications of all the available evidence

Cluster analysis detected differences in PROs between the subtypes soon after diabetes diagnosis. The findings provide evidence that diabetes subtyping can be useful for identifying individuals at risk of future depression symptoms or worsening wellbeing, HRQOL, and diabetes-related distress. The suspected associations between insulin resistance and subclinical inflammation with the PROs require further study. Although the predictive power of our analyses is low, the analyses establish the basis for future research (eg, on depression symptoms among diabetes subtypes) and call for inclusion of mental health conditions in precision diabetology.

autoimmunity, glycaemic control, and a homeostasis-based model assessment of β-cell function and insulin resistance (HOMA-B, HOMA-IR), a cluster approach identified the following five distinct subtypes of adult-onset diabetes: severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD). This approach has since been widely used and validated.[15–17] Importantly, these subtypes differ not only in phenotypic characteristics but also in their risk for cardiovascular disease, chronic kidney disease, non-alcoholic fatty liver disease, peripheral neuropathy, and in men, erectile dysfunction.[15,16,18–20] Some phenotypic characteristics and diabetes-related complications also show a different time course over the first 5 years after diabetes diagnosis.[16] Depression in diabetes has been shown to be associated with insulin resistance[21] and impaired glycaemic control.[22] These associations might be due to shared biological and behavioral mechanisms of depression and diabetes.[23,24] Such biological mechanisms include stress-induced increased activity in the hypothalamic–pituitary–adrenal axis and subclinical inflammation.[23,25] Persistent psychosocial stress, as one of many factors, is thought to promote the development of depression. Psychosocial stressors cause subclinical hypercortisolism through hyperactivity of the hypothalamic–pituitary–adrenal axis. With prolonged exposure, hypercortisolism leads to visceral obesity, increased insulin resistance, dyslipidaemia, and hypertension, possibly promoting the development of type 2 diabetes.[26]

Although the subtypes differ in insulin sensitivity, glycaemic control, and subclinical inflammation,[27] no study to date has examined the partially overlapping PROs, depression symptoms, wellbeing, HRQOL, and diabetes-related distress across subtypes. We hypothesised that PROs would be differentially distributed across the new diabetes subtypes at baseline. Furthermore, we expected that subtypes would predict changes in PROs at the 5-year follow-up. In particular, because of the suspected associations between insulin resistance, subclinical inflammation, and depression, we expected that the SIRD subtype (lowest insulin sensitivity and most pronounced proinflammatory profile compared with other subtypes) would have more symptoms of depression, lower wellbeing, lower HRQOL, and higher diabetes-related distress than the other subtypes.

Methods

Study design and population

This study used baseline and 5-year follow-up data from the German Diabetes Study (GDS), which is an ongoing, prospective, observational, multicentre study in different regions of Germany. It enrols White individuals who were diagnosed with diabetes within the previous 12 months on the basis of American Diabetes Association diagnosis criteria[28] and aims to investigate the course and consequences of diabetes. GDS data come from comprehensive metabolic phenotyping, detailed physical examinations, and standardised questionnaires and interviews. Participants were between the ages of 18 and 69 years and were enrolled in the GDS between September, 2005 and October, 2022. Exclusion criteria were diabetes from other causes (ie, monogenic diabetes syndromes, diseases of the exocrine pancreas, and gestational diabetes); pregnancy; acute or severe chronic

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cardiac, hepatic, or renal disorders; or severe psychiatric disorders (eg, major depression). People treated with tricyclic antidepressants, lithium, or neuroleptics were excluded, but individuals with mild-to-moderate depression reporting selective serotonin reuptake inhibitors or no antidepressants were eligible to participate in the GDS. The study design and participant recruitment have been described elsewhere.[29] Participants underwent a standardised protocol for blood sampling, adhering to established operating procedures.[29] Routine laboratory measurements were performed at the German Diabetes Center in accordance with established protocols. Insulin secretion and sensitivity were assessed with the modified Botnia clamp, consisting of an intravenous glucose tolerance test followed by a hyperinsulinaemic-euglycaemic clamp with repeated measurements of blood glucose, C-peptide, and insulin levels as described previously.[29] Insulin secretion was determined by measuring the incremental area under the curve of C-peptide levels during the intravenous glucose tolerance test. Whole-body insulin sensitivity (M value) was assessed with average glucose infusion rates during a stable period. The adipose tissue insulin resistance index was based on the concentrations of insulin and free fatty acids after fasting. All participants underwent measurement of diabetes-related autoantibodies. Glutamic acid decarboxylase antibodies were quantified by a radioligand assay, islet-cell autoantibodies were quantified by indirect immunofluorescence, and insulin autoantibodies were assessed by radioimmunoassay.[29,30] Maximal aerobic capacity (VO2max) as a physical fitness indicator was assessed by an incremental exhaustive exercise test with a cycle ergometer (Ergometrics 900; Ergoline, Bitz, Germany).[29] Furthermore, overall medication use (measured by the German Anatomical Therapeutic Chemical [ATC] Classification), current smoking behavior (yes *vs* no), hypertension (yes *vs* no), hyperlipidaemia (yes *vs* no), retinopathy (yes *vs* no), metabolic dysfunction-associated steatotic liver disease defined as hepatocellular lipid content greater than 5% (yes *vs* no), nephropathy defined as eGFR 90 or less (mL/min per 1·73 m²; yes *vs* no) were documented.

Ethical approval for the GDS was obtained from the ethics committee of the Medical Faculty of Heinrich Heine University Düsseldorf, Germany (reference number 4508). The study is registered with ClinicalTrials.gov, NCT01055093, and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Allocation to diabetes subtypes in the GDS cohort was based on age at diagnosis, BMI, insulin resistance (HOMA-IR), glycaemic control (HbA_{1c}), homeostasis model assessment of β-cell function (HOMA-B), and the presence of glutamic acid decarboxylase antibodies (GADA) using the nearest centroid approach from the sex-specific clustering algorithm by Ahlqvist and colleagues at baseline.[15] The presence of diabetes-related autoantibodies identified membership to SAID, which is consistent with the established classification of type 1 diabetes. For the remaining participants we used the so-called cluster centroids, found in the cluster analysis and described by Ahlqvist and colleagues.[15] Cluster centroids are points in the five dimensional Euclidian space with HbA_{1c}, BMI, age, HOMA-B, and HOMA-IR being Cartesian coordinate axes. Finally, participants were allocated to a cluster (SIDD, SIRD, MOD, or MARD) that corresponded to their smallest Euclidian distance. Consequently, the SIDD, SIRD, MOD, and MARD clusters would be classified as having type 2 diabetes. The clustering performed at baseline was used in all analyses. The laboratory data for the clustering variables were determined centrally at the German Diabetes Center in Düsseldorf, Germany. For the cross-sectional analyses in the total sample, we used a consecutive sample with all participants from the ongoing GDS with complete baseline data for the allocation to diabetes subtypes. For the longitudinal analyses, we included all participants from the total sample who had already completed the 5-year follow-up examination, building the subsample.

Outcomes

Depression symptoms, wellbeing, HRQOL, and diabetes-related distress were assessed with paper-pencil questionnaires. All questionnaires are available and comprehensively validated in the German language and have been widely used in studies of people with diabetes.[31,32] The Center for Epidemiologic Studies Depression Scale is recommended for measuring depression symptoms in people with diabetes.[33] For 20 items, respondents indicated how often (0=rarely or none of the time, 1=some or a little of the time, 2=moderately or much of the time, 3=most or almost all the time) they had experienced various depression symptoms in the past week on a 4-point Likert scale. Scores ranged from 0 to 60, with higher scores indicating more severe depression symptoms. Clinically relevant depression symptoms were identified using a cutoff of 22 or higher.[33]

Wellbeing was assessed with the WHO 5-point Well-Being Index (WHO-5 Index),[34,35] which asks respondents to rate the extent to which five positive statements about wellbeing applied to them in the past 14 days on a 6-point Likert scale ranging from "at no time" (0) to "all of the time" (5). The raw score, which ranges from 0 (absence of wellbeing) to 25 (maximal wellbeing) is converted into a percentage scale ranging from 0 (absent) to 100 (maximal), with higher values indicating greater wellbeing.[35] Low wellbeing was identified using a cutoff score of less than 50.[5]

HRQOL was measured with the 36-item Short Form Survey.[36,37] With 36 items with different response formats, respondents are asked about their physical and mental health from the past week. Eight subscales contribute in different proportions to the assessment of a physical

(PCS) and a mental (MCS) component summary score. Calculating the PCS and MCS requires the use of a special algorithm that results in scores ranging from 0 to 100. Higher scores indicate better HRQOL, with a score of 50 considered average HRQOL.[36,37]

Diabetes-related distress was identified with the Problem Areas in Diabetes Scale,[38,39] which comprises 20 items pertaining to diabetes-specific stress situations. Each item can be answered on a 5-point Likert scale ranging from 0 (no problem) to 4 (major problem). Ranging from 0 to 100, the score indicates the level of diabetes-related distress, with a value of 40 or higher representing high diabetes-related distress.[39]

Potential confounders

We first identified potential confounders on the basis of the literature and the "standard set of person-centered outcomes for diabetes mellitus" defined by the International Consortium for Health Outcomes Measurement.[40] Afterwards, all models were checked with directed acyclic graphs using the browser-based environment DAGitty. According to the directed acyclic graph concept, the independent variables in each model form the minimally sufficient set of adjustments. At baseline, we collected data on sex (female *vs* male), employment status (yes *vs* no), place of birth (Germany *vs* elsewhere), and education, and asked about the highest level of general education attained, which was then categorised as "no or lower level" (no schooling or completion of junior high after 9 years), "medium level" (completion of junior high after 10 years), and "high level" (general qualification for university entrance), in line with the literature.[41,42] Age (years) and BMI (kg/m²) are also strongly associated with PROs. However, as both variables are part of the definitions of the subtypes, we did not include them as confounders in the main analyses but only in the sensitivity analyses. In further sensitivity analyses, we examined the influence of antihyperglycaemic therapy (no therapy *vs* insulin or oral glucose-lowering drugs) and self-reported previous episode of depression (no *vs* yes).

Statistical analysis

The data are presented as mean (SD), median (IQR), or frequency (%). PROs, laboratory and clinical data, and potential confounders were compared across five subtypes of diabetes for the total sample (at baseline) as well as the subsample (at baseline and follow-up, respectively) using the Kruskal-Wallis and Chi-square test (or Fisher's exact test, in case Chi-square assumptions were not fulfilled), depending on the nature of the underlying variables. In the case of extremely high computational time for Fisher's exact test, we used the Monte Carlo approach to estimate Fisher's exact p value. Changes in PROs from baseline to 5-year follow-up per subtype were compared with the Wilcoxon signed-rank test.

Multiple linear regressions were computed to estimate the associations between diabetes subtypes and PROs in the total sample using one of the baseline PROs as the dependent variable and diabetes subtypes and potential confounders as independent variables.

For the longitudinal analysis in the subsample, we computed multiple linear regressions using one PRO at the 5-year follow-up as the dependent variable, with diabetes subtypes, baseline PRO, and potential confounders as independent variables. These models are equivalent to the corresponding models with a change in one PRO from baseline to the 5-year follow-up as a dependent variable and the same set of independent variables.[43] This enables conclusions to be drawn about PROs at the 5-year follow-up and changes in PROs from baseline to the 5-year follow-up.

All models were fitted separately for each PRO. In each model, p values for the ten pairwise comparisons of the five diabetes subtypes were adjusted for multiple comparisons with the Bonferroni–Holm procedure. As described above, we adjusted for age and BMI in the sensitivity analyses. In addition, we included antihyperglycaemic therapy and previous episodes of depression as additional confounding variables in further sensitivity analyses. To enhance comparability with other studies, we also calculated models using the widely employed cutoff values for the Center for Epidemiologic Studies Depression Scale, WHO-5, and Problem Areas in Diabetes Scale as sensitivity analyses using modified Poisson models.[44] We carefully checked the assumptions of the Chi-square test, Kruskal–Wallis test, Wilcoxon signed-rank test, linear models, and modified Poisson models. The significance level was set at $\alpha=0{\cdot}05$. Data analyses were computed with SAS version 9.4.

For more on **DAGitty** see https://www.dagitty.net/

Role of the funding source

The funding sources had no role in the study design, data collection, data analysis, data interpretation, or report writing.

Results

At baseline, 417 (30·0%) of the total sample (n=1391) were assigned to SAID, 33 (2·4%) to SIDD, 150 (10·8%) to SIRD, 354 (25·4%) to MOD, and 437 (31·4%) to MARD (table 1). The follow-up analysis comprised a subsample (n=659) whose distribution of participant characteristics was similar to the total sample.

Participants' laboratory and clinical data for the total sample (at baseline) and for the subsample (at baseline and follow-up) are presented in table 2, categorised by subtype. We observed considerable differences between diabetes subtypes for almost all variables.

At baseline, depression symptoms in the total sample were highest in participants assigned to the SIRD subtype (median 9·0 [IQR 5·0–17·0]) and SAID subtype (9·0 [5·0–14·0]) and lowest in the SIDD subtype (7·5 [4·0–17·0]; table 3). Participants with SIDD had the highest mean wellbeing (mean 66·1 [SD 19·0]), and

	Total	SAID	SIDD	SIRD	MOD	MARD	p value
Number of participants							
Total sample	1391	417 (30%)	33 (2%)	150 (11%)	354 (25%)	437 (31%)	..
Subsample	659	191 (29%)	13 (2%)	57 (9%)	174 (26%)	224 (34%)	..
Age (years)							
Total sample (n=1391)	48·1 (13·3)	37·7 (12·7)	44·1 (12·5)	56·9 (9·0)	45·0 (9·9)	57·8 (7·6)	<0·0001
Subsample (n=659)	48·4 (13·2)	37·4 (12·3)	38·9 (10·6)	58·0 (8·8)	45·4 (9·4)	58·0 (7·7)	<0·0001
Female							
Total sample (n=1391)	523 (38%)	193 (46%)	7 (21%)	51 (34%)	157 (44%)	115 (26%)	<0·0001
Subsample (n=659)	224 (34%)	86 (45%)	1 (8%)	15 (26%)	75 (43%)	47 (21%)	<0·0001
Male							
Total sample (n=1391)	868 (62%)	224 (54%)	26 (79%)	99 (66%)	197 (56%)	322 (74%)	<0·0001
Subsample (n=659)	435 (66%)	105 (55%)	12 (92%)	42 (74%)	99 (57%)	177 (79%)	<0·0001
Education							
No/lower							
Total sample (n=1389)	257 (19%)	34/416 (8%)	8 (24%)	38 (25%)	71 (20%)	106/436 (24%)	<0·0001
Subsample (n=658)	121 (18%)	13 (7%)	0	18 (32%)	31 (18%)	59/223 (27%)	<0·0001*
Medium							
Total sample	365 (26%)	88/416 (21%)	9 (27%)	51 (34%)	107 (30%)	110/436 (25%)	..
Subsample	176 (27%)	47 (25%)	3 (23%)	15 (26%)	53 (31%)	58/223 (26%)	..
High							
Total sample	767 (55%)	294/416 (71%)	16 (49%)	61 (41%)	176 (50%)	220/436 (51%)	..
Subsample	361 (55%)	131 (69%)	10 (77%)	24 (42%)	90 (52%)	106/223 (48%)	..
Employment (yes)							
Total sample (n=1389)	988 (71%)	318 (76%)	27 (82%)	91/149 (61%)	275/353 (78%)	277 (63%)	<0·0001
Subsample (n=658)	476 (72%)	147 (77%)	11 (85%)	35/56 (63%)	139 (80%)	144 (64%)	0·0013
Place of birth (Germany)							
Total sample (n=1389)	1247 (90%)	377/416 (91%)	28 (85%)	143 (95%)	315/353 (89%)	384 (88%)	0·089
Subsample (n=658)	595 (90%)	174/190 (92%)	10 (77%)	53 (93%)	156 (90%)	202 (90%)	0·46

Data are presented as mean (SD) or n (%). Total sample with variables at baseline and subsample with variables at baseline. The Kruskal-Wallis test and Chi-square test (or Fisher's exact test in case Chi-square assumptions were not fulfilled) were used to compare the five diabetes subtypes with respect to sociodemographic variable at baseline. A low p value of the Kruskal-Wallis test indicates that the distribution of the corresponding (continuous) variable differs for at least two of the five subtypes. A low p value of the Chi-square test or Fisher's exact test indicates a dependence between a (categorised) variable and diabetes subtypes. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MARD=moderate age-related diabetes. MOD=moderate obesity-related diabetes. *Monte Carlo estimates of p value related to the Fisher's exact test.

Table 1: **Baseline characteristics**

participants with SAID had the lowest (60·5 [18·3]). Participants with MARD had the highest MCS of HRQOL (mean 50·9 [SD 11·2]), and people with SIRD had the lowest PCS of HRQOL (46·6 [10·4]). Diabetes-related distress was highest in the SAID subtype (median 21·3 [IQR 11·3–38·8]) and lowest in the SIDD subtype (10·0 [5·0–28·8]).

The analyses of dichotomous PROs showed that 128 (11%) of 1203 participants in the total sample reported clinically relevant depression symptoms (highest for SIRD; 19/131 [15%]), 343 (25%) of 1358 participants reported low wellbeing (highest for SIRD; 46/144 [32%]), and 146 (16%) of 924 reported high diabetes-related distress (highest for SAID; 71/300 [24%]; table 3).

After 5 years of disease progression, the SIRD subtype showed the largest increase (figure A) and continued to have the highest mean depression symptom score (median 11·0 [IQR 6·0–18·0], table 3). Across all subtypes in the subsample, except for MARD (figure B), wellbeing decreased on average from baseline to follow-up. The MCS of HRQOL increased in participants with SAID, SIDD, and MARD and decreased in SIRD and MOD (figure C). Participants with SIRD continued to have the lowest PCS of HRQOL (mean 47·1 [SD 8·9], table 3). PCS of HRQOL decreased slightly in all subtypes, except for SIDD (figure D). Diabetes-related distress decreased on average for all subtypes (figure E) from baseline to follow-up. Participants with SAID had the highest diabetes-related distress score at follow-up (median 13·8 [IQR 6·3–32·5], table 3). At follow-up, 64 (12%) of 555 participants exhibited clinically relevant depression symptoms (highest percentage for SIRD; 8/50 [16%]), 123/625 (20%) showed low wellbeing (highest percentage for SIRD; 17/55 [31%]), and 51/584 (9%) reported a high level of diabetes-related distress (highest percentage for SAID; 24/169 [14%], table 3).

	Total	SAID	SIDD	SIRD	MOD	MARD	p value
Number of participants							
Total sample	1391	417 (30%)	33 (2%)	150 (11%)	354 (25%)	437 (31%)	..
Subsample	659	191 (29%)	13 (2%)	57 (9%)	174 (26%)	224 (34%)	..
Treatment modalities							
Insulin							
Total sample at BL (n=1309)	389 (30%)	312/399 (78%)	15/32 (47%)	2/128 (2%)	30/332 (9%)	30/418 (7%)	<0·0001
Subsample at BL (n=637)	189 (30%)	151/190 (80%)	9 (69%)	0	13/168 (8%)	16/214 (7%)	<0·0001*
Subsample at FU (n=584)	194 (33%)	152/180 (84%)	8 (62%)	0	19/154 (12%)	15/191 (8%)	<0·0001*
Insulin + OGLD							
Total sample at BL (n=1309)	57 (4%)	15/399 (4%)	1/32 (3%)	4/128 (3%)	23/332 (7%)	14/418 (3%)	..
Subsample at BL (n=637)	24 (4%)	9/190 (5%)	0 (0%)	2/52 (4%)	9/168 (5%)	4/214 (2%)	..
Subsample at FU (n=584)	41 (7%)	12/180 (7%)	2 (15%)	5/46 (11%)	16/154 (10%)	6/191 (3%)	..
OGLD							
Total sample at BL (n=1309)	470 (36%)	37/399 (9%)	12/32 (38%)	74/128 (58%)	164/332 (49%)	183/418 (44%)	..
Subsample at BL (n=637)	232 (36%)	18/190 (9%)	3 (23%)	32/52 (62%)	84/168 (50%)	95/214 (44%)	..
Subsample at FU (n=584)	242 (41%)	10/180 (6%)	3 (23%)	31/46 (67%)	86/154 (56%)	112/191 (59%)	..
None							
Total sample at BL (n=1309)	393 (30%)	35/399 (9%)	4/32 (13%)	48/128 (38%)	115/332 (35%)	191/418 (46%)	..
Subsample at BL (n=637)	192 (30%)	12/190 (6%)	1 (8%)	18/52 (35%)	62/168 (37%)	99/214 (46%)	..
Subsample at FU (n=584)	107 (18%)	6/180 (3%)	0	10/46 (22%)	33/154 (21%)	58/191 (30%)	..
Number of medications							
Total sample at BL (n=1309)	2·0 (1·0–4·0)	2·0 (2·0–3·0)	2·0 (1·0–4·0)	4·0 (2·0–6·0)	2·0 (1·0–4·0)	2·0 (1·0–4·0)	<0·0001
Subsample at BL (n=637)	2·0 (1·0–4·0)	2·0 (2·0–3·0)	2·0 (1·0–2·0)	4·0 (2·0–6·0)	2·0 (1·0–4·0)	3·0 (1·0–4·0)	<0·0001
Subsample at FU (n=584)	3·0 (2·0–5·0)	2·0 (2·0–3·5)	2·0 (1·0–3·0)	5·0 (4·0–7·0)	3·0 (2·0–5·0)	3·0 (2·0–5·0)	<0·0001
BMI (kg/m^2)							
Total sample at BL (n=1390)	29·4 (6·4)	25·4 (5·0)	27·2 (3·9)	34·4 (4·8)	34·8 (6·5)	27·3 (3·4)	<0·0001
Subsample at BL (n=659)	29·3 (6·3)	25·2 (5·0)	26·1 (4·1)	34·3 (4·0)	34·7 (6·3)	27·4 (3·3)	<0·0001
Subsample at FU (n=599)	29·9 (5·9)	26·8 (5·2)	26·9 (5·4)	34·6 (5·1)	34·2 (5·9)	28·1 (3·7)	<0·0001
Current smoking behavior (yes)							
Total sample at BL (n=801)	293 (37%)	95/230 (41%)	10/17 (59%)	30/97 (31%)	76/194 (39%)	82/263 (31%)	0·026
Subsample at BL (n=337)	115 (34%)	29/82 (35%)	2/6 (33%)	9/35 (26%)	35/86 (41%)	40/128 (31%)	0·51
Subsample at FU (n=379)	105 (28%)	32/92 (35%)	2/7 (29%)	10/38 (26%)	30/102 (29%)	31/140 (22%)	0·33
Fasting blood glucose (mg/dL)							
Total sample at BL (n=1376)	125·4 (35·5)	131·2 (43·3)	182·9 (54·6)	108·2 (28·0)	127·7 (30·4)	119·7 (24·4)	<0·0001
Subsample at BL (n=652)	125·1 (32·9)	131·5 (40·9)	160·4 (35·3)	110·2 (21·0)	129·2 (33·1)	118·4 (23·2)	<0·0001
Subsample at FU (n=585)	149·3 (49·6)	155·3 (51·8)	163·9 (63·4)	133·9 (46·3)	163·6 (57·5)	136·4 (34·9)	<0·0001
C-peptide (ng/dL)							
Total sample at BL (n=1384)	2·4 (1·3–3·6)	0·9 (0·6–1·6)	1·8 (1·3–3·2)	5·1 (4·0–6·2)	3·2 (2·4–4·1)	2·3 (1·7–3·0)	<0·0001
Subsample at BL (n=656)	2·3 (1·3–3·4)	1·0 (0·5–1·5)	1·3 (1·0–1·8)	5·1 (4·1–5·9)	3·2 (2·6–4·1)	2·3 (1·7–2·9)	<0·0001
Subsample at FU (n=586)	2·3 (0·6–3·4)	0·2 (0·1–0·5)	1·1 (0·5–1·5)	4·4 (3·9–6·2)	3·0 (2·3–4·0)	2·5 (1·9–3·4)	<0·0001
HbA_{1c} (NGSP, %)							
Total sample at BL (n=1389)	6·5 (1·0)	6·6 (1·1)	8·7 (1·2)	6·2 (0·7)	6·5 (0·9)	6·3 (0·7)	<0·0001
Subsample at BL (n=659)	6·4 (0·9)	6·5 (1·0)	8·2 (1·2)	6·1 (0·5)	6·4 (0·9)	6·2 (0·7)	<0·0001
Subsample at FU (n=592)	6·9 (1·1)	7·0 (1·0)	7·6 (1·6)	6·5 (0·8)	7·2 (1·4)	6·7 (0·8)	<0·0001
HbA_{1c} (mmol/mol)							
Total sample at BL (n=1389)	47·1 (10·5)	48·4 (11·7)	71·6 (13·2)	44·4 (7·4)	47·0 (9·7)	45·0 (7·6)	<0·0001
Subsample at BL (n=659)	46·2 (9·9)	47·6 (11·1)	66·6 (13·0)	43·0 (6·0)	46·8 (9·9)	44·0 (7·5)	<0·0001
Subsample at FU (n=592)	52·1 (11·7)	53·4 (10·4)	60·0 (17·8)	47·5 (8·9)	54·8 (14·8)	49·5 (9·0)	<0·0001
hsCRP (mg/dL)							
Total sample at BL (n=1350)	0·2 (0·1–0·4)	0·1 (0·1–0·2)	0·2 (0·1–0·3)	0·3 (0·2–0·5)	0·3 (0·2–0·6)	0·2 (0·1–0·3)	<0·0001
Subsample at BL (n=631)	0·2 (0·1–0·4)	0·1 (0·1–0·2)	0·1 (0·0–0·2)	0·3 (0·1–0·6)	0·3 (0·2–0·7)	0·2 (0·1–0·3)	<0·0001
Subsample at FU (n=553)	0·2 (0·1–0·3)	0·1 (0·1–0·3)	0·2 (0·0–0·2)	0·2 (0·1–0·4)	0·2 (0·1–0·4)	0·1 (0·1–0·3)	<0·0001

(Table 2 continues on next page)

	Total	SAID	SIDD	SIRD	MOD	MARD	p value
(Continued from previous page)							
ADIPO-IR (a. u.)							
Total sample at BL (n=762)	7·7 (4·1–14·0)	5·3 (2·8–10·1)	8·9 (5·9–15·5)	15·4 (9·3–20·9)	11·3 (7·3–17·9)	5·9 (3·8–10·2)	<0·0001
Subsample at BL (n=293)	7·7 (4·3–13·3)	6·5 (3·2–11·0)	8·5 (7·0–15·5)	16·6 (9·3–22·9)	11·1 (7·4–17·0)	5·3 (4·0–8·4)	<0·0001
Subsample at FU (n=533)	7·5 (3·6–15·1)	5·3 (2·3–14·9)	4·6 (1·8–19·7)	15·9 (8·3–23·3)	10·8 (6·5–18·0)	6·2 (3·6–10·5)	<0·0001
VO2max (mL/min per kg)							
Total sample at BL (n=743)	23·4 (7·8)	28·6 (7·8)	23·6 (7·7)	17·4 (4·3)	19·4 (5·6)	22·4 (6·4)	<0·0001
Subsample at BL (n=394)	23·4 (7·5)	28·3 (7·6)	25·2 (7·1)	17·6 (4·6)	19·8 (5·4)	22·3 (6·4)	<0·0001
Subsample at FU (n=378)	23·4 (8·2)	28·4 (9·3)	26·6 (10·6)	18·2 (4·5)	20·1 (5·5)	21·2 (6·0)	<0·0001
Hypertension (yes)							
Total sample at BL (n=1364)	749 (55%)	116/410 (28%)	18 (55%)	109/146 (75%)	215/346 (62%)	291/429 (68%)	<0·0001
Subsample at BL (n=653)	364 (56%)	56/190 (29%)	5 (38%)	45/56 (80%)	106/172 (62%)	152/222 (68%)	<0·0001
Subsample at FU† (n=601)	81 (13%)	24/176 (14%)	1 (8%)	6/55 (11%)	27/156 (17%)	23/201 (11%)	0·50
Hyperlipidemia (yes)							
Total sample at BL (n=1378)	914 (66%)	165/410 (40%)	19 (58%)	130/149 (87%)	276/352 (78%)	324/434 (75%)	<0·0001
Subsample at BL (n=655)	424 (65%)	76/188 (40%)	7 (54%)	51 (98%)	129 (74%)	161/223 (72%)	<0·0001
Subsample at FU† (n=601)	74 (12%)	26/175 (15%)	2 (15%)	4/55 (7%)	14/156 (9%)	28/202 (14%)	0·34
Retinopathy (yes)							
Total sample at BL (n=964)	19 (2%)	5/317 (2%)	0	3/80 (4%)	3/262 (1%)	8/279 (3%)	0·38
Subsample at BL (n=496)	11 (2%)	1/158 (1%)	0	3/41 (7%)	1/131 (1%)	6/157 (4%)	0·048‡
Subsample at FU (n=471)	12 (3%)	2/144 (1%)	0	1/38 (3%)	3/131 (2%)	6/148 (4%)	0·62‡
MASLD (yes)							
Total sample at BL (n=364)	133 (37%)	15/140 (11%)	3/8 (38%)	20/22 (91%)	51/87 (59%)	44/107 (41%)	<0·0001
Subsample at BL (n=168)	56 (33%)	9/61 (15%)	1/5 (20%)	5/7 (71%)	22/42 (52%)	19/53 (36%)	0·0003‡
Subsample at FU (n=151)	67 (44%)	6/56 (11%)	1/4 (25%)	8/10 (80%)	26/37 (70%)	26/44 (59%)	<0·0001‡
Nephropathy (eGFR [mL/min per 1·73 m²] <90)							
Total sample at BL (n=1220)	549 (45%)	88/367 (24%)	5/28 (18%)	102/140 (73%)	141/305 (46%)	213/380 (56%)	<0·0001
Subsample at BL (n=586)	265 (45%)	42/172 (24%)	0	38/52 (73%)	72/152 (47%)	113/200 (57%)	<0·0001
Subsample at FU (n=494)	246 (50%)	40/143 (28%)	1/9 (11%)	41/50 (82%)	60/125 (48%)	104/167 (62%)	<0·0001
Previous episode of depression (yes)							
Total sample at BL (n=1388)	139 (10%)	30 (7%)	2/32 (6%)	24/149 (16%)	43 (12%)	40/436 (9%)	0·014
Subsample at BL (n=659)	49 (7%)	6 (3%)	1 (8%)	7 (12%)	19 (11%)	16 (7%)	0·038

Data are presented as mean (SD), median (IQR), or n (%). Total sample with variables at baseline and subsample with variables at baseline and follow-up. The Kruskal-Wallis test and Chi-square test (or Fisher's exact test, in case Chi-square assumptions were not fulfilled) were used to compare the five diabetes subtypes with respect to sociodemographic variable at baseline or 5-year follow-up. A low p value of the Kruskal-Wallis test indicates that the distribution of the corresponding (continuous) variable differs for at least two of the five subtypes. A low p value of the Chi-square test or Fisher's exact test indicates a dependence between a (categorised) variable and diabetes subtypes. Severe nephropathy (eGFR <60 mL/min per 1·73 m²) was an exclusion criterion in the German Diabetes Study. ADIPO-IR= adipose tissue insulin resistance index. a.u.=arbitrary units. eGFR=estimated glomerular filtration rate. BL=baseline. FU=5-year follow-up. hsCRP=high-sensitivity C-reactive protein. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MASLD=metabolic dysfunction-associated steatotic liver disease. MARD=moderate age-related diabetes. MOD=moderate obesity-related diabetes. NGSP=National Glycohemoglobin Standardization Program. OGLD=oral glucose-lowering drugs. VO2max=maximal aerobic capacity. *Monte Carlo estimates of p value related to the Fisher's exact test. †Post-baseline new manifestations. ‡P value of the Fisher's exact test.

Table 2: **Description of laboratory and clinical data at baseline for the total sample (at baseline), the subsample (at baseline and follow-up), and the diabetes subtypes**

At baseline, multiple linear regression analyses estimated that participants with SAID (1·87 [95% CI 0·62–3·12]), SIRD (2·49 [0·83–4·16]), and MOD (1·48 [0·19–2·77]) had higher depression symptom scores than participants with MARD (table 4); comparisons for SAID and SIRD remained significant after the Bonferroni–Holm multiple adjustment with respect to all ten subtype comparisons. Compared with participants with MARD, participants with SAID exhibited lower wellbeing scores (–3·54 [95% CI –6·29 to –0·78]), as did participants with SIRD (–4·27 [–7·99 to –0·55]). Furthermore, participants with SAID had lower MCS of HRQOL than participants with MARD (–3·34 [–5·01 to –1·67]), which remained significant after the Bonferroni–Holm adjustment. MCS of HRQOL in the MOD subtype (–1·79 [–3·50 to –0·07]) was lower than in the MARD subtype. PCS of HRQOL was lower in the SIRD subtype than in MARD (–3·49 [–4·95 to –2·04]), MOD (–2·69 [–4·19 to –1·19]), SAID (–5·64 [–7·12 to –4·16]), or SIDD (–5·29 [–8·23 to –2·35]). Moreover, PCS of HRQOL in participants with SAID was higher than in participants with MARD (2·14 [1·07 to 3·22]) and MOD (2·95 [1·84

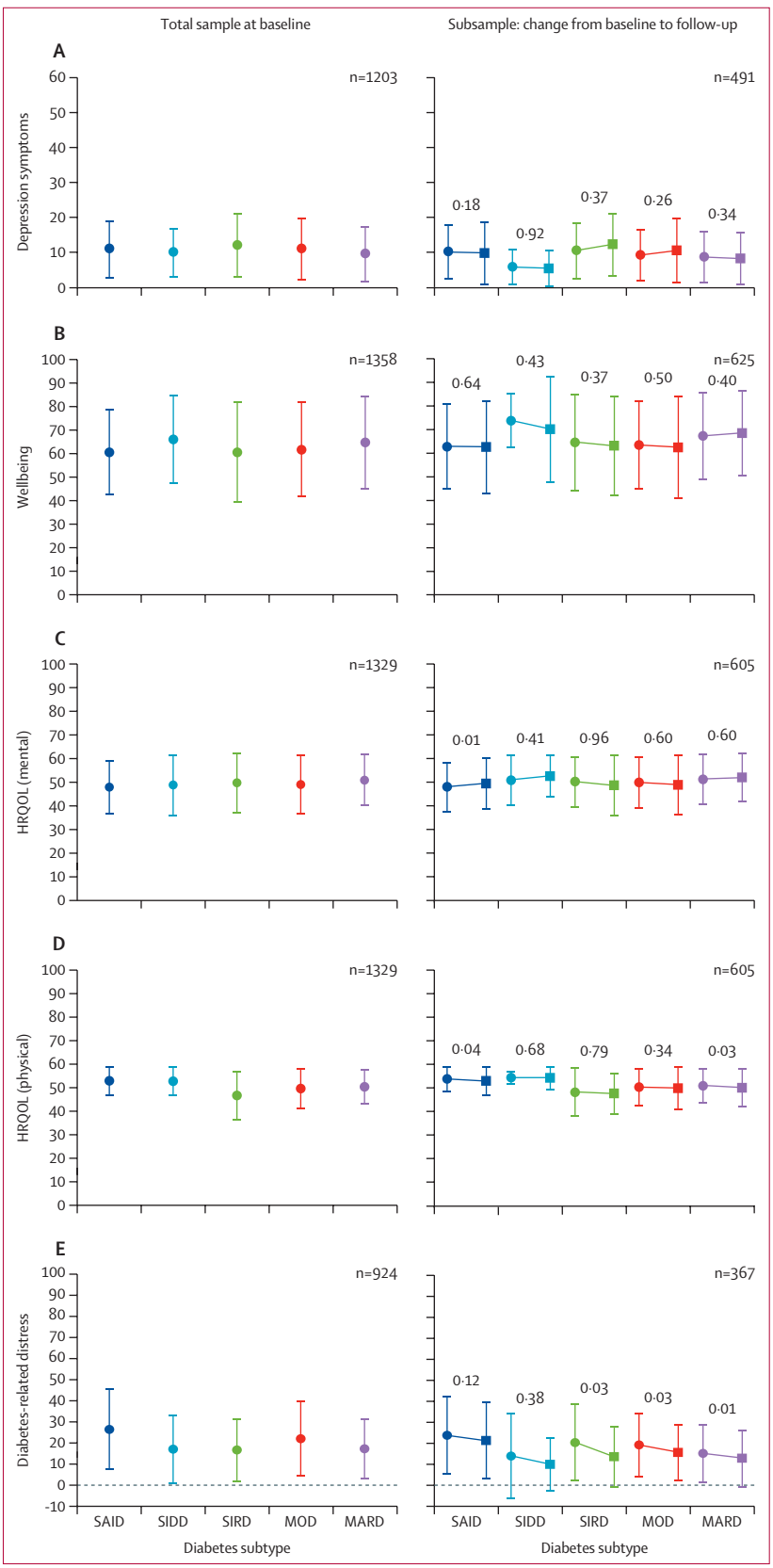
	Total	SAID	SIDD	SIRD	MOD	MARD	p value
Number of participants							
Total sample	1391	417 (30%)	33 (2%)	150 (11%)	354 (25%)	437 (31%)	..
Subsample	659	191 (29%)	13 (2%)	57 (9%)	174 (26%)	224 (34%)	..
Depression symptoms (linear)							
Total sample at BL (n=1203)	8·0 (5·0–14·0)	9·0 (5·0–14·0)	7·5 (4·0–17·0)	9·0 (5·0–17·0)	8·0 (5·0–14·0)	8·0 (4·0–13·0)	0·029
Subsample at BL (n=584)	7·0 (4·0–13·0)	8·0 (5·0–13·0)	5·5 (2·0–8·0)	8·0 (5·0–15·0)	7·0 (4·0–13·0)	6·0 (4·0–11·0)	0·081
Subsample at FU (n=555)	7·0 (4·0–14·0)	7·0 (4·0–14·0)	3·0 (2·0–9·0)	11·0 (6·0–18·0)	8·0 (4·0–16·0)	7·0 (3·0–12·0)	0·011
Depression symptoms (dichotomous, cutoff ≥22)							
Total sample at BL (n=1203)	128 (11%)	42/369 (11%)	3/28 (11%)	19/131 (15%)	32/298 (11%)	32/377 (8%)	0·39
Subsample at BL (n=584)	44 (8%)	14/174 (8%)	0	3/50 (6%)	9/150 (6%)	18/198 (9%)	0·66
Subsample at FU (n=555)	64 (12%)	23/171 (13%)	0	8/50 (16%)	21/140 (15%)	12/185 (6%)	0·060
Wellbeing (linear)							
Total sample at BL (n=1358)	62·3 (19·8)	60·5 (18·3)	66·1 (19·0)	60·6 (21·6)	61·7 (20·3)	64·8 (19·9)	0·0004
Subsample at BL (n=657)	64·8 (18·6)	63·1 (18·2)	73·8 (11·6)	64·6 (20·2)	63·2 (19·0)	67·1 (18·5)	0·014
Subsample at FU (n=627)	64·8 (20·1)	62·7 (19·8)	70·2 (22·5)	62·8 (21·1)	62·4 (21·8)	68·4 (18·3)	0·020
Wellbeing (dichotomous, cutoff <50)							
Total sample at BL (n=1358)	343 (25%)	109/413 (26%)	7/32 (22%)	46/144 (32%)	91/344 (26%)	90/425 (21%)	0·095
Subsample at BL (n=657)	131 (20%)	39/190 (21%)	1 (8%)	12/56 (21%)	40 (23%)	39 (17%)	0·52
Subsample at FU (n=627)	123 (20%)	39/181 (22%)	1 (8%)	17/55 (31%)	37/164 (23%)	29/214 (14%)	0·018
MCS of HRQOL							
Total sample at BL (n=1329)	49·3 (11·8)	47·8 (11·3)	48·7 (13·0)	49·7 (12·8)	49·1 (12·6)	50·9 (11·2)	<0·0001
Subsample at BL (n=642)	50·4 (10·7)	48·8 (10·6)	51·5 (10·8)	50·3 (11·1)	50·5 (10·8)	51·7 (10·6)	0·0023
Subsample at FU (n=621)	50·7 (11·5)	49·9 (11·0)	53·1 (8·9)	49·2 (12·6)	49·4 (13·0)	52·5 (10·4)	0·022
PCS of HRQOL							
Total sample at BL (n=1329)	50·5 (8·0)	52·8 (6·3)	52·7 (6·3)	46·6 (10·4)	49·5 (8·7)	50·3 (7·4)	<0·0001
Subsample at BL (n=642)	51·3 (7·6)	53·6 (5·3)	54·2 (2·9)	48·2 (10·4)	50·0 (8·5)	50·9 (7·4)	<0·0001
Subsample at FU (n=621)	50·5 (8·2)	52·8 (6·3)	54·2 (5·1)	47·1 (8·9)	49·6 (9·2)	49·9 (8·2)	<0·0001
Diabetes-related distress (linear)							
Total sample at BL (n=924)	17·5 (7·5–30·0)	21·3 (11·3–38·8)	10·0 (5·0–28·8)	12·5 (3·8–25·0)	17·5 (7·5–32·5)	15·0 (7·5–23·8)	<0·0001
Subsample at BL (n=416)	15·0 (7·5–27·5)	18·8 (10·0–36·3)	8·1 (2·5–10·0)	13·1 (6·3–25·0)	15·6 (6·3–28·1)	11·3 (6·3–21·3)	0·0022
Subsample at FU (n=584)	11·3 (3·8–23·8)	13·8 (6·3–32·5)	6·3 (0·0–13·8)	7·5 (3·8–21·3)	11·9 (4·4–26·3)	6·3 (2·5–17·5)	<0·0001
Diabetes-related distress (dichotomous, cutoff ≥40)							
Total sample at BL (n=924)	146 (16%)	71/300 (24%)	2/17 (12%)	8/103 (8%)	43/227 (19%)	22/277 (8%)	<0·0001
Subsample at BL (n=416)	53 (13%)	25/127 (20%)	1/6 (17%)	5/34 (15%)	14/112 (13%)	8/137 (6%)	0·021
Subsample at FU (n=584)	51 (9%)	24/169 (14%)	1/11 (9%)	4/49 (8%)	12/156 (8%)	10/199 (5%)	0·040

Data are presented as n (%), mean (SD), or median (IQR). Total sample with variables at baseline and subsample with variables at baseline and follow-up. The Kruskal–Wallis test and Chi-square test were used to compare the five diabetes subtypes with respect to sociodemographic variable at baseline or 5-year follow-up. A low p value of the Kruskal–Wallis test indicates that the distribution of the corresponding (continuous) variable differs for at least two of the five subtypes. A low p value of the Chi-square test indicates a dependence between a (categorised) variable and diabetes subtypes. Depression symptoms (Center for Epidemiologic Studies Depression Scale, higher values indicate more severe depression symptoms; range: 0–60, depression symptoms were considered clinically relevant if the score was ≥22), wellbeing (WHO-5, higher values indicate higher well-being; range: 0–100, values <50 indicate low wellbeing), HRQOL (SF-36, higher values indicate higher HRQOL; range: 0–100). Diabetes-related distress (Problem Areas in Diabetes Scale, higher values indicate higher diabetes-related distress; range 0–100, values ≥40 indicate severe diabetes-related distress). BL=baseline. FU=5-year follow-up. HRQOL=Health related quality of life. MARD=moderate age-related diabetes. MCS=mental component summary score. MOD=moderate obesity-related diabetes. PCS=physical component summary. PRO=patient-reported outcome. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes.

Table 3: **Description of PROs in the total sample (at baseline), in the subsample (at baseline and follow-up), and the diabetes subtypes**

to 4·06]). All PCS comparisons remained statistically significant after the Bonferroni–Holm adjustment.

Diabetes-related distress was highest in the SAID subtype compared with all other subtypes (MARD: 8·15 [95% CI 5·35–10·96]; MOD: 4·57 [1·64–7·49]; SIRD: 8·82 [4·99–12·64]; SIDD: 8·54 [0·35–16·74]). In addition, diabetes-related distress was higher in MOD than in the MARD (3·59 [0·60–6·58]) or SIRD subtypes



(4·25 [0·31–8·20]). After the Bonferroni–Holm adjustment, the differences between SAID and the three subtypes MARD, MOD, and SIRD remained statistically significant.

The sensitivity analysis showed that after adjusting for age, the differences between the subtypes in depression symptoms and wellbeing decreased or disappeared with respect to the MCS of HRQOL (appendix 2 p 1). Differences between the subtypes in the PCS of HRQOL and diabetes-related distress were still observed. Including antihyperglycaemic therapy, BMI, and previous episode of depression as an independent variable did not result in any systematic changes in the findings (appendix 2 pp 2–4). Results of the sensitivity analyses of dichotomous PROs at baseline are shown in appendix 2 (p 9).

At follow-up, participants with SIRD showed different changes from baseline in depression symptom scores compared with participants with MARD. On average, SIRD was 2·81 (95% CI 0·27–5·36]; table 5) points higher than MARD at the 5-year follow-up. The SAID subtype showed 3·16 (0·02–6·30) points higher diabetes-related distress than MOD, adjusted for baseline value and other confounders. There were no associations between baseline subtype and changes in wellbeing, MCS, or PCS of HRQOL from baseline to the 5-year follow-up. There were no statistically significant differences after the Bonferroni–Holm adjustment. Additional adjustments for age, changes in antihyperglycaemic therapy, BMI, and previous episode of depression did not alter the aforementioned results (appendix 2 pp 5–8). Results of the sensitivity analyses of dichotomous PROs at follow-up are shown in appendix 2 (p 10).

Discussion

Previous analyses of differences across diabetes subtypes based on phenotypic clustering have focused on diabetes-related somatic comorbidities and complications, such as cardiovascular, renal, and hepatic diseases.[15,16] In the present study, we examined whether PROs differ by diabetes subtype and whether the subtypes predict changes in PROs at 5 years.

Figure: **PROs of participants with newly diagnosed SAID, SIDD, SIRD, MOD, and MARD at baseline and after 5 years of disease progression**
Plots show depression symptoms (A), wellbeing (B), HRQOL mental component summary score (C), HRQOL physical component summary score (D), and diabetes-related distress (E). Circles and squares are means at baseline and 5-year follow-up, respectively; whiskers show SDs. The change in PROs is shown for participants who had data available at both baseline (circles) and follow-up (squares) including p values of Wilcoxon signed rank test for each cluster separately. HRQOL=health-related quality of life. MARD=moderate age-related diabetes. MOD=moderate obesity-related diabetes. PRO=patient-reported outcome. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes.

	Depression symptoms (n=1197)		Wellbeing (n=1352)		HRQOL (n=1323)				Diabetes-related distress (n=919)	
	Expected difference in score value (95% CI)	p value	Expected difference in score value (95% CI)	p value	MCS		PCS		Expected difference in score value (95% CI)	p value
					Expected difference in score value (95% CI)	p value	Expected difference in score value (95% CI)	p value		
SAID *vs* MARD	1·87 (0·62 to 3·12)	0·0033*	−3·54 (−6·29 to −0·78)	0·012	−3·34 (−5·01 to −1·67)	<0·0001*	2·14 (1·07 to 3·22)	<0·0001*	8·15 (5·35 to 10·96)	<0·0001*
SIDD *vs* MARD	0·85 (−2·35 to 4·04)	0·60	1·12 (−5·91 to 8·16)	0·75	−2·30 (−6·57 to 1·98)	0·29	1·80 (−0·95 to 4·55)	0·20	−0·39 (−8·57 to 7·80)	0·93
SIRD *vs* MARD	2·49 (0·83 to 4·16)	0·0033*	−4·27 (−7·99 to −0·55)	0·025	−1·47 (−3·73 to 0·78)	0·20	−3·49 (−4·95 to −2·04)	<0·0001*	−0·66 (−4·46 to 3·13)	0·73
MOD *vs* MARD	1·48 (0·19 to 2·77)	0·025	−2·49 (−5·33 to 0·35)	0·086	−1·79 (−3·50 to −0·07)	0·042	−0·80 (−1·91 to 0·30)	0·15	3·59 (0·60 to 6·58)	0·019
SAID *vs* MOD	0·39 (−0·90 to 1·68)	0·55	−1·05 (−3·89 to 1·80)	0·47	−1·55 (−3·28 to 0·17)	0·078	2·95 (1·84 to 4·06)	<0·0001*	4·57 (1·64 to 7·49)	0·0022*
SIDD *vs* MOD	−0·63 (−3·86 to 2·59)	0·70	3·61 (−3·50 to 10·72)	0·32	−0·51 (−4·83 to 3·81)	0·82	2·60 (−0·18 to 5·38)	0·066	−3·98 (−12·22 to 4·27)	0·34
SIRD *vs* MOD	1·01 (−0·71 to 2·74)	0·25	−1·78 (−5·64 to 2·08)	0·37	0·31 (−2·02 to 2·65)	0·79	−2·69 (−4·19 to −1·19)	0·0004*	−4·25 (−8·20 to −0·31)	0·035
SIRD *vs* SAID	0·62 (−1·07 to 2·32)	0·47	−0·73 (−4·54 to 3·08)	0·71	1·87 (−0·44 to 4·17)	0·11	−5·64 (−7·12 to −4·16)	<0·0001*	−8·82 (−12·64 to −4·99)	<0·0001*
SIRD *vs* SIDD	1·65 (−1·75 to 5·05)	0·34	−5·39 (−12·91 to 2·13)	0·16	0·82 (−3·75 to 5·39)	0·72	−5·29 (−8·23 to −2·35)	0·0004*	−0·27 (−8·88 to 8·33)	0·95
SAID *vs* SIDD	1·03 (−2·19 to 4·24)	0·53	−4·66 (−11·74 to 2·42)	0·20	−1·04 (−5·34 to 3·26)	0·63	0·35 (−2·42 to 3·11)	0·81	8·54 (0·35 to 16·74)	0·041

Regression models have a PRO at baseline (depression symptoms, wellbeing or one of the HRQOL measures or diabetes-related distress score) as the dependent variable and diabetes subtypes and baseline sociodemographic variables (sex, employment, education, and place of birth) as independent variables. Depression symptoms were measured using Center for Epidemiologic Studies Depression Scale (higher values indicate more severe depression symptoms), wellbeing was measured using WHO-5 (higher values indicate higher wellbeing), HRQOL was measured using SF-36 (higher values indicate higher HRQOL), and diabetes-related distress was measured using Problem Areas in Diabetes Scale (higher values indicate higher diabetes-related distress). HRQOL=Health related quality of life. MCS=mental component summary score. MOD=moderate obesity-related diabetes. MARD=moderate age-related diabetes. PCS=physical component summary score. PRO=patient-reported outcome. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. *After the Bonferroni-Holm adjustment (with respect to 10 pairs of diabetes subtypes), the differences were still significant.

Table 4: **Results of multiple linear regressions for PROs at baseline**

We found that PROs are differentially distributed between the diabetes subtypes at baseline and, to a lesser extent, also at follow-up. Although individuals with a diagnosis of a severe psychiatric disorder or taking certain antidepressant medication are not included in the GDS, analyses of dichotomous PROs revealed that 11% of the total sample showed clinically relevant depression symptoms at the beginning of the study. At baseline, participants with MARD appeared to feel better mentally with lower depression symptom scores (*vs* SAID and SIRD), higher MCS of HRQOL (*vs* SAID), and lower diabetes-related distress (*vs* SAID). Diabetes-related distress was higher in participants with SAID than in participants with MARD, MOD, and SIRD. PCS of HRQOL in SIRD was lower than in all other subtypes. In addition, PCS in participants with SAID was higher than for those with MARD, MOD, and SIRD. At the 5-year follow-up, the depression symptom score increased for SIRD and decreased for MARD, rendering the observed difference between SIRD and MARD larger than at baseline. Of note, the regression analyses of the findings at follow-up lost statistical significance after adjustments for multiple testing, which is likely attributable to the smaller sample size in the clusters.

Our findings add to the literature on the effects of insulin resistance[21] and impaired glycaemic control[22] on depression symptoms, wellbeing, HRQOL, and diabetes-related distress; consistent with our hypothesis, participants with SIRD, who have the lowest insulin sensitivity compared with the other subtypes,[16] experienced higher levels of depression symptoms and lower levels of wellbeing than the other subtypes at baseline. Yet, not all of the previously reported differences between subtypes were observed after regression analyses were adjusted for multiple testing. Nevertheless, descriptive analyses revealed that clinically relevant depression symptoms and low wellbeing were almost twice and one and a half times higher, respectively, in the SIRD subtype than in the MARD subtype in the first year after diabetes diagnosis, which might be clinically relevant. Furthermore, participants with SIRD had significantly lower HRQOL PCS scores than the other subtypes. This subtype is typically older and has more overweight, indicating potential physical HRQOL restrictions. In addition, lower levels of physical activity are in line with more pronounced subclinical inflammation, which is a hallmark of SIRD.[25,27] Moreover, previous studies have

See Online for appendix 2

	Depression symptoms (n=488)		Wellbeing (n=622)		HRQOL (n=602)				Diabetes-related distress (n=364)	
	Expected difference in score value (95% CI)	p value	Expected difference in score value (95% CI)	p value	MCS		PCS		Expected difference in score value (95% CI)	p value
					Expected difference in score value (95% CI)	p value	Expected difference in score value (95% CI)	p value		
SAID *vs* MARD	0·38 (–1·39 to 2·16)	0·67	–2·32 (–5·87 to 1·23)	0·20	–0·38 (–2·50 to 1·75)	0·73	1·31 (–0·04 to 2·66)	0·057	2·84 (–0·32 to 6·00)	0·078
SIDD *vs* MARD	–1·42 (–6·55 to 3·70)	0·59	–0·87 (–10·45 to 8·70)	0·86	1·29 (–4·33 to 6·91)	0·65	1·74 (–1·81 to 5·30)	0·34	–3·35 (–13·71 to 7·01)	0·53
SIRD *vs* MARD	2·81 (0·27 to 5·36)	0·030	–3·54 (–8·65 to 1·56)	0·17	–2·35 (–5·48 to 0·79)	0·14	–0·48 (–2·46 to 1·51)	0·64	–1·85 (–6·56 to 2·86)	0·44
MOD *vs* MARD	1·57 (–0·28 to 3·43)	0·096	–2·81 (–6·38 to 0·76)	0·12	–1·65 (–3·78 to 0·48)	0·13	0·34 (–1·01 to 1·68)	0·62	–0·32 (–3·48 to 2·85)	0·84
SAID *vs* MOD	–1·19 (–3·00 to 0·63)	0·20	0·49 (–3·14 to 4·12)	0·79	1·27 (–0·88 to 3·43)	0·25	0·97 (–0·40 to 2·35)	0·17	3·16 (0·02 to 6·30)	0·049
SIDD *vs* MOD	–2·99 (–8·18 to 2·19)	0·26	1·94 (–7·75 to 11·62)	0·70	2·94 (–2·73 to 8·61)	0·31	1·41 (–2·18 to 4·99)	0·44	–3·03 (–13·46 to 7·39)	0·57
SIRD *vs* MOD	1·24 (–1·42 to 3·90)	0·36	–0·73 (–6·05 to 4·58)	0·79	–0·70 (–3·94 to 2·54)	0·67	–0·81 (–2·86 to 1·24)	0·44	–1·54 (–6·39 to 3·32)	0·53
SIRD *vs* SAID	2·43 (–0·17 to 5·02)	0·067	–1·22 (–6·54 to 4·09)	0·65	–1·97 (–5·21 to 1·28)	0·23	–1·79 (–3·87 to 0·29)	0·092	–4·69 (–9·51 to 0·12)	0·056
SIRD *vs* SIDD	4·23 (–1·26 to 9·73)	0·13	–2·67 (–13·07 to 7·73)	0·61	–3·64 (–9·79 to 2·52)	0·25	–2·22 (–6·12 to 1·68)	0·26	1·50 (–9·56 to 12·55)	0·79
SAID *vs* SIDD	1·81 (–3·34 to 6·95)	0·49	–1·45 (–11·09 to 8·19)	0·77	–1·67 (–7·32 to 3·98)	0·56	–0·43 (–4·00 to 3·13)	0·81	6·19 (–4·22 to 16·61)	0·24

Regression models have a PRO at 5-year follow-up (depression symptoms, wellbeing, one of the HRQOL measures, or diabetes-related distress score) as the dependent variable and diabetes subtypes and the corresponding PRO at baseline as well as baseline sociodemographic variables (sex, employment, education, and place of birth) as independent variables. Depression symptoms were measured using Center for Epidemiologic Studies Depression Scale (higher values indicate more severe depression symptoms), wellbeing was measured using WHO-5 (higher values indicate higher wellbeing), HRQOL was measured using SF-36 (higher values indicate higher HRQOL), and diabetes-related distress was measured using Problem Areas in Diabetes Scale (higher values indicate higher diabetes-related distress). After the Bonferroni–Holm adjustment (with respect to 10 pairs of diabetes subtypes), no differences were significant. HRQOL=Health related quality of life. MOD=moderate obesity-related diabetes. MARD=moderate age-related diabetes. MCS=mental component summary score. PCS=physical component summary score. PRO=patient-reported outcome. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes.

Table 5: **Results of multiple linear regression modelling PROs at 5-year follow-up**

found that the SIRD subtype is associated with an increased prevalence or progression of cardiovascular, renal, and hepatic disease (eg, metabolic dysfunction–associated steatotic liver disease and liver fibrosis).[15,16,18,45] Moreover, individuals with SIRD display the lowest physical fitness and a higher cardiovascular risk profile than the other subtypes.[18] Thus, the lower physical HRQOL reported in SIRD might be due to initial physical impairment caused by secondary diseases at an early stage and is therefore in agreement with recent research.[16] Moreover, previous findings indicate that insulin treatment predicts lower quality of life in people with type 2 diabetes.[42] Our results show that individuals with SIRD are often treated with insulin soon after diagnosis, which might contribute to their lower reported physical HRQOL. Participants with MARD experienced better mental health conditions and appeared to be less affected by their condition compared with SAID and, in part, SIRD.[16] The MARD subtype is characterised by older age but lower BMI (*vs* MOD and SIRD) and HbA_{1c} (*vs* SIDD). A lower prevalence of obesity and reduced insulin use among MARD participants could contribute to their lower diabetes-related distress and improved mental health status. Moreover, with an average age of 58 years, participants with MARD might have a higher overall acceptance of diabetes compared with their younger counterparts.

Participants with SAID showed higher PCS scores than almost all other subtypes (MARD, MOD, and SIRD) at baseline. This finding is not surprising, as participants with SAID were the youngest on average, and young age is inherently associated with better physical health and a lower risk of established comorbidities. In addition, SAID subtype presents with the lowest degrees of BMI and insulin resistance and the lowest inflammatory biomarker levels.[30] In contrast, individuals with SAID showed higher levels of diabetes-related distress compared with MARD, MOD, and SIRD and this was also clearly visible in the descriptive comparisons. This finding is consistent with the typical treatment of type 1 diabetes, which necessitates insulin therapy and is associated with elevated levels of diabetes-related distress.[46] Moreover, numerous factors are known to influence diabetes-related distress, including the

experience of severe hyperglycaemia and the challenge of maintaining a normal lifestyle while adhering to self-management protocols.[47] However, descriptively, participants with SAID, as well as participants with other subtypes, reported less diabetes-related distress at 5 years. Distress appears to be particularly high soon after diagnosis, as diagnosis often requires a change in lifestyle, and coping difficulties are reported.[47] After 5 years, when examining the development of clinically relevant depression symptoms using analyses of dichotomous PROs in the subsample, the total percentage of individuals exhibiting symptoms increased by 50%. Additionally, the average change in depression symptom scores was higher in participants with SIRD at baseline, compared with people with MARD. The resulting higher depression symptom scores of SIRD at the 5-year follow-up lost statistical significance after adjustment for multiple testing. Nevertheless, descriptive analyses at follow-up demonstrated that individuals with SIRD were almost three (16%) and two times (31%) more likely to have clinically relevant depression symptoms and low wellbeing, respectively, than individuals with MARD (6% and 14%). Therefore, low insulin sensitivity might explain higher depression symptoms in the future, in line with findings on the biological and behavioral mechanisms of depression and diabetes.[23–25,27]

The main strengths of this study are its longitudinal design, comprehensive phenotyping of the GDS cohort, and the analysis of different PROs using valid, widely used instruments, with generally few missing values during the course of the study. Other strengths include the comprehensive sensitivity analyses regarding the effects of some cluster variables, the effects of additional potential confounders on the PROs, and the analyses of dichotomous PROs. The former two points show that some effects became weaker (eg, when age was added) but remained generally consistent. Although we found that the effects differed slightly in the corresponding models for continuous and dichotomous PROs, we found that the direction of the effects was consistent for all cluster comparisons in both models.

Limitations of our study were the non-population-based design of the GDS, which resulted in a cohort consisting of White, mostly younger (mean age 48·1 years [SD 13·3]), more highly educated, male participants.[29] Therefore, the findings might not be representative of the broader population of individuals with diabetes in Germany or other similar populations. Second, unknown confounders or measurement errors could have biased the results; however, we took great care in selecting the confounders. Third, some subtypes (eg, SIDD) might have been somewhat underrepresented (ie, due to the exclusion of individuals with poor glycaemic control), which in turn could have underestimated the differences in PROs between SIDD and the other subtypes. Consequently, we were able to estimate the difference in PROs between subtypes with varying precisions. For instance, the expected difference in PCS at baseline between the two largest diabetes subtypes was estimated with higher precision (ie, PCS at baseline was on average 2·14 points higher for SAID than for MARD [95% CI 1·07–3·22], which has the smallest width of about 2 points on the PCS scale). In contrast, the estimated PCS difference of 5·29 for SIDD versus SIRD (ie, the smallest diabetes subtypes), was much less accurately estimated as the 95% CI (2·35–8·23) was much wider at about 6 points. Due to the much smaller subsample, 95% CIs were even larger in the 5-year follow-up analysis. Although our sample size is not large enough to estimate differences in PROs with high precision, it appears to be sufficient to detect substantial differences in PROs between diabetes subtypes. For example, the expected difference in diabetes-related distress for SAID versus SIRD of 8·82 was less accurate based on the 95% CI (4·99–12·64), with a width of about 8 points. However, with the lower 95% CI threshold of 4·99 points, the difference from 0 is clear. Fourth, clinically overt mental disorders, including major depression and the use of certain antidepressant medications, were exclusion criteria for the GDS, resulting in a healthier cohort, which might explain the rather low depression symptom scores in the present sample. Regarding the follow-up study population, we cannot exclude that participants withdrew due to depression. However, reasons for withdrawing were documented regularly, and depression was not mentioned by any participant. As with diabetes, attempts have been made to identify depression subtypes, such as immunometabolic depression, that might help explain the differential effects of antidepressant therapy.[48,49] These aspects were not the focus of our research, but they might warrant further investigation in future studies examining potential associations between depression and diabetes-specific clinical variables. Another limitation is that we considered only the PRO measurements at baseline and the 5-year follow-up. Of note, depression symptoms can vary over time, similar to wellbeing, HRQOL, and diabetes-related distress. However, the same approach was used in a number of studies which analyse the incidence of depression (eg, Nouwen and colleagues, 2010).[50] After correction for multiple testing, the effects in the regression analyses of wellbeing and MCS of HRQOL at baseline and follow-up were not statistically significant. Moreover, the reduced number of statistically significant comparisons at follow-up might be attributed to the smaller sample size.

In conclusion, this study describes novel associations between PROs and diabetes subtypes. It demonstrates that certain subtypes differ in terms of depression symptoms, wellbeing, HRQOL, or diabetes-related distress within the first year after diagnosis. In particular, participants with SIRD had higher depression symptom scores than participants with MARD and the lowest physical HRQOL among all subtypes at baseline. 5 years after diagnosis, clustering predicted no significant changes in PROs after adjustment for multiple testing, most likely due to the limited sample

size in certain subtypes, thus limiting statistical power. However, descriptive analyses showed that participants with SIRD had the largest changes in depression symptom scores leading to the highest score at the 5-year follow-up. Thus, the increased risk of participants with SIRD developing diabetes-related comorbidities and complications might therefore apply not only to somatic diseases (eg, cardiovascular, renal, and hepatic disease)[15,16] but also to depression symptoms. Even if the absolute differences are small, clustering might predict future changes in depression symptoms, particularly when analyses of dichotomous version of PROs are examined. Hence, the present findings provide a first step to help identify people with diabetes and high risk for depression, paving the way for their tailored treatment and precision medicine. Whether the observed differences in PROs apply to the subtypes in general and how they develop after 10 years should be investigated in future studies. In line with international guidelines[51,52] recommending early screening for depression, the present study highlights the importance of detecting depression very early in the course of diabetes, but also points to certain high-risk subtypes requiring intensive management to maintain mental health and thereby reduce the risk of dysglycaemia and related complications.

Study group members

The GDS Study Group consists of M Roden (speaker), H Al-Hasani, B Belgardt, G Bönhof, G Geerling, C Herder, A Icks, K Jandeleit-Dahm, J Kotzka, O Kuß, E Lammert, W Rathmann, S Schlesinger, V Schrauwen-Hinderling, J Szendroedi, S Trenkamp, R Wagner, and their co-workers who contributed to the design and conduct of the GDS.

Contributors

JSo and SOB wrote the first draft of the manuscript. AI, JSo, SOB, and VG contributed to the concept, design, and drafting of the present study. AI, JSo, SOB, and VG developed the design of the analysis. VG and KS verified all raw data in the study und conducted the formal analyses. All authors contributed to data interpretation and read and approved the final report. MR is the primary investigator of the German Diabetes Study. AI takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. All authors were permitted to access the data if they wished and accept responsibility to submit the manuscript for publication.

Declaration of interests

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Data sharing

The data sets generated or analysed for this study are not available publicly because they are subject to national data protection laws and restrictions imposed by the ethics committee to ensure study participants' privacy. However, they can be applied for through an individual project agreement with the principal investigator of the GDS. The study protocol and the individual methods have been published in the cohort profile and are available without restrictions.

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References

1 Chireh B, Li M, D'Arcy C. Diabetes increases the risk of depression: a systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. *Prev Med Rep* 2019; **14:** 100822.

2 Schram MT, Baan CA, Pouwer F. Depression and quality of life in patients with diabetes: a systematic review from the European depression in diabetes (EDID) research consortium. *Curr Diabetes Rev* 2009; **5:** 112–19.

3 Johnson B, Eiser C, Young V, Brierley S, Heller S. Prevalence of depression among young people with type 1 diabetes: a systematic review. *Diabet Med* 2013; **30:** 199–208.

4 Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2016; **70:** 70–84.

5 Roy T, Lloyd CE, Pouwer F, Holt RIG, Sartorius N. Screening tools used for measuring depression among people with Type 1 and Type 2 diabetes: a systematic review. *Diabet Med* 2012; **29:** 164–75.

6 Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom* 2015; **84:** 167–76.

7 Ali S, Stone M, Skinner TC, Robertson N, Davies M, Khunti K. The association between depression and health-related quality of life in people with type 2 diabetes: a systematic literature review. *Diabetes Metab Res Rev* 2010; **26:** 75–89.

8 de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 2001; **63:** 619–30.

9 Novak M, Mucsi I, Rhee CM, et al. Increased risk of incident chronic kidney disease, cardiovascular disease, and mortality in patients with diabetes with comorbid depression. *Diabetes Care* 2016; **39:** 1940–47.

10 Kleefstra N, Landman GWD, Houweling ST, et al. Prediction of mortality in type 2 diabetes from health-related quality of life (ZODIAC-4). *Diabetes Care* 2008; **31:** 932–33.

11 Hutter N, Schnurr A, Baumeister H. Healthcare costs in patients with diabetes mellitus and comorbid mental disorders—a systematic review. *Diabetologia* 2010; **53:** 2470–79.

12 Elsayed NA, Aleppo G, Aroda VR, et al. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes—2023. *Diabetes Care* 2023; **46** (suppl 1)**:** 49–67.

13 Herder C, Roden M. A novel diabetes typology: towards precision diabetology from pathogenesis to treatment. *Diabetologia* 2022; **65:** 1770–81.

14 Deutsch AJ, Ahlqvist E, Udler MS. Phenotypic and genetic classification of diabetes. *Diabetologia* 2022; **65:** 1758–69.

15 Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018; **6:** 361–69.

16 Zaharia OP, Strassburger K, Strom A, et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 2019; **7:** 684–94.

17 Zou X, Zhou X, Zhu Z, Ji L. Novel subgroups of patients with adult-onset diabetes in Chinese and US populations. *Lancet Diabetes Endocrinol* 2019; **7:** 9–11.

18 Saatmann N, Zaharia OP, Strassburger K, et al. Physical fitness and cardiovascular risk factors in novel diabetes subgroups. *J Clin Endocrinol Metab* 2022; **107:** 1127–39.

19 Maalmi H, Herder C, Bönhof GJ, et al. Differences in the prevalence of erectile dysfunction between novel subgroups of recent-onset diabetes. *Diabetologia* 2022; **65:** 552–62.

20 Zaharia OP, Strassburger K, Knebel B, et al. Role of patatin-like phospholipase domain– containing 3 gene for hepatic lipid content and insulin resistance in diabetes. *Diabetes Care* 2020; **43:** 2161–68.

21 Kan C, Silva N, Golden SH, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. *Diabetes Care* 2013; **36:** 480–89.

22 Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000; **23:** 934–42.

23 Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015; **3:** 461–71.

24 Schmitt A, Reimer A, Hermanns N, et al. Depression is linked to hyperglycaemia via suboptimal diabetes self-management: a cross-sectional mediation analysis. *J Psychosom Res* 2017; **94:** 17–23.

25 Herder C, Fürstos JF, Nowotny B, et al. Associations between inflammation-related biomarkers and depressive symptoms in individuals with recently diagnosed type 1 and type 2 diabetes. *Brain Behav Immun* 2017; **61:** 137–45.

26 Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. *Curr Diab Rep* 2010; **10:** 396–405.

27 Herder C, Maalmi H, Strassburger K, et al. Differences in biomarkers of inflammation between novel subgroups of recent-onset diabetes. *Diabetes* 2021; **70:** 1198–208.

28 Elsayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes—2023. *Diabetes Care* 2023; **46** (suppl 1)**:** 19–40.

29 Szendroedi J, Saxena A, Weber KS, et al. Cohort profile: the German Diabetes Study (GDS). *Cardiovasc Diabetol* 2016; **15:** 59.

30 Zaharia OP, Bobrov P, Strassburger K, et al. Metabolic characteristics of recently diagnosed adult-onset autoimmune diabetes mellitus. *J Clin Endocrinol Metab* 2018; **103:** 429–37.

31 van Dijk SEM, Adriaanse MC, van der Zwaan L, et al. Measurement properties of depression questionnaires in patients with diabetes: a systematic review. *Qual Life Res* 2018; **27:** 1415–30.

32 Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. How to screen for depression and emotional problems in patients with diabetes: comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment. *Diabetologia* 2006; **49:** 469–77.

33 Hautzinger M, Bailer M, Hofmeister D, Keller F. ADS: Allgemeine Depressionsskala. Göttingen, 2012: Hogrefe.

34 Halliday JA, Hendrieckx C, Busija L, et al. Validation of the WHO-5 as a first-step screening instrument for depression in adults with diabetes: results from diabetes MILES - Australia. *Diabetes Res Clin Pract* 2017; **132:** 27–35.

35 Brähler E, Mühlan H, Albani C, Schmidt S. Teststatistische prüfung und normierung der deutschen versionen des EUROHIS-QOL Lebensqualität-index und des WHO-5 Wohlbefindens-index. *Diagnostica* 2007; **53:** 83–96.

36 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30:** 473–83.

37 Bullinger M, Kirchberger I, Ware J. The German SF-36 health survey translation and psychometric testing of a generic instrument for the assessment of health-related quality of life. *Z Gesundhwiss* 1995; **3:** 21–36.

38 Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of diabetes-related distress. *Diabetes Care* 1995; **18:** 754–60.

39 Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. *Lancet Diabetes Endocrinol* 2015; **3:** 450–60.

40 Nano J, Carinci F, Okunade O, et al. A standard set of person-centred outcomes for diabetes mellitus: results of an international and unified approach. *Diabet Med* 2020; **37:** 2009–18.

41 Schmidt CB, Potter van Loon BJ, Torensma B, Snoek FJ, Honig A. Ethnic minorities with diabetes differ in depressive and anxiety symptoms and diabetes-distress. *J Diabetes Res* 2017; **2017:** 1204237.

42 Bradley C, Eschwège E, de Pablos-Velasco P, et al. Predictors of quality of life and other patient-reported outcomes in the PANORAMA multinational study of people with type 2 diabetes. *Diabetes Care* 2018; **41:** 267–76.

43 Twisk J, Bosman L, Hoekstra T, Rijnhart J, Welten M, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. *Contemp Clin Trials Commun* 2018; **10:** 80–85.

44 Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159:** 702–06.

45 Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023; **79:** 1542–56.

46 Paczkowski R, Poon JL, Cutts KN, et al. The burden and impacts of mealtime insulin from the perspective of people with diabetes. *Diabetes Ther* 2023; **14:** 1057–72.

47 van Duinkerken E, Snoek FJ, de Wit M. The cognitive and psychological effects of living with type 1 diabetes: a narrative review. *Diabet Med* 2020; **37:** 555–63.

48 Vreijling SR, Chin Fatt CR, Williams LM, et al. Features of immunometabolic depression as predictors of antidepressant treatment outcomes: pooled analysis of four clinical trials. *Br J Psychiatry* 2024; **224:** 89–97.

49 van Loo HM, Cai T, Gruber MJ, et al. Major depressive disorder subtypes to predict long-term course. *Depress Anxiety* 2014; **31:** 765–77.

50 Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 2010; **53:** 2480–86.

51 ElSayed NA, Aleppo G, Bannuru RR, et al. 5. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes-2024. *Diabetes Care* 2024; **47** (suppl 1)**:** S77–110.

52 IDF Europe welcomes the Commission's communication on 'A comprehensive approach to mental health' and calls for more recognition of the needs of Europeans living with NCDs such as diabetes. IDF Europe. 2023. https://idf.org/europe/news/idf-europe-welcomes-the-commissions-communication-on-a-comprehensive-approach-to-mental-health-and-calls-for-more-recognition-of-the-needs-of-europeans-living-with-ncds-such (accessed July 15, 2024).