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Representativeness of the Swiss Diabetes Registry – a single centre analysis

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Summary

OBJECTIVE: The Swiss Diabetes Registry (SwissDiab) is a multicentre, longitudinal, observational study of outpatients with diabetes receiving treatment at tertiary care centres. The aim of this study was to evaluate the representativeness of the participants at the study centre in the Division of Endocrinology and Diabetes at the Cantonal Hospital of St Gallen by comparing diabetes-related characteristics of participating and nonparticipating patients.

METHODS: The study included 493 SwissDiab participants enrolled between 1 January 2010 and 31 December 2016 and 640 nonparticipating patients treated at the centre during the same time period. For participants and nonparticipating patients, demographic characteristics, clinical findings, blood chemistry and medication were retrieved from the SwissDiab baseline visit and the medical record ±6 months from the first available outpatient visit to the clinic for diabetes-related care within the study period. Nonparticipating patients were further divided into three subgroups: (i) excluded from SwissDiab, or having received (ii) ≥6 months or (iii) <6 months of prior diabetes treatment at the centre. Differences in diabetes-related clinical characteristics were determined using simple bivariate (nonparametric) statistical analyses stratified by diabetes mellitus type 1 and type 2.

RESULTS: Compared with nonparticipants, participants smoked less (diabetes mellitus type 1: 24% vs 45%; diabetes mellitus type 2: 21% vs 29%), had higher educational attainment (diabetes mellitus type 1: 39% vs 21%; and diabetes mellitus type 2: 25% vs 18%) and lower glycated haemoglobin levels (diabetes mellitus type 1: 7.2% vs 7.8%; diabetes mellitus type 2: 7.2% vs 8.1%). In diabetes mellitus type 2, the proportion of females (30% vs 38%) and a migration background (36% vs 49%) were lower among participants. (All p-values <0.05.) In a stratified analysis SwissDiab participants had slightly better controlled diabetes than nonparticipating patients with ≥6 months of prior treatment, whereas the diabetes of patients recently referred to the clinic (with <6 months of prior treatment) and patients excluded from participation in SwissDiab were less well controlled.

CONCLUSION: The observed differences in clinical characteristics between study participants and nonparticipating patients indicate that SwissDiab is likely to overestimate the state of diabetes care and management. The results highlight the need to improve recruitment of females and patients with a migration background in diabetes mellitus type 2.

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Introduction

Switzerland lacks a nationwide diabetes registry. The Swiss Diabetes Registry (SwissDiab) is an ongoing multicentre prospective observational study of patients with diabetes treated at tertiary care centres. This is a group of patients who often have insufficiently controlled diabetes with, or at high risk of, severe diabetes-related complications and the cost are generally high, in terms of both health resources and personal suffering. The overall aim of SwissDiab is to assess diabetes care and management, prevalence and incidence of diabetes-related complications, and quality of life in this patient population to help ensure that best clinical care is provided. Patient recruitment started in 2010 with an initial 3-year pilot phase at the tertiary diabetes care centres at the Cantonal Hospital of St Gallen and the Inselspital, Bern University Hospital. Three additional centres have since joined (the tertiary diabetes care centres at the University Hospital Basel, Geneva University Hospital and Zürich University Hospital). A minimum of 500 participants per centre is intended to enhance representativeness of the patient population at each centre. However, both inclusion and exclusion criteria and possible selection biases might compromise the representativeness of the study population. Studies have shown that individuals willing to participate in clinical studies tend to have better overall health, including higher health consciousness and higher socioeconomic status, than individuals declining study participation [1–4]. As results coming out of SwissDiab may inform local and national guidelines for diabetes care and management, it is important to understand to what extent results emanating from SwissDiab are generalisable to the patient population at tertiary care centres at large. The aim of this study was therefore to compare demographics, clinical findings, blood chemistry and medication of SwissDiab participants and nonparticipating patients at one of the study centres, the Division of En-

docrinology and Diabetes at the Cantonal Hospital of St Gallen.

Research design and methods

The study was designed as a retrospective cross-sectional study. Baseline data of SwissDiab participants enrolled between 1 January 2010 and 31 December 2016 at the study centre at the Cantonal Hospital of St Gallen were compared with data from nonparticipating patients with at least one documented visit to the clinic for diabetes-related care during the same time period. The study was limited to diabetes mellitus type 1 (DM1) and type 2 (DM2). Other types of diabetes were excluded owing to the heterogeneous nature of the groups and small sample sizes.

The cantonal ethics committee of East Switzerland approved both the SwissDiab study protocol and the protocol of the current study (PB_2016-01449, and EKOS 2017-00370, respectively).

SwissDiab participants

Eligible for participation were patients ≥18 years of age regardless of diabetes type (gestational diabetes excluded), duration or treatment. Patients with a life expectancy <1 year due to severe comorbidity (e.g., end-stage cancer), inability to provide informed consent or irregular attendance, for example due to drug abuse or mental disorder, were excluded at the discretion of the attending physician.

Data were collected by trained medical staff carrying out standardised annual health examinations comprising demographics, anthropometric measurements and clinical examination, diabetes-related and general medical history, medication and biochemistry. All participants provided written informed consent.

Nonparticipating patients

Nonparticipating patients were defined as patients with DM1 or DM2 who (i) did not fulfil the inclusion criteria or (ii) declined to participate in SwissDiab or (iii) had not been asked to participate in SwissDiab. An opt-out recruitment strategy was used. A letter was sent to all identified nonparticipating patients, describing the study and asking permission to collect a set of clinical parameters from their medical record. Nonconsenting patients were asked to opt out via telephone or email. Deceased patients and patients who could not be contacted because of an invalid postal address (letter returned to sender) were excluded from the analysis. For consenting nonparticipating patients, a prespecified set of clinical parameters was manually collected by a trained medical staff member from the clinical record ±6 months from the date of the first available outpatient visit to the clinic for diabetes-related care during the study period (at which point the patient might already have had one or more previous visits to the clinic).

Diabetes definitions

Diabetes was defined in accordance with the American Diabetes Association [5]. Diabetes type was diagnosed clinically, supported by autoantibody status where appropriate [6].

Demographics

Migration background was defined by a self-reported foreign country of birth. Higher education was defined as a college degree or higher for SwissDiab participants and a profession or current occupation requiring a college degree or higher for nonparticipating patients. Family history of diabetes was defined as a relative with diabetes (first or second degree). Mental health disorder was defined as dementia, substance dependence, schizophrenia, affective disorders, depression and/or eating disorder.

Clinical and anthropometric measurements

Weight (to the nearest 0.1 kg) was measured with a digital scale with patients wearing light clothes and no shoes. Height (to the nearest 0.5 cm) was measured using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Overweight was defined as a BMI ≥25 kg/m^2. Systolic (SBP) and diastolic blood pressure (DBP) was measured once following a 5-minute rest with the patient in a seated position.

Medication

Glucose- and lipid-lowering medication at the time of the study visit was collected from the medical record. Glucose-lowering therapy was categorised as (i) classic oral antidiabetics including metformin, sulfonylureas, glinide, glitazone, and dipeptidyl peptidase-4 inhibitors, and (ii) new antidiabetics including glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors. Insulin therapy was defined as any administration of insulin. Lipid-lowering medication included statins, fibrate, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Information about ezetimibe was not available in nonparticipating patients and was not considered in the analysis.

Biochemistry

SwissDiab participants and nonparticipating patients were advised to arrive at the clinic in a fasted state (≥8 hrs). Blood was drawn from the antecubital vein and glycated haemoglobin (HbA1c) was measured using an NGSP certified, IFCC traceable assay (boronate affinity method, AFINION AS100 analyser, Abbott AG, Switzerland). Serum triglycerides and total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels were determined using an enzymatic colorimetric test (UniCel DxC800 analyser, Beckman Coulter, USA) according to routine methods at the centre of laboratory medicine at the Cantonal Hospital St Gallen (ISO/IEC 17025 accredited).

Diabetes-related complications

For SwissDiab participants, detailed information on the prevalence and history of diabetes-related complications were collected at the annual visit by the attending physician. For nonparticipating patients, information was retrieved retrospectively from the medical records. *Retinopathy* was defined as (non-)proliferative retinopathy or any related eye complication diagnosed by an ophthalmologist. *Neuropathy* was defined as (i) diagnosed pathology of the peripheral nervous system by an endocrinologist (including regular foot examinations and care), (ii) <5 on a 128 Hz scaled tuning fork over one or both lateral bony promi-

nences of the metatarsophalangeal I joints [7], (iii) ≥1 insensate point in the monofilament test at four defined plantar locations [8], or (iv) ≥2 insensate points at ten defined plantar locations [9]. *Coronary heart disease* was defined as (i) documentation of significant coronary artery pathology by invasive diagnostics, (ii) history of myocardial infarction, or (iii) evidence of a coronary artery intervention or surgical revascularisation. *Peripheral arterial disease* (PAD) was defined as documented vessel pathology by (i) non-invasive tests (doppler/duplex ultrasound), (ii) imaging techniques (e.g., computed tomography-angiography), (iii) invasive diagnostics (angiography), and (iv) an ankle brachial index (ABI) <0.9 at one or both feet were used as a surrogate marker of PAD. In SwissDiab, ABI is measured every second year. In nonparticipating patients, ABI was used whenever available (n = 17,.4%). *Stroke* was defined as a documented stroke or a transient ischaemic attack. *Nephropathy* was defined as (i) documented nephropathy by a nephrologist, (ii) diabetic nephropathy documented by an endocrinologist, (iii) documented micro- or macroalbuminuria, (iv) an albumin/creatinine ratio >3 mg/mmol, or (v) need for dialysis or kidney transplantation.

Data analysis

Demographics, clinical findings, blood chemistry, and medication of SwissDiab participants and nonparticipating patients were compared stratified by DM1 and DM2. Nonparticipating patients were further stratified into three subgroups; (i) patients with <6 months of diabetes treatment at the clinic prior to the study visit, (ii) patients with ≥6 months of diabetes treatment at the clinic prior to the study visit, and (iii) patients excluded from participation in SwissDiab. The subgroups were introduced to account for the presence of treatment bias in the analysis. Patients who are referred to tertiary care, most often by their general practitioner because of insufficient glycaemic control, often exhibit significant improvement in glycaemic control in the first 3–6 months in response to intensified care and treatment. A majority (94%) of SwissDiab participants received treatment at the clinic for at least 6 months prior to enrolment. The second subgroup of nonparticipating patients (patients with ≥6 months of treatment at the clinic) thus predominantly included patients who would be eligible for participation in SwissDiab but either were not asked or declined to participate.

Data are presented as median (interquartile range [IQR]) or absolute and relative frequencies. A two-sided Wilcoxon rank-sum test was used for continuous and a chi-square test for categorical variables. All analyses were performed using SAS 9.4 (SAS Institute Cary, NC).

Results

In the SwissDiab database, 137 patients with DM1 and 359 patients with DM2 were enrolled at the centre at the Cantonal Hospital of St. Gallen between 1 January 2010 and 31 December 2016. Three participants were excluded because of missing data, leaving 135 patients (27%) with DM1 and 358 patients (73%) with DM2 available for analysis.

During the same period, 860 patients with diabetes who were not enrolled in SwissDiab visited the centre. Of these, 74 patients (9%) diagnosed with a diabetes type other than DM1 or DM2 were excluded. A further 15 patients (2%) were excluded because they only visited the clinic once with limited data available, and in 50 patients (6%) consent could not be sought owing to an invalid postal address. Of the remaining 721 patients, 48 (7%) declined having their data used and 33 (5%) were deceased. In the end, 640 nonparticipating patients (166 [26%] with DM1 and 474 [74%] with DM2) were included in the analysis (fig. 1). Of these, 49 patients (30%) with DM1 and 186 patients (39%) with DM2 had been excluded from participation in SwissDiab by their attending physician. Of the remaining 117 patients with DM1, 74 (63%) had been treated for ≥6 months at the clinic and 43 (37%) <6 months. Of the remaining 288 patients with DM2, 109 (38%) had been treated ≥6 months at the clinic and 179 (62%) <6 months.

DM1

Compared to nonparticipating patients, SwissDiab participants had more often had higher education (39% vs 21%, p = 0.0009), included fewer smokers (24% vs 45%, p = 0.0003), lower HbA1c (7.2% vs 7.8%, p = <0.0001) and serum triglyceride levels (0.8 vs 1.2 mmol/l, p = <0.0001), and higher HDL cholesterol levels (1.5 vs 1.4 mmol/l, p = 0.02) (table 1). No significant differences in antidiabetic or lipid-lowering medication or prevalence of mental health disorder was observed. Among participants, 100% of the cases of mental health disorder were depression or affective disorders as compared with 48% among nonparticipating patients.

Among the nonparticipating patients treated for ≥6 months, no difference in HbA1c and HDL cholesterol levels was observed, but there was a significantly higher frequency of a migration background (30% vs 16%, p = 0.03) among participants (table 1).

Compared with nonparticipating patients treated <6 months, lower triglyceride and HbA1c levels, and higher HDL cholesterol was still observed among participants. In addition, participants tended to be older (42 vs 37 years, p = 0.05) and received their diagnosis at an older age (27 vs 23 years, p = 0.04) (table 1).

The differences in clinical characteristics between SwissDiab participants and excluded patients were similar to, but slightly greater than, those observed for all nonparticipating patients, with the exception that no difference in HDL cholesterol levels was observed (table 1).

Diabetes-related complications

As shown in table 2, the prevalence of coronary heart disease (CHD) was lower in SwissDiab participants than in all nonparticipating patients and those treated for ≥6 months (2.2% vs 7.2% and 9.5%, respectively). Neuropathy was more prevalent among excluded patients than participants (37% vs 21%). All p-values <0.05.

DM2

Compared with nonparticipating patients, SwissDiab participants included fewer females (30% vs 38%, p = 0.02), had longer duration of diabetes (10 vs 8 years, p <0.0001), and more often a family history of diabetes (68% vs 57%, p = 0.002) (table 3). Furthermore, participants more frequently had higher education (25% vs 18%, p = 0.03), less often a migration background (36% vs 49%, p = 0.0003),

were less often smokers (21% vs 29%, p = 0.01), had a higher BMI (32 vs 31 kg/m^2, p = 0.02), and higher prevalence of overweight and obesity (94% vs 89%, p = 0.03). No significant difference in the overall prevalence of mental health disorders was observed. Among participants, 88% of the cases were depression or affective disorders compared with 62% among nonparticipating patients. Participants also presented with lower HbA1c (7.2% vs 8.1%, p <0.0001) and diastolic blood pressure (77 vs 79 mm Hg, p = 0.04), a more favourable lipid profile (lower triglycerides [1.9 vs 2.2 mmol/l], lower total cholesterol [4.2 vs 4.5 mmol/l] and LDL cholesterol [2.4 vs 2.6 mmol/

Figure 1: Flowchart showing the exclusions applied when identifying patients with DM1 or DM2 who were not participating in SwissDiab and were eligible for the current analysis. See "Nonparticipating patients" for more details on the exclusion criteria applied. DM1 = diabetes mellitus type 1; DM2 = diabetes mellitus type 2. * Patients previously excluded from participation in SwissDiab based on inclusion/exclusion criteria.

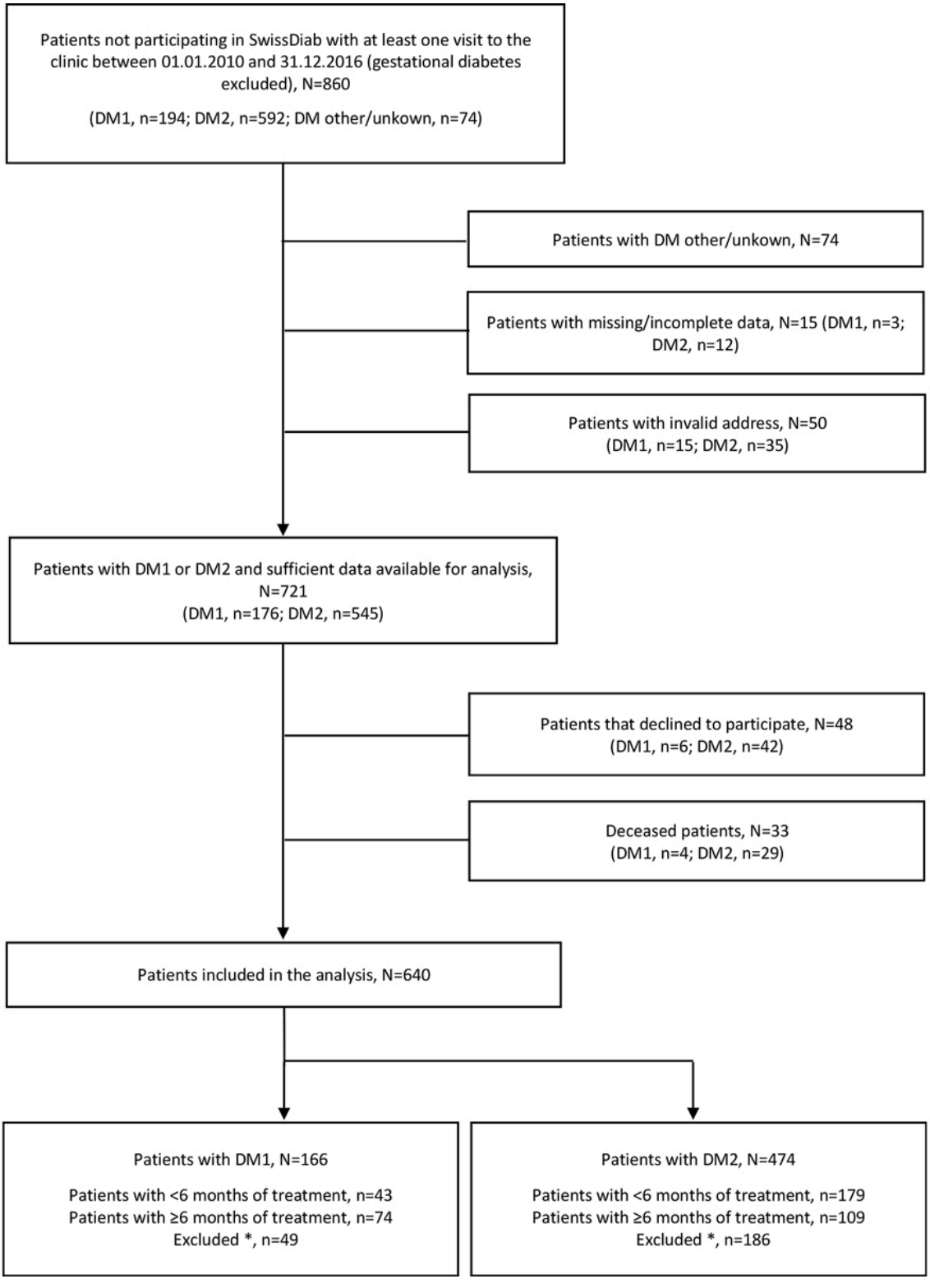

Table 1: Characteristics of SwissDiab participants and nonparticipating patients with DM1.

Characteristic	SwissDiab (n = 135)		Nonparticipating patients											
			All (n = 166)			Patients with ≥6 months of treatment (n = 74)			Patients with <6 months of treatment (n = 43)			Excluded (n = 49)		
	n	% or median (IQR)	n	% or median (IQR)	p-value*	n	% or median (IQR)	p-value†	n	% or median (IQR)	p-value‡	n	% or median (IQR)	p-value§
Females, %	56	41.5	76	45.8	0.45	30	40.5	0.89	25	58.1	0.056	21	42.9	0.87
Age, yrs	135	42.0 (29.0–54.0)	166	40.0 (28.8–52.0)	0.43	74	39.9 (29.8–52.3)	0.65	43	36.6 (25.8–46.8)	0.053	49	44.6 (30.5–55.0)	0.59
Age at diagnosis, yrs	135	27.0 (15.0–45.0)	165	24.5 (15.0–38.0)	0.087	74	24.0 (17.0–38.0)	0.29	43	23.0 (9.0–36.0)	**0.043**	49	27.0 (14.0–40.0)	0.46
Diabetes duration, yrs	135	8.0 (5.0–18.0)	166	11.0 (5.0–21.0)	0.37	74	11.0 (5.0–19.0)	0.37	43	11.0 (2.0–21.0)	0.57	49	13.0 (7.0–21.0)	0.15
Family history DM, %	68 (12)	51.2	73 (14)	48.0	0.60	37 (7)	55.2	0.60	14 (4)	35.9	0.095	22 (3)	47.8	0.69
Family history DM1, %	14 (11)	11.5	15 (14)	9.9	0.66	9 (7)	13.4	0.69	2 (4)	5.1	0.25	4 (3)	8.7	0.60
Higher education, %	51 (4)	38.9	29 (25)	20.6	**0.0009**	11 (8)	16.7	**0.0015**	11 (4)	28.2	0.22	7 (13)	19.4	**0.030**
Mental health disorder, %	12	8.9	27	16.3	0.058	12	16.2	0.11	6	14.0	0.34	9	19.4	0.074
Migration background, %	41	30.4	42	25.3	0.33	12	16.2	**0.025**	15	34.9	0.58	15	30.6	0.97
Active smoking, %	32 (3)	24.2	65 (21)	44.8	**0.0003**	32 (6)	47.1	**0.001**	13 (8)	37.1	0.13	20 (7)	47.6	**0.0039**
BMI, kg/m^2	135	24.5 (22.4–26.9)	153	25.2 (21.6–27.6)	0.88	66	25.5 (21.9–28.7)	0.43	42	24.4 (21.5–26.5)	0.30	45	24.6 (21.7–27.0)	0.70
BMI ≥25 kg/m^2, %	60	44.4	79 (13)	51.6	0.22	39 (8)	59.1	0.051	19 (1)	45.2	0.93	21 (4)	46.7	0.80
SBP, mm Hg	134	128 (118–139)	152	130 (121–143)	0.22	66	130 (120–142)	0.62	41	131 (122–138)	0.48	45	132 (120–148)	0.13
DBP, mm Hg	134	75 (67–80)	152	75 (69–82)	0.60	66	75 (68–81)	0.88	41	75 (71–83)	0.32	45	76 (68–81)	0.62
Total cholesterol, mmol/l	131	4.8 (4.3–5.4)	107	4.7 (3.9–5.4)	0.30	37	4.5 (3.8–5.1)	0.051	28	4.8 (3.9–5.6)	0.66	42	4.9 (4.1–5.6)	0.84
Triglyceride, mmol/l	130	0.8 (0.6–1.3)	106	1.2 (0.8–2.1)	**<.0001**	35	1.0 (0.8–1.4)	**0.016**	28	1.3 (1.0–2.6)	**<.0001**	43	1.3 (0.8–2.5)	**0.0002**
HDL cholesterol, mmol/l	131	1.5 (1.3–1.9)	91	1.4 (1.2–1.8)	**0.021**	30	1.4 (1.1–1.7)	0.089	24	1.2 (1.0–1.7)	**0.0079**	37	1.5 (1.2–1.8)	0.54
LDL cholesterol, mmol/l	123	2.8 (2.3–3.4)	91	2.8 (2.2.–3.5)	0.60	30	2.5 (2.0–3.0)	0.088	25	2.8 (2.4–3.5)	0.94	36	3.0 (2.4–3.5)	0.53
HbA1c, %	135	7.2 (6.7–8.0)	163	7.8 (7.0–9.6)	**<.0001**	71	7.3 (6.8–8.0)	0.92	43	9.5 (7.2–10.8)	**<.0001**	49	9.0 (7.8–9.9)	**<.0001**
Classic oral antidiabetics, %	4	3.0	7	4.2	0.56	2	2.7	0.91	3	7.0	0.24	2	4.1	0.71
New antidiabetics, %	0	0	1	0.6	0.37	0	0	–	1	2.3	0.076	0	0	–
Insulin therapy, %	135	100.0	165¶	99.4	0.37	74	100.0	–	43	100.0	–	48¶	98.0	0.096
Statin/fibrate/PCSK9i, %	34	25.2	41	24.7	0.93	21	28.4	0.62	5	11.6	0.061	15	30.6	0.46

BMI = body-mass-index; DBP = diastolic blood pressure; DM1 = diabetes mellitus type 1; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; PCSK9i = proprotein convertase subtilisin/kexin type 9-inhibitor; SBP = systolic blood pressure; yrs = years Data are median (IQR) or percentage, unless otherwise specified. Superscript numbers in brackets indicate number of participants/patients with missing data. * SwissDiab participants vs all nonparticipating patients;† SwissDiab participants vs patients with ≥6 months of treatment at the centre; ‡ SwissDiab participants vs patients with <6 months of treatment at the centre; § SwissDiab participants vs excluded patients. ¶ One patient was insulin independent following pancreatic islet transplantation

Table 2: Prevalence of diabetes-related complications in SwissDiab participants and nonparticipating patients with DM1.

Complication	SwissDiab (n = 135)		Nonparticipating patients											
			All (n = 166)			Patients with ≥6 months of treatment (n = 74)			Patients with <6 months of treatment (n = 43)			Excluded (n = 49)		
	n	%	n	%	p-value*	n	%	p-value†	n	%	p-value‡	n	%	p-value§
Retinopathy, %	23	17.0	30	18.1	0.81	10	13.5	0.50	7	16.3	0.91	13	26.5	0.15
Neuropathy, %	28	20.7	41	24.7	0.42	14	18.9	0.75	9	20.9	0.98	18	36.7	**0.027**
Coronary heart disease, %	3	2.2	12	7.2	**0.047**	7	9.5	**0.019**	3	7.0	0.13	2	4.1	0.49
PAD, %	14	10.4	8	4.8	0.066	5	6.8	0.38	2	4.7	0.25	1	2.0	0.068
Stroke, %	1	0.7	4	2.4	0.26	3	4.1	0.095	0	0	0.57	1	2.0	0.45
Nephropathy, %	24	17.8	37	22.3	0.33	18	24.3	0.26	7	16.3	0.82	12	24.5	0.31

DM1 = diabetes mellitus type 1; PAD = peripheral arterial disease Data are percentages, unless other specified. For the definition of each complication see Method section "Diabetes-related complications". * SwissDiab participants vs all nonparticipating patients;† SwissDiab participants vs patients with ≥6 months of treatment at the centre; ‡ SwissDiab participants vs patients with <6 months of treatment at the centre; § SwissDiab participants vs excluded patients.

l], and higher HDL cholesterol levels [1.1 vs 1.1 mmol/l], all p-values <0.05). No difference in antidiabetic therapy was observed, whereas lipid-lowering medication was more common among participants than nonparticipating patients (70% vs 60%, p = 0.003). In both groups, 99% of individuals treated with lipid-lowering medication received a statin, 4% of participants and 5% of nonparticipating patients received fibrates, and one participant was regularly treated with a PCSK9 inhibitor.

Among nonparticipating patients treated for ≥6 months, the differences in migration background, HDL cholesterol, and HbA1c remained statistically significant. In addition, participants were older at the time of diagnosis (50 vs 46 years, p = 0.04) (table 3).

The differences in clinical characteristics between SwissDiab participants and nonparticipating patients treated <6 months and excluded patients were generally similar to those observed with all nonparticipating patients. However, there was no difference in gender, family history, smoking, BMI, overweight, or diastolic blood pressure as compared with patients treated <6 months, and no difference in BMI, HDL and LDL cholesterol compared with excluded patients. Lipid-lowering medication was more common among participants than nonparticipating patients treated <6 months and excluded patients (70% vs 54% and 60%, respectively, all p-values <0.02), and insulin therapy was less common in patients treated <6 months (55 vs 66%, p = 0.02) (table 3).

Table 3: Characteristics of SwissDiab participants and nonparticipating patients with DM2.

Characteristic	SwissDiab (n = 358)		Nonparticipating patients											
			All (n = 474)			Patients with ≥6 months of treatment (n = 109)			Patients with <6 months of treatment (n = 179)			Excluded (n = 186)		
	n	% or median (IQR)	n	% or median (IQR)	p-value*	n	% or median (IQR)	p-value†	n	% or median (IQR)	p-value‡	n	% or median (IQR)	p-value§
Females, %	107	29.9	180	38.0	**0.015**	42	38.5	0.090	68	38.0	0.059	70	37.6	0.067
Age, yrs	358	61.0 (54.0–68.0)	474	59.4 (51.9–67.7)	0.16	109	59.8 (52.5–68.3)	0.88	179	58.2 (51.5–68.6)	0.11	186	60.3 (51.3–67.0)	0.27
Age at diagnosis, yrs	358	50.0 (43.0–57.0)	469	49.0 (41.0–57.0)	0.51	108	46.0 (39.0–56.0)	**0.039**	178	50.0 (43.0–60.0)	0.54	183	49.0 (41.0–57.0)	0.66
Diabetes duration, yrs	358	10.0 (6.0–16.0)	469	8.0 (3.0–14.0)	**<0.0001**	108	12.0 (7.0–17.0)	0.15	178	5.0 (2.0–11.0)	**<0.0001**	183	8.0 (3.0–15.0)	**0.0003**
Family history DM, %	232 (17)	68.0	241 (51)	57.0	**0.002**	61 (8)	60.4	0.15	98 (16)	60.1	0.081	82 (27)	51.6	**0.0004**
Family history, DM2, %	228 (16)	66.7	236 (57)	56.6	**0.005**	61 (10)	61.6	0.35	94 (20)	59.1	0.10	87 (27)	50.9	**0.0008**
Higher education, %	86 (17)	25.2	69 (98)	18.4	**0.026**	25 (19)	27.8	0.62	24 (30)	16.1	**0.026**	20 (49)	14.6	**0.012**
Mental health disorder, %	66	18.4	95	20.0	0.51	22	20.2	0.68	33	18.4	1.0	40	21.5	0.39
Migration background, %	129	36.0	231	48.7	**0.0003**	60	55.1	**0.0004**	82	45.8	**0.029**	89	47.9	**0.0077**
Active smoking, %	76 (2)	21.4	121 (62)	29.4	**0.011**	28 (8)	27.7	0.18	42 (24)	27.1	0.16	51 (30)	32.7	**0.0062**
BM, kg/m^2	356	31.5 (28.4–36.3)	457	31.0 (27.6–34.9)	**0.019**	107	30.2 (27.1–34.7)	0.063	172	31.2 (28–34.6)	0.17	178	31.0 (27.5–35.0)	0.052
BMI ≥25 kg/m^2, %	333 (2)	93.5	408 (17)	89.3	**0.034**	97 (2)	90.7	0.31	156 (7)	90.7	0.24	155 (8)	87.1	**0.012**
SBP, mm Hg	355	140 (128–150)	458	140 (127–152)	0.79	107	135 (126–151)	0.19	175	140 (126–152)	0.84	176	143 (130–153)	0.20
DBP, mm Hg	355	77 (70–84)	458	79 (70–86)	**0.039**	107	76 (66–83)	0.33	175	79 (70–86)	0.094	176	80 (73–87)	**0.0016**
Total cholesterol, mmol/l	350	4.2 (3.6–4.9)	407	4.5 (3.7–5.5)	**<.0001**	90	4.4 (3.7–5.4)	0.21	157	4.7 (3.8–5.7)	**0.0001**	160	4.5 (3.8–5.5)	**0.0030**
Triglyceride, mmol/l	351	1.9 (1.3–2.7)	397	2.2 (1.5–3.2)	**0.0006**	87	2.1 (1.5–2.9)	0.13	156	2.4 (1.5–3.4)	**0.0003**	154	2.1 (1.4–3.1)	**0.044**
HDL cholesterol, mmol/L	350	1.1 (1.0–1.3)	375	1.1 (0.9–1.3)	**0.039**	87	1.0 (0.9–1.2)	**0.019**	146	1.0 (0.9–1.2)	**0.011**	142	1.1 (1.0–1.3)	0.82
LDL cholesterol, mmol/l	326	2.4 (1.9–3.0)	373	2.6 (1.9–3.3)	**0.029**	87	2.4 (1.8–3.2)	0.99	145	2.6 (1.9–3.6)	**0.019**	141	2.6 (2.0–3.2)	0.052
HbA1c, %	358	7.2 (6.6–7.9)	470	8.1 (7.0–9.4)	**<.0001**	108	7.5 (6.8–8.3)	**0.0070**	177	8.4 (7.3–9.6)	**<.0001**	185	8.3 (7.0–9.4)	**<.0001**
Classic oral antidiabetics, %	281	78.5	368	77.6	0.77	76	69.7	0.059	150	83.8	0.15	142	76.3	0.57
New antidiabetics, %	86	24.0	103	21.7	0.43	27	24.8	0.87	39	21.8	0.56	37	19.9	0.27
Insulin therapy, %	236	65.9	296	62.5	0.30	82	75.2	0.068	99	55.3	**0.017**	115	61.8	0.34
Antidiabetics + insulin, %	177	49.4	218	46.0	0.32	60	55.1	0.31	81	45.3	0.36	77	41.4	0.075
Statin/fibrate/PCSK9i, %	251	70.1	285	60.1	**0.0029**	78	71.6	0.77	96	53.6	**0.0002**	111	59.7	**0.014**

BMI = body-mass-index; DBP = diastolic blood pressure; DM2 = diabetes mellitus type 2; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; PCSK9i = proprotein convertase subtilisin/kexin type 9-inhibitor; SBP = systolic blood pressure; yrs = years Data are median (IQR) or percentage, unless otherwise specified. Superscript numbers in brackets indicate number of participants/patients with missing data. * SwissDiab participants vs all nonparticipating patients;† SwissDiab participants vs patients with ≥6 months of treatment at the centre; ‡ SwissDiab participants vs patients with <6 months of treatment at the centre; § SwissDiab participants vs excluded patients.

Diabetes-related complications

As shown in table 4, the prevalence of CHD and PAD was higher in SwissDiab participants than in nonparticipating patients (30% vs 20%, p = 0.001, and 20% vs 8%, p <0.0001, respectively).

Female participants vs female nonparticipating patients with DM2

To explore underlying reasons for the observed underrepresentation of females with DM2 in SwissDiab, we determined the proportion of females among nonparticipating patients who declined to participate (n = 142) or had not been asked to participate (n = 146) in SwissDiab. Compared with 30% female participants in SwissDiab (table 3), 37% of patients that declined (n = 53, p = 0.11) and 39% of patients that were not asked to participate (n = 57, p = 0.047) were females.

Migration background

In an attempt to highlight underlying reasons for the observed underrepresentation in SwissDiab of patients with a migration background and DM2, we determined the proportion of patients with a migration background among the nonparticipating patients who declined to participate or had not been asked to participate in SwissDiab. Compared with the 36% of SwissDiab participants with migration background (table 3), 60% of patients who declined to participate (n = 85, p <0.0001) and 39% of patients not asked to participate (n = 57, p = 0.53) in SwissDiab had a migration background. As shown in table 3, 48% (p = 0.008) of patients excluded from participation in SwissDiab had a migration background.

Discussion

Overall, SwissDiab participants have relatively well-controlled diabetes: a previous publication has shown that a majority of the national targets for good disease management in diabetes were achieved [10]. This study shows that there are differences in diabetes-related clinical characteristics between SwissDiab participants and nonparticipating patients at the tertiary diabetes care centre at the Cantonal Hospital of St Gallen. In general, SwissDiab participants with DM1 had a lower HbA1c, smoked less and had a higher educational attainment than nonparticipating patients with DM1. The same differences were observed in DM2, along with a better lipid profile and an underrepresentation of females and patients with a migration background among SwissDiab participants. Among nonparticipating patients who had received their diabetes treatment ≥6 months at the tertiary diabetes care centre, i.e., the subgroup of patients from which SwissDiab participants were most likely to be recruited, the differences were less pronounced. Although participants are commonly observed to be healthier than nonparticipating individuals in studies investigating the representativeness of human study populations in voluntary study settings in general [1–4], there is limited information available on external validity in diabetes-specific registers, cohort studies and trials [11, 12]. This study highlights the challenges, despite limited exclusion criteria, in obtaining representative patient data in an observational study setting.

SwissDiab participants had better glycaemic control than nonparticipating patients, regardless of diabetes type. One contributing factor is that nonparticipating patients include those who had been excluded from participation in SwissDiab because of a life expectancy <1 year (e.g., due to end-stage cancer), or due to very irregular diabetes treatment and frequent no-shows, often in connection with underlying drug abuse or mental disorder. Maintaining good glycaemic control under such conditions is more challenging. Mental health disorders including depression are by themselves not a reason for exclusion from SwissDiab. On the contrary, mental health disorder is an important variable in successful diabetes treatment as it can present a major obstacle for good diabetes self-management [13]. Overall, no significant differences in the prevalence of mental health disorders were observed between SwissDiab participants and nonparticipating patients.

Another factor contributing to better glycaemic control among SwissDiab participants is that the majority had received treatment for a longer period of time at the tertiary diabetes care centre, as compared with non-participating patients. Based on experience, patients who are referred to tertiary care usually exhibit an initial improvement in glycaemic control during the first 3–6 months in response to intensified care and treatment. In SwissDiab, 94% of participants had received ≥6 months of treatment at the centre prior to enrolment, compared with just 29% of nonparticipating patients. In line with this, participants had significantly lower HbA1c than nonparticipating patients treated <6 months at the centre, but compared with nonpar-

Table 4: Prevalence of diabetes-related complications in SwissDiab participants and nonparticipating patients with DM2.

Complication	SwissDiab (n = 358)		Nonparticipating patients											
			All (n = 474)			Patients with ≥6 months of treatment (n = 109)			Patients with <6 months of treatment (n = 179)			Excluded (n = 186)		
	n	%	n	%	p-value*	n	%	p-value†	n	%	p-value‡	n	%	p-value§
Retinopathy, %	72	20.1	74	15.6	0.091	34	31.2	**0.016**	17	9.5	**0.0018**	23	12.4	**0.024**
Neuropathy, %	186	52.0	230	48.5	0.33	62	56.9	0.37	76	42.5	**0.038**	92	49.5	0.58
Coronary heart disease, %	108	30.2	96	20.3	**0.001**	31	28.4	0.73	30	16.8	**0.0008**	35	18.2	**0.0043**
PAD, %	72	20.1	39	8.2	**<0.0001**	12	11.0	**0.030**	11	6.2	**<0.0001**	16	8.6	**0.0005**
Stroke, %	27	7.5	26	5.5	0.23	7	6.4	0.69	7	3.9	0.10	12	6.5	0.64
Nephropathy, %	167	46.7	192	40.5	0.077	57	52.3	0.30	60	33.5	**0.0037**	75	40.3	0.16

DM2 = diabetes mellitus type 2; PAD = peripheral arterial disease Data are percentages, unless other specified. For the definition of each complication see Method section "Diabetes-related complications". * SwissDiab participants vs all nonparticipating patients;† SwissDiab participants vs patients with ≥6 months of treatment at the centre; ‡ SwissDiab participants vs patients with <6 months of treatment at the centre; § SwissDiab participants vs excluded patients.

ticipating patients treated ≥6 months there was no longer a difference in DM1. In DM2 the absolute difference in HbA1c was reduced by almost 1% comparing nonparticipating patients treated ≥6 months vs <6 months at the centre. In DM1, unequal access to the diabetes education programme that is offered to all patients treated at the centre might also have contributed to the observed difference in HbA1c. The programme is provided in collaboration with physicians, diabetes educators and nutritionists, and is focused on educating and empowering patients with DM1 in flexible intensive insulin therapy. Nonparticipating patients with <6 months of treatment at the tertiary diabetes care centre might not have had the same opportunity to attend and profit as the participants and nonparticipating patients who had been treated for 6 months or longer.

A more beneficial metabolic lipid profile (i.e., low triglycerides, low LDL cholesterol, and high HDL cholesterol levels) was observed in SwissDiab participants as compared with nonparticipating patients in general. However, in both DM1 and DM2, the difference was most pronounced compared with nonparticipating patients treated <6 months. This subgroup of nonparticipating patients did not receive lipid-lowering medication to the same extent as participants, indicating that these patients might have had suboptimal lipid-lowering therapy at the time of referral to tertiary care. No difference in lipid-lowering therapy was observed between nonparticipating patients treated ≥6 months and SwissDiab participants. Better adherence to therapy might also have contributed to the more beneficial lipid profile and lower HbA1c levels among SwissDiab participants. Addressing questions related to patient adherence is, however, beyond the scope of SwissDiab.

The higher proportion of overweight among participants compared with nonparticipating patients with DM2 was mainly driven by a lower prevalence of overweight in the excluded patients. This could potentially be attributed to a combination of the expected higher prevalence of severe comorbidities in this group (e.g., cancer, data not available), more pronounced glycosuria in light of the significantly higher HbA1c and, although not statistically significantly different, fewer being treated with insulin.

No differences in the prevalence of diabetes-related complications were observed in SwissDiab participants compared with nonparticipating patients with DM1, apart from a higher prevalence of CHD in the latter group. In DM2, a higher prevalence of CHD and PAD was observed among participants. The higher prevalence of PAD among participants is likely an overestimation: with regular measurement of ABI being part of the SwissDiab study protocol, PAD is more likely to be diagnosed at an earlier stage in participants than nonparticipating patients.

A slight underrepresentation of females with DM2 was observed in SwissDiab. From the results we are unable to draw any clear conclusions as to why, but the secondary analysis shows that females were less frequently asked to participate, and tended to be more frequent among the patients who declined or were excluded from participation. It is unclear why females are less frequently asked to participate in SwissDiab and this warrants further investigation to improve recruitment.

An underrepresentation of patients with a migration background in DM2 was also observed in SwissDiab. Language barriers should not be a key underlying factor as interpreters are routinely utilised in daily clinical care at the centre. This is supported by a migration background being equally common among participants and the group of patients not asked to participate, as well as among the excluded group of patients. However, 60% of the patients with DM2 who declined to participate in SwissDiab had a migration background, indicating that cultural differences (including language barriers) might be an underlying reason.

This study has several limitations. It is limited to one of the SwissDiab study centres. At the time of analysis, >60% of data available in the SwissDiab database derived from the centre in St Gallen. Data regarding nonparticipating patients were not readily available, or recruitment had just started at the other study centres. As Gerber et al. have shown, clinical characteristics can differ significantly between regions even in a small country like Switzerland [14]. This emphasises the need for Swiss-wide standardised data to be collated to get a representative picture of the standard of diabetes care in Switzerland. In line with this, SwissDiab is continuing to expand, having recently included the tertiary diabetes care centres in Basel and Geneva. With the ongoing prospective data collection and new study centres joining SwissDiab, the representativeness of the study participants at each centre should ideally be assessed, and re-assessed over time as the study progress. As mentioned above, for already published [10] and ongoing research studies, the majority of data originate from the study centre at the Cantonal Hospital of St Gallen.

Another limitation is the retrospective collection of data on the nonparticipating patients, which does not provide the same quality as the standardised prospective data collection in SwissDiab; for example,, information on education was not directly available for nonparticipating patients and was approximated based on occupation. A higher educational attainment among study participants is commonly reported in clinical studies [15–17], as was observed in the current study. However, among nonparticipating patients with DM1 and DM2 information on occupation was missing in 15% and 21%, respectively, and the results should be interpreted with caution. Missing information was also relatively frequent among nonparticipating patients in terms of smoking status. Smoking is a significant and modifiable risk factor and it is therefore less likely that physicians would have failed to note this in the patient records. With the assumption that missing information equals not currently smoking, a higher prevalence of smokers among nonparticipating patients would still be observed in DM1 but not in DM2.

The cross-sectional design is a further limitation as no information on the longitudinal trajectory of, for example, HbA1c or LDL cholesterol was considered. Data from the baseline SwissDiab visit was used for the participants in the current analysis, minimising the likelihood that any observed differences are attributable to changes in behaviour as a direct result of study participation [18]. There is, however, a difference in how long participants and nonparticipating patients on average received prior treatment at the tertiary diabetes care centre, and as the results show, this influences the representativeness of the SwissDiab participants. Regardless of diabetes type, the results indicate

that patients participating in SwissDiab are similar but slightly better controlled than the corresponding group of nonparticipating patients treated ≥6 months, whereas patients newly referred to the clinic (i.e., patients treated <6 months) have significantly worse diabetes control. The fact that newly referred patients generally improve their metabolic control during the first 3–6 months in response to intensified treatment makes it difficult to capture this group of patients within the setting of SwissDiab, where annual study visits are conducted and patients are unlikely to be enrolled at their first visit to the clinic.

It is important to emphasise that SwissDiab is an observational study of outpatients with diabetes treated in tertiary care and as such does not represent diabetes care in Switzerland in general. Patients with DM2 are usually referred to tertiary care at a later or more critical stage of the disease. This is supported by results from a study by Gerber et al. including 1121 patients with DM2 treated by general practitioners in Switzerland. The patients had a similar age but shorter diabetes duration compared with the SwissDiab participants, who have higher HbA1c, blood pressure and BMI, and substantially more of whom receive insulin therapy [10, 14]. In a more recent study by Corcillo et al., the 1359 patients with DM2 treated in primary care were older and had slightly shorter diabetes duration compared with the SwissDiab participants [19]. Similar differences to those in the study by Gerber et al. were observed. In addition, the prevalence of diabetes-related complications (retinopathy and neuropathy) and CHD was notably higher among SwissDiab participants. Higher prevalence of diabetes-related complications and more patients receiving insulin therapy among SwissDiab participants with DM2 was also observed as compared with a population-based observational study of 519 patients with diabetes recruited through community pharmacies in Switzerland (CoDiab-VD) [20]. Prevalence and incidence of diabetes-related complications and level of medication in DM2 are thus likely higher in SwissDiab than in the overall patient population in Switzerland. Because of the complexity of the treatment of DM1, a majority of patients are treated by an endocrinologist/diabetologist in a private or a tertiary care setting. Fewer differences between SwissDiab participants and the overall Swiss patient population are thus expected in DM1.

Conclusion

Overall, SwissDiab participants at the tertiary diabetes centre in St Gallen show better glycaemic control and more health-beneficial characteristics compared to nonparticipating patients. Participants are overall similar, albeit slightly better controlled than comparable nonparticipating patients (i.e., patients treated ≥6 months at the clinic), whereas two groups of patients are less well represented; patients recently referred to the tertiary diabetes centre and patients who have been excluded from participation based on study exclusion criteria. SwissDiab is thus likely to overestimate the overall state of diabetes care and management. The results further revealed an underrepresentation of females and patients with a migration background in DM2, highlighting the need to improve recruitment in these two demographic groups.

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Potential competing interests

No conflict of interest relevant to this article was reported.

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