Research paper: Diabetic foot syndrome (DFS) in patients with diabetes. A multicenter German/Austrian DPV analysis on 33,870 DFS patients among 358,986 adult subjects with diabetes

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Abstract

Aims: The diabetic foot syndrome (DFS) is a serious complication in patients with diabetes increasing the risk for minor/major amputations. This analysis aimed to examine differences in diabetes patients with or without DFS stratified by type 1 (T1D) or type 2 diabetes (T2D).

Material and Methods: Adult patients (≥20y of age) with diabetes from the German/Austrian DPV-registry were included. The cross-sectional study comprised 45,722 subjects with T1D (n_{DFS}=2,966) and 313,264 with T2D (n_{DFS}=30,904). In DFS, minor/major amputations were analyzed. To compare HbA_{1C}, neuropathy, nephropathy, cardiovascular disease risk factors, and macrovascular complications between patients with our without DFS, regression models were conducted. Confounders: age, sex, diabetes duration.

Results: In patients with DFS, a minor amputation was documented in 27.2% (T1D) and 25.9% (T2D), a major amputation in 10.2% (T1D) and 11.3% (T2D). Regression models revealed that neuropathy was more frequent in subjects with DFS compared to patients without DFS (T1D: 70.7 vs. 29.8%; T2D: 59.4% vs. 36.9%; both p<0.0001). Hypertension, nephropathy, peripheral vascular disease, stroke, or myocardial infarction were more common compared to patients without DFS (all p<0.0001). In T1D with DFS, a slightly higher HbA_{1C} (8.11% vs. 7.95%; p<0.0001) and in T2D with DFS a lower HbA_{1C} (7.49% vs. 7.69%; p<0.0001) was observed.

Conclusions: One third of the patients with DFS had an amputation of the lower extremity. Especially neuropathy or peripheral vascular disease were more prevalent in patients with DFS. New concepts to prevent DFS-induced amputations and to reduce cardiovascular risk factors before the occurrence of DFS are necessary.

Keywords: diabetic foot; minor amputations; major amputations; cardiovascular risk, lifestyle

Introduction

Worldwide, the diabetic foot syndrome (DFS) is a major complication in patients with diabetes and the most common reason for hospitalization.[1] DFS, as defined by the World Health Organization, is an “ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection”. The etiology of the DFS is complex due to the interaction of diabetic neuropathy, peripheral vascular disease (PVD), foot deformity, and infection.[1] The prevalence of DFS is estimated between 2% and 10%.[2] An analysis of diabetes practices in Germany (Disease Analyzer database, IMS Health) indicated a higher prevalence in patients with type 2 (T2D) compared to type 1 diabetes (T1D).[3] It is assumed that during their lifetime, up to 25% of patients with diabetes develop a DFS which can result in minor or even major amputations of the lower extremities.[1,4] Compared to the general population, subjects with diabetes have a 20-fold higher risk of amputations.[2] A recently published analysis of data from the German Federal Statistical Office confirmed the high proportion of patients with diabetes and a lower limb amputation.[5] In the year 2014, 85.6% of all hospitalized patients with a minor amputation and 63.7% with a major amputation had diabetes.[5] However, the study also revealed that based on all patients with an amputation, the proportion of diabetes patients decreased during the last decade.[5]

Aside from physical impairment, patients with diabetes and DFS have a lower quality of life compared to subjects without DFS.[6-8] Qualitative studies reported for example a reduction of social activities, increased family tensions, and limited employment.[9] Furthermore, the DFS is associated with a high economic burden for the health system and for patients themselves.[9-13]

This analysis aimed to examine sociodemographic and clinical differences between T1D or T2D patients with DFS compared to those without DFS from the German/Austrian DPV registry.

Materials and Methods

Data source and subjects

Subjects for the present study were retrieved from the multicenter standardized diabetes patient follow-up registry (DPV). Currently, 452 specialized diabetes centers from Germany (n=385), Austria (n=38), Switzerland (n=2), and Luxembourg (n=1) prospectively document demographic and clinical data of patients with any type of diabetes. Twice a year, locally collected data are anonymized and transferred to the University of Ulm, Germany, for central analysis and quality assurance. Data are screened for inconsistency or implausibility and are reported back to the centers for verification or correction. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and national research committee as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval of the DPV initiative has been obtained from the ethics committee of the University of Ulm. Data collection has been approved by the local review boards of each participating center.

Until September 2016, 453,580 patients with diabetes were documented in the database. For the present analysis, adult patients (≥ 20 years of age) with T1D or T2D were included (n=358,986). The final study comprised 45,722 subjects with T1D (documented DFS in n=2,966) and 313,264 subjects with T2D (documented DFS in n=30,904) (Fig. 1). The DPV software provides a sub-screen for the entry of DFS and DFS-specific information. In addition, free-text can be entered by the physician or the diabetes care team. To analyse information provided in free-text fields, a string-search with specific items was conducted. Patients with DFS included both, subjects with an acute DFS and a history of DFS. For each patient, the most recent year of treatment was analyzed. In case of multiple data sets per patient, data were aggregated as median (e.g., HbA1c, serum lipids).

Outcome variables

Aside from sociodemographic characteristics (age, sex, and diabetes duration), clinical data (including information on foot examinations conducted by the diabetes care team), lifestyle factors, macrovascular complications and the presence of neuropathy were considered in all patients. In patients with DFS (previous or current), the severity of DFS by Wagner classification (grade 1 to 5)[14] as well as the number of minor amputations (under the ankle) and major amputations (above the ankle) were analyzed. Severity of DFS and the proportion with amputations of the lower extremities in patients with DFS were also considered stratified by foot examination conducted in the most recent year of treatment.

Clinical data

Clinical characteristics comprised HbA_{1C}, serum lipids, systolic and diastolic blood pressure, and body mass index (BMI). HbA_{1C} was mathematically standardized to the reference range of 20–42 mmol/mol (diabetes control and complication trial: 4.05–6.05 %) by applying the multiple-of-the-mean transformation method.[15] Systolic and diastolic blood pressure as well as serum lipids were measured in local laboratories following the RILI-BÄK requirements (Richtlinie der Bundesärztekammer) including internal and external quality control.[16] Hypertension was defined as increased systolic (≥140mmHg) or increased diastolic (≥90mmHg) blood pressure[17], or the use of antihypertensive drugs. Dyslipidemia was defined as at least one elevated value of total cholesterol (≥200 mg/dL), LDL cholesterol (≥100 mg/dL), triglycerides (fasting ≥150 mg/dL, not fasting ≥500 mg/dL) and/or decreased levels of HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women)[17], or use of lipid-lowering drugs. BMI was calculated as the ratio of the body weight in kilograms and the squared body height in meters (kg/m^2).

Lifestyle factors

Information on smoking (yes/no) and physical activity (yes/no) was based on patient self-reports to their diabetes-care teams.

Macrovascular complications, nephropathy, and neuropathy

The proportion of patients with nephropathy (stage 3 or higher), neuropathy, a history of myocardial infarction, stroke, or PVD was evaluated. These complications can be entered via sub-screens and/or free-text fields. To specify the diagnosis of neuropathy, there are entry-masks stratified by peripheral and autonomic neuropathy. For peripheral neuropathy, e.g. vibration or pain sensation, tuning fork test or reflexing tests can be documented. For autonomic neuropathy, symptoms of orthostatism, gastroparesis, or erectile dysfunction can be entered. Subjects were classified as having PVD when claudicatio intermittens or the absence of palpable pulse were documented. To analyse information provided in free-text fields, a string-search with indication-specific items was conducted. Nephropathy was diagnosed if glomerular filtration rate (GFR) was <60ml/min/1.73m² (estimated by MDRD equation).[18]

Statistical analysis

Sociodemographic characteristics were presented as median (Q1;Q3), or as percentage. To compare characteristics between groups, Chi square ($\chi 2$) test was used for dichotomous variables, and Kruskal–Wallis test was used for continuous variables. The false discovery rate (FDR) was applied to correct p-values for multiple comparisons. In order to adjust for demographic differences (sex, age, and diabetes duration) between patients with or without DFS (Table 1), regression models were created stratified by T1D or T2D. In T1D, the confounder age was categorized as 20-<25, ≥ 25-<40, ≥40-<55, ≥55 years and diabetes duration as <2, ≥2-<5, ≥5 years. In T2D, age was categorized as ≥20-<65, ≥65-<75, ≥75 years and diabetes duration as <5 / ≥5 years. Logistic regression was applied for binary variables, linear regression models were created for continuous variables. Treatment center was included as a random effect in order to adjust for between-center variation. To compare differences in patients with DFS by the height of foot amputation (minor vs. major amputation), a further regression model (adjusted for age, sex, and diabetes duration) was implemented. Patients with both minor and major amputation were assigned to the group “major amputation”

A two sided p value <0.01 was considered significant. All statistical analyses were implemented with SAS 9.4 (Statistical Analysis Software, SAS Institute, Cary, NC, USA).

Results

Study population

In patients with T1D (n=45,722) (male 53.2%), median age was 43.4 (28.7; 57.8) years and median diabetes duration 15.0 (6.5; 25.9) years. In T1D, DFS was documented in 6.5% (n=2,966). T2D patients (n=313,722) (male: 52.4%) had a median age of 70.2 (60.5; 77.8) years and a median diabetes duration of 8.3 (2.9; 14.9) years. DFS was reported in 9.9% (n=30,904) of the T2D patients. In all subjects considered, foot examinations were documented in 65.8% (T1D) and 80.6% (T2D). In patients with DFS, foot examinations were conducted in 80.6% (T1D) and 86.4% (T2D).

Of those patients with available information on the extent of DFS according to Wagner classification, a deep ulcer (Wagner 2 and 3) was documented in 41.9% (T1D) or 49.4% (T2D), and necrosis (limited (Wagner 4) or extensive (Wagner 5)) in 9.6% (T1D) and 12.5% (T2D) (Table 1). 33.0% of the patients with DFS had an amputation of the lower extremities. A minor/major amputation was reported in 27.2%/10.2% of the patients with T1D and DFS. Among those patients with T2D and DFS, a minor/major amputation was present in 25.9%/11.3% (Table 1). DFS was more severe in those with documented foot examinations compared to those without foot examinations: Wagner stadium 2, 3 and 4 were more frequently documented and foot amputations were more prevalent (Table 2).

Sociodemographic differences between patients with or without DFS

The comparison between patients with or without DFS showed a higher proportion of men with DFS. Patients with DFS were older and had a longer diabetes duration compared to patients without DFS (Table 1).

Clinical differences between patients with or without DFS

Regression models (adjusted for age, sex and diabetes duration) revealed in T1D and T2D with DFS a higher prevalence of neuropathy compared to patients without DFS (T1D: 70.7% vs. 29.8%; T2D: 59.4% vs. 36.9%; both p<0.0001; Fig.2a/b). In those patients with available information on the type of neuropathy, peripheral neuropathy was more common than autonomic neuropathy (Fig. 2a/b). PVD was more frequent in subjects with DFS compared to those without DFS (T1D: 11.6% vs. 3.0%; T2D: 35.8% vs. 10.3%; both p<0.0001; Fig.3a/b).

In patients with DFS, hypertension was more prevalent than in subjects without DFS (T1D: 53.8% vs. 41.5%; T2D: 74.6% vs. 71.0%; both p<0.0001; Fig. 3a/b). Differences in dyslipidemia were less pronounced (T1D: 85.4% vs. 83.1%, p=0.0237; T2D: 94.7% vs. 94.9%, p=0.1583; Fig. 3a/b). Results on BMI, individual components of serum lipids and systolic or diastolic blood pressure are given in Table 3. The proportion of patients with nephropathy, stroke or myocardial infarction was higher in subjects with DFS (Fig. 3a/b). In T1D, HbA_{1C} was slightly higher among those with DFS, (8.11% (65.1 mmol/mol) vs. 7.95% (63.4 mmol/mol); p<0.0001), whereas in T2D, patients with DFS had lower HbA1c than those without DFS (7.49% (58.4 mmol/mol) vs. 7.69% (60.6 mmol/mol); p<0.0001).

Differences in lifestyle factors between patients with or without DFS

In T1D, the number of patients who reported to be physically inactive was higher in those with DFS compared to patients without DFS (73.6% vs. 58.0%; p<0.0001), Fig. 3a). In T2D, patients with DFS were less active, but the difference was negligible (89.9% vs. 86.1%; p<0.0001; Fig. 3b). In T1D and T2D, the number of self-reported smokers was similar in both patient groups (Fig. 3a/b).

Differences in subjects with DFS by the height of amputation (minor vs. major amputation)

Patients with DFS and a minor amputation were slightly younger (median age: 70.7 years (Q1:62.3, Q3:77.4) than patients with a major amputation (71.7 years (63.2; 78.2); p=0.0002)

and the median diabetes duration was longer (15.4 years (9.2; 24.3) vs. 14.9 years (8.5 vs. 23.3); p=0.0051). In both patient groups, there was a male preponderance (70.4% vs. 69.4%; p=0.30482).

Regression models (adjusted for age, sex, and diabetes duration) indicated significant differences between DFS patients by the height of amputation. In DFS patients with a minor amputation, neuropathy was more common compared to patients with a major amputation (69.1% vs. 59.9%; p<0.0001). Myocardial infarction (15.6% vs. 12.9%; p=0.0002), stroke (13.9% vs. 11.1%; p<0.0001), PVD (62.0% vs. 54.2%; p<0.0001) and smoking (13.3% vs. 10.7%; p=0.0007) were more prevalent in subjects with a major amputation compared to those with a minor amputation. No further differences were observed (Table 4).

Discussion

This study aimed to investigate sociodemographic and clinical differences between diabetes patients with or without DFS from the German/Austrian DPV registry. Subjects with DFS were older, more frequently male, and had a longer diabetes duration. CVD risk factors and comorbidities (e.g. neuropathy, nephropathy, or peripheral vascular disease (PVD)) were more common in patients with DFS compared to those without DFS.

In the present analysis, DFS (current or previous) was documented in 9.4% of all individuals with diabetes. DFS was more common in T2D compared to T1D (9.8% vs. 6.5%). A higher prevalence of DFS in T2D was also observed in other studies.[3,19] However, the documented frequency of DFS in our analysis was higher compared to the prevalence reported in another German analysis including about 30.000 patients with diabetes from specialized practices (T2D: 6.7%; T1D: 1.2%).[3] One explanation for the lower prevalence could be that in contrast to our analysis, Lauterbach and colleagues only included patients with an active foot ulcer.[3]

One main complication in patients with DFS is a lower limb amputation.[1,2,4,5] A recently conducted meta-analysis identified hypertension, ischemic heart disease, cerebrovascular disease, and PVD as predisposing factors for higher major amputation rates in subjects with

diabetes.[20] Results of the CANVAS-R study further reported a two-fold higher amputation risk in T2D subjects with canagliflozin compared to patients with a placebo.[21,22] A review from Armstrong et al. revealed that in 20% of diabetes patients with moderate or severe diabetic foot infections an amputation was required.[23] In our analysis, at least one minor or major amputation was documented in 33.0% of the patients with DFS. Two systematic reviews confirmed a higher proportion of amputations (major or minor) in diabetes subjects with DFS from Germany compared to some other European countries as the Netherlands, Spain, Italy or UK.[24,25] In 2003, a certification procedure for diabetic foot centres was developed by the German Working Group on the Diabetic Foot.[26] It is assumed that the implementation of these quality criteria for interdisciplinary diagnosis and treatment of DFS has led to a reduction in the rate of diabetes-related amputations in Germany.[5,26] However, many clinics are still without certification which can lead to premature amputations. Moreover, in the DPV registry, there are mainly specialized private practices and clinics with patients who have more complex healthcare needs. This could also have contributed to the higher proportion of amputations.

Sociodemographic and clinical differences between patients with or without DFS

In subjects with a previous or acute DFS, we found a higher proportion of men, a higher age, and a longer diabetes duration compared to individuals without DFS (Table 1). This is in line with results of other studies.[1,19]

The main risk factor for the development of DFS in patients with diabetes is the occurrence of neuropathy, especially peripheral neuropathy.[1,27-29] There is evidence that neuropathy leads to 50% of all foot ulcerations in diabetes.[1,27-29] In our study population, the proportion of subjects with DFS and any neuropathy was significantly higher compared to subjects without DFS (T1D: 70.7% vs. 29.8%; T2D 59.4% vs. 36.9%); peripheral neuropathy was more common than autonomous neuropathy (Fig. 2a/b). Our findings also revealed a higher prevalence of peripheral neuropathy in patients with a minor amputation compared to those

with a major amputation (Table 4). The presence of PVD is another important risk factor for DFS (alone or in combination with neuropathy) and influences treatment results significantly.[1,27-29] PVD is an important risk factor for the absence of wound healing and for amputations.[20,30-32] Studies demonstrated that vascular diagnostics, catheter interventions and surgical revascularizations decrease the rate of major amputations dramatically.[30-32] In our DPV study population we observed that PVD was more common in patients with a major amputation compared to those with a minor amputation (Table 4). The comparison between patients with or without DFS indicated that especially in T2D with DFS, PVD was more common compared to patients without DFS (35.8% vs. 10.2%; Fig. 2b). But even in T1D, significant differences could be observed (11.6% vs. 3.0%; Fig. 2a). Findings from a study with T2D patients also indicated a higher frequency of peripheral neuropathy (82.6% vs. 71.4%) or PVD (41.9% vs. 13.4%) in subjects with DFS compared to those without DFS.[33] Although these are well established risk factor for DFS, no causality can be demonstrated due to the cross sectional design of our analysis.

A high prevalence of cardiovascular risk factors and cardiovascular comorbidity is an overall problem in individuals with diabetes.[34-36] Moreover, there is some evidence that DFS might be a predictor for cardiovascular disease and could also increase the progression.[33,37,38] In our study population, the frequency of hypertension was higher in patients with DFS compared to those without DFS (Fig. 3a/b). Differences were more distinct in T1D (53.8% vs. 41.5%) than in T2D (74.6% vs. 71.0%). A higher prevalence of hypertension was confirmed by a previously published systematic review and meta-analysis (63.4% vs. 53.1%).[19] A prospective follow-up study by Pinto and colleagues with T2D patients with or without DFS found a similar number in both groups (60.3% vs. 60.9%).[38] The authors explained this unexpected finding by a high prevalence of hypertension in subjects with diabetes, independently of DFS.[38] In our analysis, the frequency of dyslipidemia was high in both subjects with or without DFS (T1D >80%; T2D >90%). Although the comparison revealed some differences (slightly higher in T1D with DFS; Fig. 3a), the clinical relevance

seems to be negligible. In other studies, dyslipidemia was more common in subjects with DFS compared to those without DFS.[37-39]

Our analysis indicated a higher proportion of patients with DFS and myocardial infarction (T1D: 3.2% vs. 1.6%; T2D: 9.5% vs. 7.0%) or stroke (T1D: 2.3% vs. 1.1%; T2D: 8.2% vs. 6.2%) compared to subjects without DFS (Fig. 3a/b) and we observed that cardiovascular complications were more common in patients with an amputation of the lower extremities which is in line with other studies.[20,38,39,40] The comparison between subjects with a minor amputation and a major amputation further revealed a higher prevalence in patients with a major amputation: Myocardial infarction (15.6% vs. 12.9%; p=0.0002), stroke (13.9% vs. 11.1%; p<0.0001), and PVD (62.0% vs. 54.2%; p<0.0001). A retrospective analysis demonstrated that individuals with DFS are more likely to have a previous cardiovascular morbidity compared to patients without DFS.[38] They further found a higher incidence of new-onset cardiovascular morbidity in patients with DFS compared to those without DFS. Even after correction for other risk factors, the presence of DFS remained a strong predictor for cardiovascular endpoints.[38] As already mentioned, due to the cross-sectional study design of our DPV analysis, it remains unclear, whether the presence of cardiovascular comorbidities in our study population has affected the development of DFS or whether DFS increased the risk for cardiovascular morbidity.

Differences in lifestyle factors between patients with or without DFS

The number of physically inactive T1D patients with DFS was higher compared to patients without DFS (83.7 vs. 64.7%; Fig. 3a). In T2D, differences were marginal with most patients being inactive (91.1 vs. 90.0%; Fig. 3b). Overall, the number of physically inactive patients was higher compared to the general population of Germany.[41] Results of the German Health Update 2009 survey which was based on 21,262 telephone interviews observed that 36% of the German population was not engaged in sports.[41] It was also described that physical inactivity increased with age. In German adults aged 70 years or older, about 50% to 55% of the participants reported to be inactive.[41] It is assumed that patients included in our study

were older compared to the German Health Update 2009 survey which could be one explanation for this discrepancy. Differences between subjects with or without DFS could be explained by mobility restrictions (e.g. inability to stand or walk, or therapeutic offloading) resulting from acute DFS or the fear of foot ulcer recurrence.[42] In our analysis, the number of patients stated to be smokers did not differ between subjects with or without DFS (Fig. 3a/b). Findings from Pinto and colleagues were consistent with our results[38], whereas some other studies reported a higher number of smokers in subjects with DFS.[19,33]

Irrespective of the presence of DFS, we could reveal a large number of diabetes subjects with cardiovascular risk factors and cardiovascular morbidity. Additionally, in those patients without DFS, a high proportion was already affected by neuropathy (T1D: 29.8%; T2D: 36.9%). In one third of the individuals with DFS, at least a minor amputation was documented. There are several studies demonstrating that a multidisciplinary treatment approach including education units led to lower rates of DFS-induced amputations.[27,42] Adherence to treatment has also been confirmed to play an important role in clinical outcomes.[35,44,45] However, the attainment of treatment goals in diabetes care has been reported to be poor.[35,44,45] Unfortunately, available information in the DPV database does not allow the investigation whether the implementation of guidelines for the prevention or treatment of DFS was satisfactory. However, data on foot examinations are available. In 20% to 35% of all patients with diabetes, no foot examination was documented. Even in those patients with an acute DFS or a history of DFS, there remain 13% to 20% without foot examination. Due to the cross-sectional study design, no correlations between foot examinations and the development of DFS or the severity of DFS (including amputation rates) can be analyzed. However, we observed that DFS was more severe in those with documented foot examinations (Table 2). The higher proportion of patients with a more severe DFS (including a higher number with amputations) could be interpreted to mean that physicians pay more attention to this complication and the need for foot examinations in those patients who are (were) already affected. Regular after-care and preventative

measures are of very high importance to minimize the risk of repeated ulcers and amputation. A review from Volmer-Thole and Lobmann pointed out that in those patients with suboptimal care, about 70% have at least one recurrence of ulcer and, within five years of the initial foot lesion, an amputation is needed in 12%.[1] They further showed that in those with an amputation, the risk for reamputation is about 27% in the following year, and 61% after five years.[1] From a prevention perspective, more research should focus on new concepts to prevent DFS subsequent amputations including the promotion of invasive revascularization as well as to reduce risk factors before the development of DFS.

Strengths and Limitations

The main strength of this multicenter study is its large sample size. Some limitations need to be mentioned. The present study only included patients from participating DPV centers. A selection bias and therefore limited generalizability of our results might be possible. Moreover, due to the cross-sectional design of this study, observed associations cannot prove causal effects. Another shortcoming is that clinical characteristics were not available for all patients included. Underreporting of smoking cannot be excluded since information was based on patients' self-reports. Another weakness could be that in subjects without DFS, complications as for example neuropathy or PVD could be underreported compared to those patients with DFS. It is also possible that some patients with DFS could not be identified due to missing information. There was also no possibility to differentiate between an acute DFS and a history of DFS. Another limitation is that adherence to DFS guidelines or information on quality of life could not be assessed.

Conclusions

Of all diabetes subjects included, nearly 10% had an acute foot ulcer or a documented history of DFS. 33% of the patients with DFS had at least a minor amputation. Compared to patients without DFS, especially the proportion of neuropathy or PVD was higher in patients with DFS. Additionally, cardiovascular risk factors and cardiovascular comorbidity were more

common in those with DFS. Even in diabetes patients without DFS, the prevalence of cardiovascular and DFS risk factors was high. It is therefore urgently needed to develop new concepts to prevent DFS and DFS-induced amputations and to reduce cardiovascular risk factors before the occurrence of DFS.

Author Contributions. B.B. wrote/edited the manuscript and created figures. A.G., C.G., M.P., C.W., N.H., F.B., P.F., and R.W.H. contributed to the discussion and reviewed/edited the manuscript. R.W.H. conceptualized the study. R.W.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest. None

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Figure Legends

Figure 1 Selection of study population

Figure 2: Differences in the occurrence of neuropathy, peripheral vascular disease, or nephropathy (stage 3 or higher) between patients with or without DFS, stratified by **a)** type 1 or **b)** type 2 diabetes

Figure 3: Differences in cardiovascular risk/complications and lifestyle factors between patients with or without DFS, stratified by **a)** type 1 or **b)** type 2 diabetes

Table 1: Demographic differences between patients with or without DFS, and extent of DFS, stratified by T1D or T2D

	Type 1 Diabetes (n=45,722)					Type 2 Diabetes (n=313,264)				
	n	**DFS (n=2,966)**	**n**	**no DFS (42,756)**	**p***	**n**	**DFS (n=30,904)**	**n**	**no DFS (n=282,360)**	**p***
Men, %	2,966	61.4	42,756	52.6	<0.0001	30,904	62.6	282,360	51.2	<0.0001
Age [years]	2,966	61.8 (50.2; 73.4)	42,756	41.9 (27.9; 56.2)	<0.0001	30,904	72.6 (64.4; 79.2)	282,360	69.9 (60.1; 77.6)	<0.0001
Diabetes duration [years]	2,966	26.5 (16.4; 37.7)	42,756	14.3 (6.1; 24.8)	<0.0001	30,904	13.0 (7.3; 20.4)	282,360	7.8 (2.6; 14.3)	<0.0001
Severity of DFS										
Wagner 1, %	1,966	48.4				17,816	38.0			
Wagner 2, %	1,966	24.8				17,816	28.4			
Wagner 3, %	1,966	17.1				17,816	21.0			
Wagner 4, %	1,966	8.5				17,816	11.3			
Wagner 5, %	1,966	1.1				17,816	1.2			

Unadjusted data are given as medians (Q1; Q3), or percentage (%)
*p for difference between patients with or without DFS, adjusted for multiple comparisons by FDR

Table 2: Severity of DFS and proportion of DFS subjects with foot amputations, stratified by foot examinations (yes/no)

	Patients with DFS		
	no foot exams (n=4,789)	**foot exams (n=29,053)**	**p***
Severity of DFS			
Wagner 1, %	48.9	37.7	<0.0001
Wagner 2, %	25.8	28.4	0.00103
Wagner 3, %	17.8	21.0	<0.0001
Wagner 4, %	6.1	11.7	<0.0001
Wagner 5, %	1.4	1.2	0.55883
Amputation, %	17.8	35.5	<0.0001
minor amputation, %	13.3	28.1	<0.0001
major amputation, %	6.4	12.0	<0.0001

Unadjusted data are given as percentage (%)

*p for difference between DFS patients with or without documented foot examinations, adjusted for multiple comparisons by FDR

Table 3: Clinical differences between patients with or without DFS, stratified by T1D or T2D, adjusted by age, sex, and diabetes duration

	Type 1 Diabetes (n=45,722)					Type 2 Diabetes (n=313,264)				
	n	DFS (n=2,966)	n	no DFS (42,756)	p*	n	DFS (n=30,904)	n	no DFS (n=282,360)	p*
HbA_{1c} [%]	2,625	8.11	38,650	7.95	<0.0001	26,468	7.49	253,085	7.69	<0.0001
HbA_{1c} [mmol/mol]	2,625	65.1	38,650	63.4	0.0312	26,468	58.4	253,085	60.6	<0.0001
BMI [kg/m^2]	2,686	25.8	38,017	25.4	0.0014	26,709	30.5	249,650	30.5	0.4092
systolic BP+ [mmHg]	2,697	130.7	37,707	130.2	0.1691	27,357	136.0	258,939	136.5	<0.0001
diastolic BP+ [mmHg]	2,695	75.2	37,682	76.6	<0.0001	27,335	76.7	258,635	77.9	<0.0001
Antihypertensives, %	2,966	32.9	42,756	22.1	<0.0001	30,904	57.1	280,360	52.5	<0.0001
Total C [mg/dL]	2,057	187.5	28,764	194.2	<0.0001	20,599	184.5	190,404	193.3	<0.0001
LDL-C [mg/dL]	1,914	105.5	25,806	109.7	<0.0001	18,836	109.3	167,128	114.0	<0.0001
HDL-C [mg/dL]	1,928	55.9	26,248	60.1	<0.0001	19,015	45.0	170,476	46.5	<0.0001
Triglycerides [mg/dL]	2,020	144.4	27,988	131.7	<0.0001	19,960	177.4	184,674	190.4	<0.0001
Lipid-lowering drugs, %	2,966	12.2	42,756	9.1	<0.0001	30,904	27.8	282,360	26.4	<0.0001

Adjusted data are given as least square means (LS-means) or percentage (%); *p for difference between patients with or without DFS, +BP=blood pressure

Table 4: Differences on clinical characteristics and smoking in DFS patients with minor vs. major foot amputation

	Minor amputation (n=7,362)	Major amputation (n=3,797)	p*
HbA1c [%]	7.63	7.62	0.7751
Neuropathy, %	69.1	59.9	<0.0001
peripheral neuropathy, %	60.1	51.1	<0.0001
autonomic neuropathy, %	16.9	15.0	0.0149
Nephropathy, %	58.7	60.0	0.2280
Hypertension, %	76.1	76.5	0.6141
Dyslipidemia, %	94.1	94.9	0.1030
Myocardial infarction (MI), %	12.9	15.6	0.0002
Stroke, %	11.1	13.9	<0.0001
PVD, %	54.2	62.0	<0.0001
Smoking, %	10.7	13.3	0.0007

Adjusted data are given as percentage (%); *p for difference between DFS-patients with minor amputation compared to major amputation

Figure 1

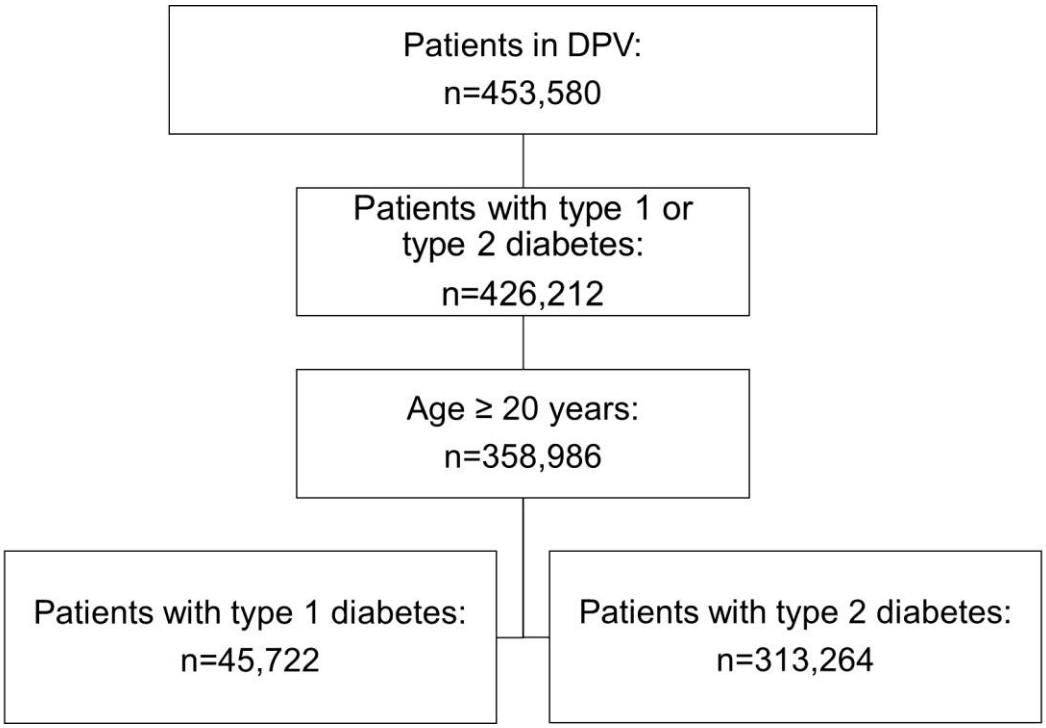

Patients in DPV:
n=453,580
Patients with type 1 or type 2 diabetes:
n=426,212
Age ≥ 20 years:
n=358,986
Patients with type 1 diabetes:
n=45,722
Patients with type 2 diabetes:
n=313,264

Figure 2

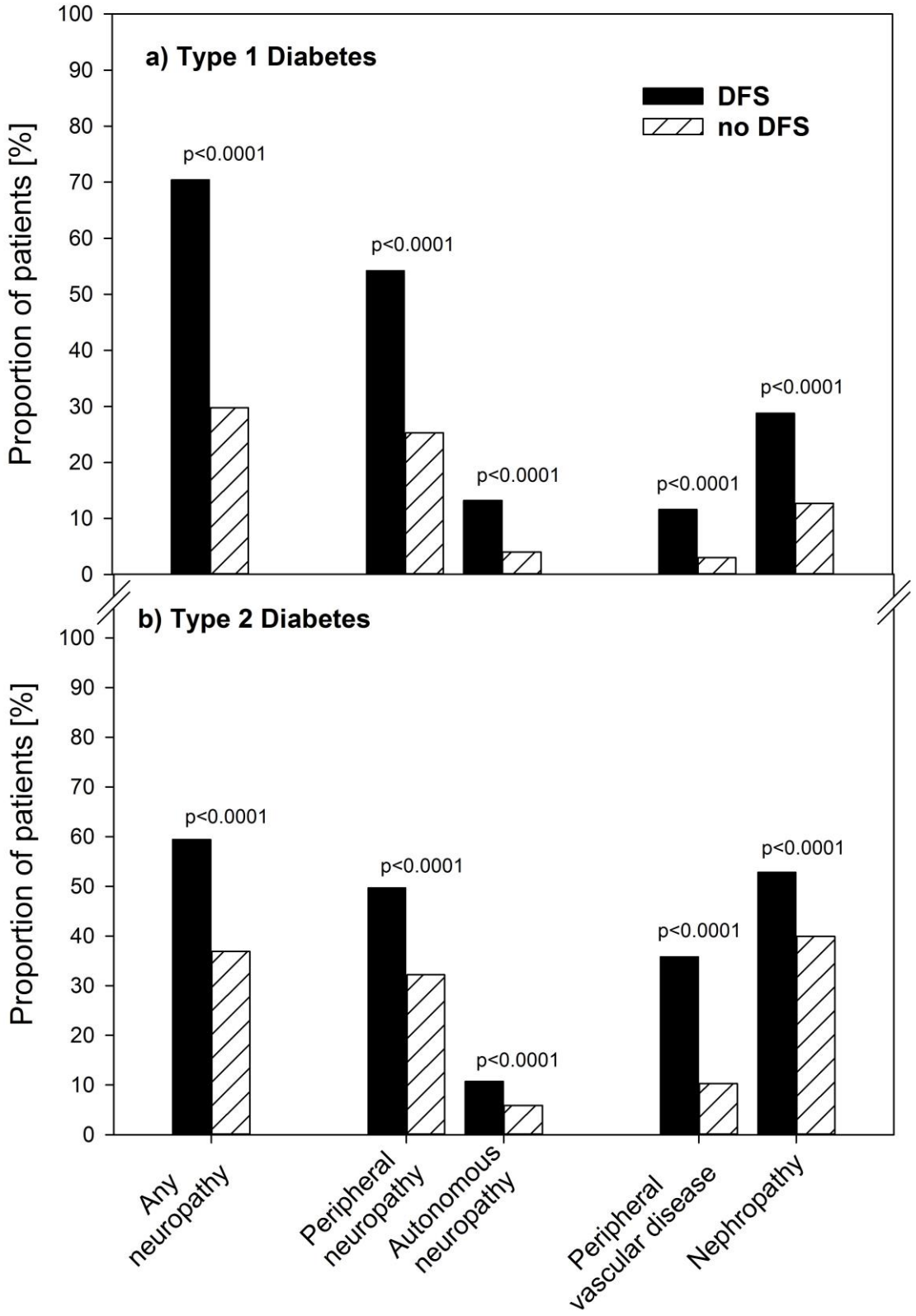
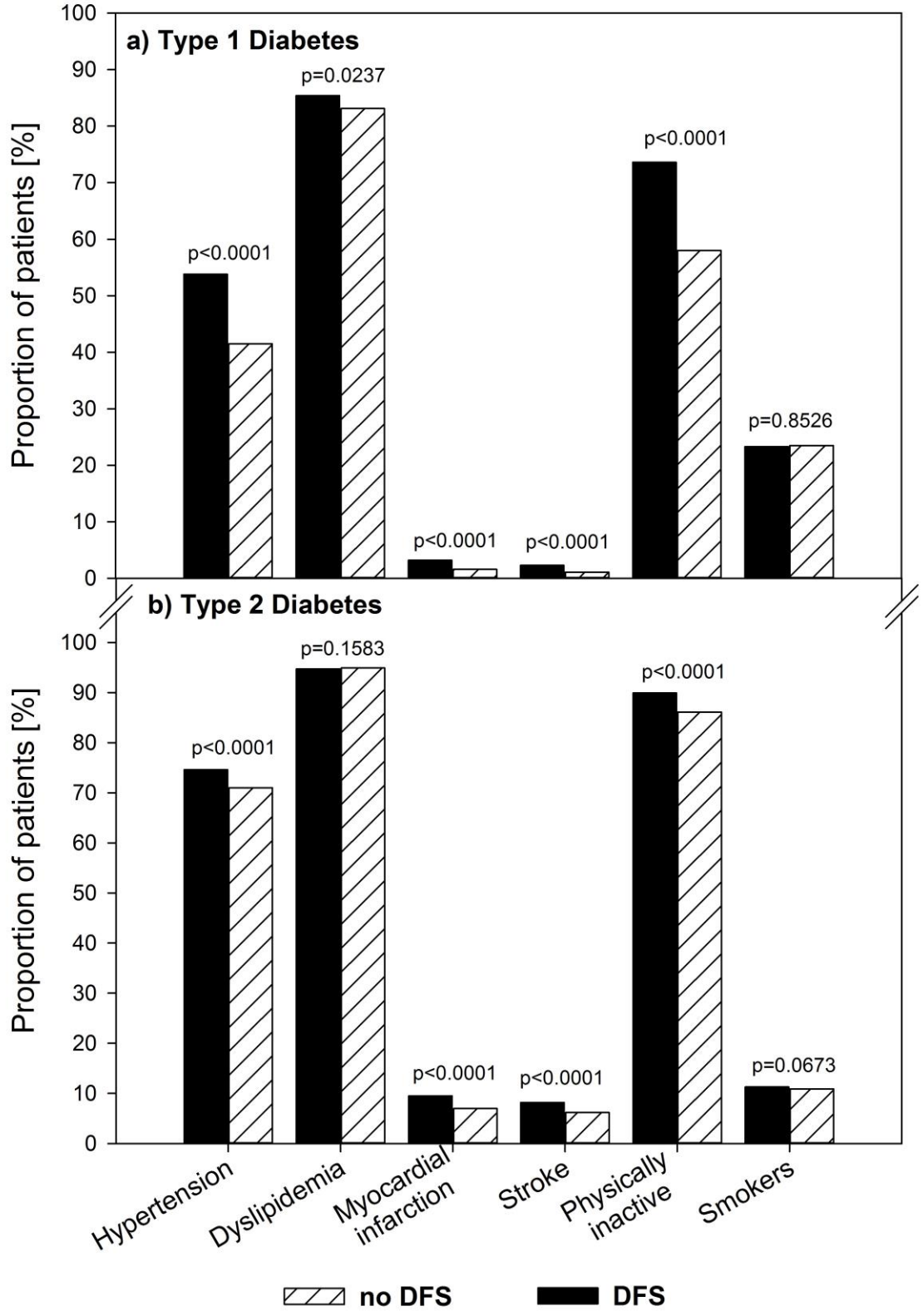

a) Type 1 Diabetes
DFS
no DFS
Proportion of patients [%]
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
b) Type 2 Diabetes
Proportion of patients [%]
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
Any neuropathy
Peripheral neuropathy
Autonomous neuropathy
Peripheral vascular disease
Nephropathy

Figure 3


a) Type 1 Diabetes
b) Type 2 Diabetes
Proportion of patients [%]
p<0.0001
p=0.0237
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p=0.8526
p<0.0001
p=0.1583
p<0.0001
p<0.0001
p<0.0001
p=0.0673
Hypertension
Dyslipidemia
Myocardial infarction
Stroke
Physically inactive
Smokers
no DFS
DFS

S1 Appendix: Collaborating DPV centers

Aachen - Innere RWTH, Aachen - Uni-Kinderklinik RWTH, Aalen Kinderklinik, Ahlen St. Franziskus Kinderklinik, Aidlingen Praxisgemeinschaft, Altötting-Burghausen Innere Medizin, Asbach Kamillus-Klinik Innere, Aue Helios Kinderklink, Augsburg IV. Med. Klinik, Augsburg Kinderklinik Zentralklinikum, Aurich Kinderklinik, Bad Aibling Internist. Praxis, Bad Driburg / Bad Hermannsborn Innere, Bad Hersfeld Innere, Bad Hersfeld Kinderklinik, Bad Kreuznach-St.Marienwörth-Innere, Bad Krozingen Klinik Lazariterhof Park-Klinikum, Bad Kösen Median Kinderklinik, Bad Lauterberg Diabeteszentrum Innere, Bad Mergentheim - Gemeinschaftspraxis DM-dorf Althausen, Bad Oeynhausen Herz-und Diabeteszentrum NRW, Bad Orb Spessart Klinik, Bad Orb Spessart Klinik Reha, Bad Reichenhall Kreisklinik Innere Med., Bad Salzungen Kinderklinik, Bad Säckingen Hochrheinklinik Innere, Bad Waldsee Kinderarztpraxis, Bautzen Oberlausitz KK, Bayreuth Innere Medizin, Berchtesgaden CJD, Berchtesgaden MVZ Innere Med, Berlin DRK-Kliniken Pädiatrie, Berlin DRK-Kliniken Westend Innere, Berlin Endokrinologikum, Berlin Evang. Krankenhaus Königin Elisabeth, Berlin Klinik St. Hedwig Innere, Berlin Lichtenberg - Kinderklinik, Berlin Oskar Zieten Krankenhaus Innere, Berlin Parkklinik Weissensee, Berlin Schlosspark-Klinik Innere, Berlin St. Josephskrankenhaus Innere, Berlin Virchow-Kinderklinik, Berlin Vivantes Hellersdorf Innere, Bern Universitätsklinik InselSpital Innere Medizin, Bielefeld Kinderklinik Gilead, Bocholt Kinderklinik, Bochum Universitäts St. Josef, Bochum Universitätskinderklinik St. Josef, Bonn Uni-Kinderklinik, Bottrop Knappschaftskrankenhaus Innere, Braunfels-Wetzlar Innere, Braunschweig Kinderarztpraxis, Bremen - Kinderklinik Nord, Bremen - Mitte Innere, Bremen Zentralkrankenhaus Kinderklinik, Bremerhaven Kinderklinik, Bruchweiler Edelsteinklinik Kinder-Reha, Böblingen Kinderklinik, Castrop-Rauxel Rochus-Hospital, Celle Klinik für Kinder- und Jugendmedizin, Chemnitz Kinderklinik, Chemnitz-Hartmannsdorf Innere Medizin - DIAKOMED-1, Coburg Innere Medizin, Coesfeld Kinderklinik, Coesfeld/Dülmen Innere Med., Darmstadt Innere Medizin, Darmstadt Kinderklinik Prinz. Margaret, Datteln Vestische Kinderklinik, Deggendorf Gemeinschaftspraxis, Deggendorf Medizinische Klinik II, Delmenhorst Kinderklinik, Detmold Kinderklinik, Dornbirn Innere Medizin, Dornbirn Kinderklinik, Dortmund Kinderklinik, Dortmund Knappschaftskrankenhaus Innere, Dortmund Medizinische Kliniken Nord, Dortmund-Hombruch Marienhospital, Dortmund-St. Josefshospital Innere, Dortmund-West Innere, Dresden Uni-Kinderklinik, Duisburg Evang. und Johanniter Krhs Innere, Duisburg Malteser Rhein-Ruhr St. Anna Innere, Duisburg Malteser St. Johannes, Duisburg Sana Kinderklinik, Duisburg-Huckingen, Duisburg-Huckingen Malteser Rhein-Ruhr ST. Johannes, Duisburg-St.Johannes Helios, Düren-Birkesdorf Kinderklinik, Düsseldorf Uni-Kinderklinik, Eberswalde Klinikum Barnim Werner Forßmann - Innere, Eisleben Lutherstadt Helios-Klinik, Erfurt Kinderklinik, Erlangen Uni Innere Medizin, Erlangen Uni-Kinderklinik, Essen Diabetes-Schwerpunktpraxis, Essen Elisabeth Kinderklinik, Essen Uni-Kinderklinik, Esslingen Klinik für Kinder und Jugendliche, Eutin Kinderklinik, Eutin St.-Elisabeth Innere, Feldkirch Kinderklinik, Filderstadt Kinderklinik, Forchheim Diabeteszentrum SPP, Frankenthal Kinderarztpraxis, Frankfurt Diabeteszentrum Rhein-Main-Erwachsenendiabetologie (Bürgerhospital), Frankfurt Uni-Kinderklinik, Frankfurt Uni-Klinik Innere, Frankfurt Uni-Klinik Innere, Frankfurt-Sachsenhausen Innere, Frankfurt-Sachsenhausen Innere MVZ, Freiburg Kinder-MVZ, Freiburg Uni Innere, Freiburg Uni-Kinderklinik, Friedberg Innere Klinik, Fulda Innere Medizin, Fulda Kinderklinik, Fürth Kinderklinik, Garmisch-Partenkirchen Kinderklinik, Geislingen Klinik Helfenstein Innere, Gelnhausen Innere, Gelnhausen Kinderklinik, Gelsenkirchen Kinderklinik Marienhospital, Gera Kinderklinik, Gießen Ev. Krankenhaus Mittelhessen, Gießen Uni-Kinderklinik, Graz Uni

Innere, Graz Uni-Kinderklinik, Göppingen Innere Medizin, Göppingen Kinderklinik am Eichert, Göttingen Uni Gastroenterologie, Göttingen Uni-Kinderklinik, Güstrow Innere, Hachenburg Kinderpraxis, Hagen Kinderklinik, Halberstadt Innere Med. AMEOS Klinik, Halberstadt Kinderklinik AMEOS, Halle Uni-Kinderklinik, Halle-Dölau Städtische Kinderklinik, Hamburg Altonaer Kinderklinik, Hamburg Endokrinologikum, Hamburg Kinderklinik Wilhelmstift, Hamburg-Nord Kinder-MVZ, Hameln Kinderklinik, Hamm Kinderklinik, Hanau Kinderklinik, Hanau St. Vincenz - Innere, Hannover Henriettenstift - Innere, Hannover Kinderklinik MHH, Hannover Kinderklinik auf der Bult, Haren Kinderarztpraxis, Heide Kinderklinik, Heidelberg St. Josefskrankenhaus, Heidelberg Uni-Kinderklinik, Heidelberg Uniklinik Innere, Heidenheim Arztpraxis Allgemeinmed, Heidenheim Kinderklinik, Heilbronn Innere Klinik, Heilbronn Kinderklinik, Herdecke Kinderklinik, Herford Innere Med I, Herford Kinderarztpraxis, Herford Klinikum Kinder & Jugendliche, Heringsdorf Inselklinik, Herne Evan. Krankenhaus Innere, Herten St. Elisabeth Innere Medizin, Herzberg Kreiskrankenhaus Innere, Hildesheim GmbH - Innere, Hildesheim Kinderarztpraxis, Hildesheim Kinderklinik, Hinrichsegen-Bruckmühl Diabetikerjugendhaus, Hof Kinderklinik, Homburg Uni-Kinderklinik Saarland, Idar Oberstein Innere, Ingolstadt Klinikum Innere, Innsbruck Uni-Kinderklinik, Innsbruck Universitätsklinik Innere, Iserlohn Innere Medizin, Itzehoe Kinderklinik, Jena Uni-Kinderklinik, Jena diabetol. Schwerpunktpraxis, Kaiserslautern Kinderarztpraxis, Kaiserslautern-Westpfalzklinikum Kinderklinik, Kamen Klinikum Westfalen Hellmig Krankenhaus, Karlsburg Klinik für Diabetes & Stoffwechsel, Karlsruhe Städtische Kinderklinik, Kassel Klinikum Kinder- und Jugendmedizin, Kassel Rot-Kreuz-Krankenhaus Innere, Kaufbeuren Innere Medizin, Kempen Heilig Geist - Innere, Kempen Heilig Geist-KHS - Innere, Kempten Oberallgäu Kinderklinik, Kiel Städtische Kinderklinik, Kiel Universitäts-Kinderklinik, Kirchen DRK Krankenhaus Kinderklinik, Kirchheim-Nürtingen Innere, Klagenfurt Innere Med I, Kleve Innere Medizin, Koblenz Kemperhof 1. Med. Klinik, Koblenz Kinderklinik Kemperhof, Konstanz Innere Klinik, Konstanz Kinderklinik, Krefeld Alexianer Innere, Krefeld Innere Klinik, Krefeld Kinderklinik, Krefeld-Uerdingen St. Josef Innere, Kreischa-Zscheckwitz Klinik Bavaria, Köln Kinderklinik Amsterdamerstrasse, Köln Uni-Kinderklinik, Landau Innere, Landau/Annweiler Innere, Landshut Kinderklink, Lappersdorf Kinderarztpraxis, Leipzig Uni-Kinderklinik, Leoben LKH Kinderklinik, Leverkusen Kinderklinik, Lienz Diabetesschwerpunktpraxis für Kinder und Jugendliche, Lilienthal Diabeteszentrum, Limburg Innere Medizin, Lindenfels Luisenkrankenhaus Innere, Lindenfels Luisenkrankenhaus Innere 2, Linz AKH - 2. Med, Linz KUK/MedCampus IV Kinderklinik, Linz Krankenhaus Barmherzige Schwestern Kardiologie Abt. Int. II, Linz Krankenhaus der Barmherzigen Schwestern Kinderklinik, Lippstadt Evangelische Kinderklinik, Ludwigsburg Innere Medizin, Ludwigsburg Kinderklinik, Ludwigshafen diabetol. SPP, Luxembourg - Centre Hospitalier, Lübeck Uni-Kinderklinik, Lübeck Uni-Klinik Innere Medizin, Lüdenscheid Hilfswerk Kinder & Jugendliche, Lüdenscheid Märkische Kliniken - Kinder & Jugendmedizin, Lünen Klinik am Park, Magdeburg Städtisches Klinikum Innere, Magdeburg Uni-Kinderklinik, Mainz Uni-Kinderklinik, Malchower See Rehaklinik, Mannheim Uni-Kinderklinik, Mannheim Uniklinik Innere Medizin, Marburg - UKGM Endokrinologie & Diabetes, Marburg Uni-Kinderklinik, Marktredwitz Innere Medizin, Marpingen-SPP, Melk Kinderklinik, Memmingen Internistische Praxis, Memmingen Kinderklinik, Minden Kinderklinik, Moers - St. Josefskrankenhaus Innere, Moers Kinderklinik, Murnau am Staffelsee - diabetol. SPP, Mutterstadt Kinderarztpraxis, Mödling Kinderklinik, Mölln Reha-Klinik Hellbachtal, Mönchengladbach Kinderklinik Rheydt Elisabethkrankenhaus, Mühlacker Enzkreiskliniken Innere, Mühldorf am Inn Kinderarztpraxis, München Diabetes-Zentrum Süd, München Kinderarztpraxis diabet.

SPP, München Schwerpunktpraxis, München von Haunersche Kinderklinik, München-Gauting Kinderarztzentrum, München-Harlaching Kinderklinik, München-Schwabing Kinderklinik, Münster Clemens-Hospital Innere, Münster Herz Jesu Innere, Münster Uni-Kinderklinik, Münster pädiat. Schwerpunktpraxis, Nagold Kreiskrankenhaus Innere, Nauen Havellandklinik, Neuburg Kinderklinik, Neumarkt Innere, Neunkirchen Innere Medizin, Neunkirchen Marienhausklinik Kohlhof Kinderklinik, Neuruppin Kinderklinik, Neuss Lukaskrankenhaus Kinderklinik, Neuwied Kinderklinik Elisabeth, Neuwied Marienhaus Klinikum St. Elisabeth Innere, Nidda Bad Salzhausen Klinik Rabenstein/Innere-1 Reha, Nidda Bad Salzhausen Klinik Rabenstein/Innere-2 Reha, Nürnberg Cnopfsche Kinderklinik, Nürnberg Med. Klinik 4, Nürnberg Zentrum f Neugeb./Kinder & Jugendl., Oberhausen Innere, Oberhausen Kinderklinik, Oberhausen Kinderpraxis, Oberhausen St.Clemens Hospitale Sterkrade, Oberndorf Gastroenterologische Praxis Schwerpunkt Diabetologie, Offenbach/Main Innere Medizin, Offenbach/Main Kinderklinik, Oldenburg Kinderklinik, Oldenburg Schwerpunktpraxis, Oschersleben MEDIGREIF Bördekrankenhaus, Osnabrück Christliches Kinderhospital, Osterkappeln Innere, Ottobeuren Kreiskrankenhaus, Oy-Mittelberg Hochgebirgsklinik Kinder-Reha, Paderborn St. Vincenz Kinderklinik, Papenburg Marienkrankenhaus Kinderklinik, Passau Kinderklinik, Pforzheim Kinderklinik, Pfullendorf Innere Medizin, Pirmasens Städtisches Krankenhaus Innere, Plauen Vogtlandklinikum, Prenzlau Krankenhaus Innere, Rastatt Gemeinschaftspraxis, Rastatt Kreiskrankenhaus Innere, Ravensburg Kinderklink St. Nikolaus, Recklinghausen Dialysezentrum Innere, Regensburg Kinderklinik St. Hedwig, Remscheid Kinderklinik, Rendsburg Kinderklinik, Reutlingen Kinderarztpraxis, Reutlingen Kinderklinik, Reutlingen Klinikum Steinenberg Innere, Rheine Mathiasspital Kinderklinik, Rodalben St. Elisabeth, Rosenheim Innere Medizin, Rosenheim Schwerpunktpraxis, Rostock Uni-Kinderklinik, Rostock Universität Innere Medizin, Rotenburg/Wümme Agaplesion Diakonieklinikum Kinderabteilung, Rüsselsheim Kinderklinik, Saaldorf-Surheim Diabetespraxis, Saalfeld Thüringenklinik Kinderklinik, Saarbrücken Kinderklinik Winterberg, Saarbrücken Kinderklinik Winterberg 2, Salzburg Universitäts-Kinderklinik, Scheibbs Landesklinikum, Scheidegg Reha-Kinderklinik Maximilian, Schw. Gmünd Stauferklinik Kinderklinik, Schweinfurt Kinderklinik, Schwerin Innere Medizin, Schwerin Kinderklinik, Schwäbisch Hall Diakonie Innere Medizin, Schwäbisch Hall Diakonie Kinderklinik, Siegen Kinderklinik, Singen Kinderarztpraxis, Sinsheim Innere, Spaichingen Innere, Speyer Diakonissen Stiftungskrankenhaus Pädiatrie, St. Augustin Kinderklinik, St. Pölten Universitäts-Kinderklinik, St. Pölten Universitätsklinik Innere, Stade Kinderklinik, Stockerau Landeskrankenhaus, Stolberg Kinderklinik, Stuttgart Bethesda Agaplesion, Stuttgart Olgahospital Kinderklinik, Suhl Kinderklinik, Sylt Rehaklinik, Tettnang Innere Medizin, Timmendorfer Strand, Traunstein diabetol. Schwerpunktpraxis, Trier Kinderklinik der Borromäerinnen, Trostberg Innere, Tübingen Uni-Kinderklinik, Ulm Agaplesion Bethesda-Krankenhaus, Ulm Endokrinologikum, Ulm Schwerpunktpraxis Bahnhofsplatz, Ulm Uni Innere Medizin, Ulm Uni-Kinderklinik, Vechta Kinderklinik, Viersen Kinderkrankenhaus St. Nikolaus, Villach Kinderklinik, Villingen-Schwenningen SPP, Villingen-Schwenningen Schwarzwald-Baar-Klinikum Innere, Waldshut Kinderpraxis, Waldshut-Tiengen Kinderpraxis Biberbau, Wangen Oberschwabenklinik Innere Medizin, Waren-Müritz Kinderklinik, Weiden Kinderklinik, Weingarten Kinderarztpraxis, Weisswasser Kreiskrankenhaus, Wels Innere, Wels Klinikum Pädiatrie, Wernberg-Köblitz SPP, Wetzlar Schwerpunkt-Praxis, Wien 3. Med. Hietzing Innere, Wien Preyersches Kinderspital, Wien Rudolfstiftung, Wien SMZ Ost Donauspital, Wien Uni Innere Med III, Wien Uni-Kinderklinik, Wien Wilhelminenspital 5. Med. Abteilung, Wiesbaden Helios Horst-Schmidt-Kinderkliniken, Wiesbaden Kinderklinik DKD, Wilhelmshaven Klinikum Kinderklinik, Wilhelmshaven St.

Willehad Innere, Winnenden Rems-Murr Kinderklinik, Wittenberg Innere Medizin, Wolgast Innere Medizin, Worms - Weierhof, Worms Kinderklinik, Wuppertal Kinderklinik, Zweibrücken Ev. KH. Innere.