



The TUDID Study – Background and Design of a Prospective Cohort

Authors

Benjamin Assad Jaghutriz^{1, 2, 3}, Robert Wagner^{1, 2, 3}, Stephanie Kullmann^{1, 2, 5}, Louise Fritsche^{1, 2}, Sabine S. Eckstein^{1, 2}, Corinna Dannecker^{1, 2}, Caroline Willmann^{2, 3}, Elko Randrianarisoa^{1, 2}, Angela Lehn-Stefan^{1, 2}, Anja Hieronimus^{2, 3}, Sarah Hudak^{1, 2, 3}, Dorothea Vosseler^{2, 3}, Apostolia Lamprinou^{1, 2, 3}, Philipp Huber³, Andreas Vosseler^{1, 2, 3}, Gabriel Willmann⁶, Nils Heyne³, Diana Wolff⁷, Norbert Stefan^{1, 2, 3}, Hans-Ulrich Häring^{1, 2, 3}, Andreas L. Birkenfeld^{1, 2, 3}, Andreas Peter^{1, 2, 4}, Andreas Fritsche^{1, 2, 3} , Martin Heni^{1, 2, 3, 4} 

Affiliations

- 1 Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany
- 2 German Center for Diabetes Research (DZD e.V.), Tübingen, Germany
- 3 Department of Internal Medicine, Division of Endocrinology, Diabetology, and Nephrology, University Hospital Tübingen, Tübingen, Germany
- 4 Institute for Clinical Chemistry and Pathobiochemistry, Department for Diagnostic Laboratory Medicine, University Hospital Tübingen, Tübingen, Germany
- 5 Institute of Medical Psychology and Behavioral Neurobiology/fMEG Center, Eberhard Karls University Tübingen, Tübingen, Germany
- 6 University Eye Hospital Tübingen, Tübingen, Germany
- 7 Department of Conservative Dentistry, University Hospital Tübingen, Tübingen, Germany

Key words

diabetes complications, observational, prospective

received 15.05.2020

revised 03.07.2020

accepted 17.07.2020

published online 10.09.2020

Bibliography

Exp Clin Endocrinol Diabetes 2022; 130: 43–48

DOI 10.1055/a-1221-9618

ISSN 0947-7349

© 2020, Thieme. All rights reserved.

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Prof. Martin Heni, MD
University Hospital Tübingen, Internal Medicine IV
Otfried-Müller-Str. 10
72076 Tübingen
Germany
Tel.: +49 7071 2982714, Fax: +49 7071 292784
martin.heni@med.uni-tuebingen.de

ABSTRACT

Prevalence of both type 1 and type 2 diabetes mellitus is growing worldwide and one major cause for morbidity and mortality. However, not every patient develops diabetes-related complications, but causes for the individual susceptibility are still not fully understood. As a platform to address this, we initiated the TUDID (TUebingen Diabetes Database) study, a prospective, monocentric, observational study that includes adults with diabetes mellitus who are treated in the inpatient clinic of a University Hospital in southern Germany. Besides a thorough clinical examination and extensive laboratory tests (with integrated biobanking), major study focuses are the kidneys, the eyes, the vasculature as well as cognition and mood where standardized investigations for early stages for diabetes complications are performed. Analyses of the data generated by this precise characterization of diabetes-related complications will contribute to our understanding of the development and course of such complications, and thus facilitate the implementation of tailored treatment options that can reduce the risk and severity of diabetes-related complications.

Introduction

Diabetes is a non-communicable disease, with an increasing tendency towards epidemic proportions [1]. In addition to the acute challenge in diabetes to control blood glucose, several further substantial diabetes-related complications may or may not occur in the course of the disease. Diabetes-related complications can be

categorized in micro- and macrovascular complications and include neuropathy, retinopathy, nephropathy, and peripheral artery disease. Furthermore, patients with diabetes have a substantially higher risk of developing depression, impaired cognition and even Alzheimer's disease. Diabetes-related complications occur in up to 30% of such patients. Major risk factors for the development of

complications include diabetes manifestation at a young age, duration of the disease, and quality of treatment [2, 3]. Although a number of risk factors for the development of complications have already been studied in depth, it still remains unclear as to why some patients are more susceptible to developing severe diabetes-related complications than others.

One of the major microvascular complications is diabetic neuropathy [4]. This condition can occur in heterogeneous forms and is a major health problem, since such a diagnosis considerably increases the risk of foot ulcerations and amputations of the lower extremities [2]. In addition, approximately 15% of patients suffer from neuropathic pain [5]. Since up to 50% of affected patients are clinically asymptomatic [6], those who are not afflicted by these burdensome symptoms run the serious risk of under-diagnosis of diabetic neuropathy.

Diabetic nephropathy, a further major microvascular diabetes complication, affects approximately 20–40% of patients [7]. One of the earliest detectable signs of glomerular damage is the filtration of larger molecules. In clinical routine, albumin in the urine is already a well-established marker, and even slight elevations in urinary albumin (microalbuminuria) are predictive of further decline in renal function. In developed countries, diabetic nephropathy is the major cause of end-stage renal disease, with subsequent need of dialysis [1, 8].

The leading cause of blindness among the world's working population is diabetic retinopathy [9, 10]. However, the occurrence of diabetic retinopathy strongly depends on both the duration of the disease and the quality of glycemic control [11, 12]. The overall prevalence of diabetic retinopathy is estimated to be as high as 34% [9]. Proliferative retinopathy occurs in advanced stages of diabetic retinopathy and it is a major cause of vision loss in patients with diabetes. Furthermore, diabetic retinopathy is a possible surrogate for other complications such as coronary heart disease and stroke [12, 13].

The prevalence of peripheral artery disease as a macrovascular complication is estimated to be as high as 40% in patients with diabetes [14]. Since changes in the vasculature are often not limited to the extremities but occur in all arterial beds, peripheral artery disease is a strong predictor for cardiovascular and cerebrovascular events [15]. On the other hand, approximately 25% of patients with peripheral artery disease also suffer from diabetes. Amputation rates among patients with diabetes and peripheral artery disease are seven times higher than in those with normal glucose metabolism [14]. Furthermore, together with diabetic neuropathy, peripheral artery disease is a key determinant of the diabetic foot syndrome [16].

Research over the last few years has shown that patients with diabetes have a conspicuously high prevalence of psychiatric and cognitive disorders such as depression or dementia [17–22]. *Vice versa*, depression is associated with an increased prevalence for other diabetes-related complications [22, 23]. However, the molecular mechanism interlinking diabetes, cognition and mood have still not been fully investigated.

Besides the classic diabetes-related complications, more attention is being focused on other potential sequelae of diabetes such as diabetes-related periodontal disease, as impaired glycemic con-

trol and diabetes appear to be linked to periodontal disease [24–26]. However, since knowledge is still somewhat lacking on this issue, large prospective studies are required for further elucidation.

For patients with diabetes, the relative risk of developing one or more of the aforementioned complications is estimated to be 2–20 fold higher than in individuals without diabetes [27, 28]. A more detailed understanding of the pathomechanisms that lead to complications and a determination of individual risk for diabetes-related complications are essential, as the latter contribute considerably to the morbidity and mortality of the disease. In addition, chronic diseases such as diabetes are a burden not only to the individual, but also to the public health sector [29].

To identify the parameters responsible for the development and course of diabetes-related complications, we recently initiated the TUDID (TUebingen DIabetes Database) study, a structured and standardized prospective study in a cohort of patients with diabetes (► Figs. 1 and ► 2). In this program, microvascular and macrovascular complications are systematically assessed already in their early, subclinical stages.

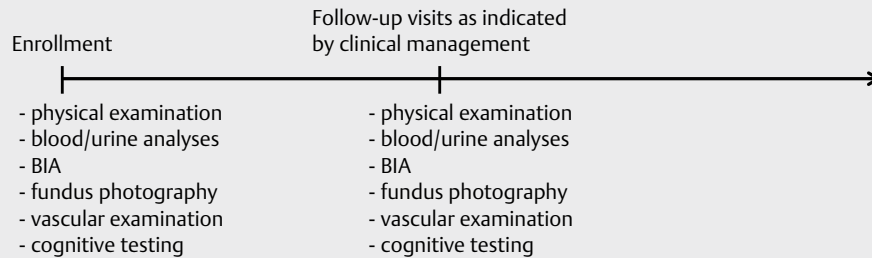
Methods

Study design

This prospective, monocentric, observational study consists of adults with diabetes mellitus who have been diagnosed in accordance with the criteria of the American Diabetes Association [30]. The study started August 13, 2018 and is ongoing. Patients are recruited from the inpatient clinic of the University Hospital of the Eberhard-Karls-University Tübingen, Department of Internal Medicine IV, Division of Endocrinology, Diabetology, and Nephrology, Germany. All participants provide informed written consent prior to study enrollment. The study is registered at ClinicalTrials.gov (NCT03658512), is in conformity with the principles outlined in the Declaration of Helsinki, and has been approved by the local ethics committee of the Eberhard-Karls-University Tübingen.



► Fig. 1 Schematic overview of the major organ systems investigated in the TUDID study.



► **Fig. 2** Timeline of the TUDID study.

Medical history, physical examination

Medical history is assessed by an experienced physician in a structured manner. It includes diabetes-related information, current and previous pharmacological treatments, and general medical history. Anthropometric measurements (body weight, height and BMI) are recorded at the beginning and during follow-up visits. A detailed physical examination is performed during each visit and comprises the following examinations: general appearance, skin (including hair and nails), EENT (ears, eyes, nose, throat), neck/thyroid, chest/lungs, cardiovascular, gastrointestinal, genito-urinary (optional), neurological, lymphatic and musculoskeletal. Blood pressure, pulse rate and oral or tympanic membrane (auricular) temperature. Diabetic neuropathy is assessed by applying the Michigan Diabetic Neuropathy Screening Instrument (MDNSI), which has been shown to be a valid screening instrument of distal diabetic neuropathy in patients with type 1 and type 2 diabetes [31–33].

Laboratory analyses

Extensive blood and urine analyses are performed during the trial. C-peptide, TSH (thyroid stimulating hormone), thyroid hormones, cortisol and high sensitive troponin I are determined using immunoassays on the ADVIA Centaur XPT System. Plasma parameters, including glucose, triglycerides (TGs), HDL, low-density lipoprotein cholesterol levels, plasma enzyme activities, C-reactive protein, creatinine (enzymatic), and Cystatin C are measured using the ADVIA XPT clinical chemical analyzer. Urine albumin is measured on the BN Prospec Nephelometer (all Siemens Healthineers, Eschborn, Germany). Fresh urine samples are also subjected to a standard urinalysis (iChemVELOCITY) including a digital urine microscopy (iQ200) (Beckman Coulter, Krefeld, Germany). Hematological parameters are determined on the Sysmex XN-10 (Sysmex GmbH, Norderstedt, Germany) and HbA1c measurements are performed using the Tosoh glycohemoglobin analyzer HLC-723G8 (Tosoh Bioscience Tokyo Japan). Once they reach the diagnostic laboratory biobank, samples of serum, heparinized and citrated plasma, urine and buffy coat are generated and rapidly transferred to -80 °C storage. All measurements are performed in the Institute of Clinical Chemistry and Pathobiochemistry of the University Hospital Tübingen which is accredited with the German accreditation body (DAkkS).

Bioelectric impedance analysis

Bioelectric impedance analysis (BIA) is a valid method for the quantification of body composition in individuals [34]. In the current study, BIA is performed by a single-frequency BIA device (50 kHz) in accordance with the manufacturer's protocol (BIA 101 BIVA, Akern, Germany). Using the results from BIA analysis and anthropometric characteristics, body composition is calculated with the software provided (Cyprus Akern, Germany). Fat-free mass, extracellular water, total body water, body cell mass and body fat mass are thereby computed.

Fundus photography

In this study, fundus photography of both eyes is performed using a handheld fundus camera (Optomed, Finland) in a non-mydriatic state, enabling an analysis of the central 35° of the retina including the optic disc and macula. These images are evaluated by an experienced ophthalmologist.

Vascular examination

Assessment of functional and morphological changes of the arterial wall is performed by an experienced vascular physician during the study and on follow-up visits. Vascular examinations are performed in a lying position after a 10-minute rest at room temperature. Determination of ankle-brachial-index – the first diagnostic step following clinical examination – is performed in a lying position in accordance with Xu et al [35] using Doppler ultrasound by ELCAT vasolab®320 and handydop® (Wolfratshausen, Germany) with a 4 and 8 MHz pin probe. To obtain reliable results even in the presence of medial calcification, we additionally assess toe-brachial-index (TBI) using the software provided (ELCAT vasolab®320, Wolfratshausen, Germany) with a TBI cut-off <0.70 to diagnose peripheral artery disease [36]. In addition, high-resolution ultrasound with a linear transducer 10–3 MHz (CX50, Philips, Hamburg, Germany), analyzing both the right brachial and the femoral artery, is used to screen patients for medial calcification of the arterial wall. Using the aforementioned linear transducer, ultrasound of both common carotid arteries is examined in supine position, while the head is slightly extended and turned 45° to the contralateral side of the scanning. In B-mode, IMT (Intima-media thickness) is assessed on the far wall of the artery approximately 10 mm proximal to the carotid bulb. The carotid artery, including carotid bulb region, is screened for plaque burden and categorized by carotid

plaque presence and morphology [37]. Diameter of infrarenal aorta abdominalis and screening for aortic plaque is performed with a 5–1 MHz convex transducer (PureWave technology, Philips, Hamburg, Germany). To assess arterial stiffness, pulse wave amplitude (PWA) and pulse wave velocity (PWV) are measured on the right upper arm using the Arteriograph™ device (TensioMed, Budapest, Hungary). For the assessment of advanced glycation end products (AGEs), skin AGEs are measured on the ventral side of the right forearm (AGE Reader™, DiagnOptics Technologies B.V., Groningen, Netherlands).

Questionnaires

The Beck Depression Inventory II (BDI II) is used as a psychometric screening test for depression. To investigate different cognitive domains, the Cambridge Neuropsychological Test Automated Battery (CANTAB) is applied on an iPad (Apple Inc., Cupertino, California). The test battery includes multiple tasks (duration of approx. 1 hour) to assess executive function, episodic memory, visual memory, information processing, and sustained attention (CANTAB® [Cognitive assessment software], Cambridge Cognition (2019)). The following tests are included: Motor Screening Task (MOT), Paired Associates Learning (PAL), Pattern Recognition Memory (PRM), Reaction Time (RTI), Spatial Working Memory (SWM), Rapid Visual Information Processing (RVP) and Delayed Matching Sample (DMS).

Discussion/Outlook

Prospective cohort studies are essential to identify trajectories for the development of diabetes complications. In the past few years, several studies have been initiated that focus on the epidemiology of type 1 and type 2 diabetes, risk factors, specific sub-phenotypes, nutritional impact, and the effects of different therapeutic strategies [38–45]. A number of these studies are, however, not diabetes specific and tend instead to focus on the prevalence and incidence of diabetes [44]. Others focus on subjects with newly-diagnosed diabetes or selectively examined subjects with pre-specified types of diabetes [43, 45–47]. Cohorts aiming to precisely characterize the various facets of diabetes-related complications in all types of diabetes beyond standard approaches in clinical routine are still scarce. We therefore initiated the TUDID study that focuses on individuals with all types of diabetes who are treated in a university hospital setting. By searching for microvascular, macrovascular, periodontal as well as psychiatric and cognitive impairments, the TUDID study aims to capture the major features of these diabetes-related complications. We thereby aim to identify and validate determinants of diabetes-related complications. In future, these data will be able to contribute to personalized concepts of prevention and attenuation of diabetes-related complications.

One of the strengths of the TUDID study is that comprehensive data on complications are assessed in patients with different diabetes durations. This facilitates a detailed analysis of the characteristics of diabetes-related complications at different stages of the disease. By including patients with a long history of diabetes, the TUDID study enables us to compare patients with and without distinct complications after many years of altered glucose metabolism. By de-

sign, the TUDID study mirrors real-world conditions in Germany and provides insight into the heterogeneous course of the disease. The TUDID study, therefore, might uncover findings in patients who are often excluded from randomized controlled trials.

In addition, the TUDID study provides the opportunity to make an in-depth assessment of the micro- and macrovascular complications of diabetes. We thereby aim to analyze the broadly intertwined facets of the vascular complications of diabetes from different angles and to gain a clearer picture of their complexity.

One main feature of the TUDID study is the collection and storage of complex datasets and specimens in a state-of-the-art prospective biobank. The usage of biobanks has emerged as a strong tool in research, facilitating large-scale analysis and detailed phenotyping of diseases [48, 49]. Due to its prospective design, the TUDID study may profit from current and future advantages of biobanking. Since one major focus of our project is sample quality, we implemented strict workflows to minimize pre-analytic errors. Therefore, we anticipate that advanced OMICS approaches will be possible that rely on such an excellent sample quality (e. g. metabolomics) [50]. Among the limitations is the monocentric design at a large University Hospital in Germany and the follow-up of patients that currently relies on clinical indication for re-examination in the hospital.

In summary, the TUDID trial is a comprehensive approach for the characterization of micro- and macrovascular diabetes-related complications that goes beyond the commonly recommended screening instruments. We are confident that a precise characterization of diabetes-related complications will contribute to our understanding of the development and course of such complications, and thus facilitate the implementation of tailored treatment options that can reduce the risk and severity of diabetes-related complications [51, 52].

Author Contributions

The principal investigator of this study is Prof. Andreas Fritsche. B.A.J. and M.H. wrote the manuscript. B.A.J., R.W., S.K., C.W., E.R., A.L.S., A.H., S.H., D.V., A.L., P.H., A.V., G.W. and M.H. performed examinations. All authors contributed to the conception of the study, discussion of the manuscript and approved the final version before submission.

Funding

This study was partly supported by a grant (01GI0925) from the Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.). We acknowledge support by the Deutsche Forschungsgemeinschaft and the Open Access Publishing Fund of the University of Tübingen.

Acknowledgments

We thank all research volunteers and all investigators for their participation. We thank Sonja Hülskämper for artistic support in preparation of the figure.

Conflict of interest:

As of 01/2020, B.A. Jaghutriz is an employee of Eli Lilly and Company. Outside of the current work, R.W. reports lecture fees from Novo Nordisk and travel grants from Eli Lilly. Outside of the current work, M.H. reports research grants from Boehringer Ingelheim and Sanofi (both to the University Hospital of Tübingen) and lecture fees from Sanofi, Novo Nordisk, Eli Lilly and Merck Sharp & Dohme. Outside of the current work, A.F. reports lecture fees and advisory board membership from Sanofi, Novo Nordisk, Eli Lilly, AstraZeneca. Outside of the current work, N.S. was and presently is consulting and was and is a member of the speaker bureau of Allergan, AstraZeneca, Boehringer Ingelheim, Gilead, Genkyotex, Intercept Pharma, MSD, Novartis, Novo Nordisk, Pfizer and Sanofi. Furthermore, he conducted clinical trials with support from AstraZeneca, Boehringer Ingelheim, Sanofi, DSM Nutritional Products and Roche Diagnostics. Outside of the current work, A.B. received advisory board fees and fees for serving on a speakers bureau from Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Sanofi and Boehringer Ingelheim. None of the other authors report a conflict of interest.

References

- [1] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018; 14: 88–98
- [2] Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. *Phys Ther* 2008; 88: 1254–1264
- [3] Steffes MW, Sibley S, Jackson M et al. β -cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 2003; 26: 832–836
- [4] Said G. Diabetic neuropathy—a review. *Nat Rev Neurol* 2007; 3: 331–340
- [5] Davies M, Brophy S, Williams R et al. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2006; 29: 1518–1522
- [6] Pop-Busui R, Boulton AJM, Feldman EL et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; 40: 136–154
- [7] Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. *Nat Rev Endocrinol* 2008; 4: 444–452
- [8] Tuttle KR, Bakris GL, Bilous RW et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. *Diabetes Care* 2014; 37: 2864–2883
- [9] Yau JWY, Rogers SL, Kawasaki R et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes Care* 2012; 35: 556–564
- [10] Ting DSW, Cheung GCM, Wong TY. Diabetic retinopathy: Global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Experiment Ophthalmol* 2016; 44: 260–277
- [11] Thomas RL, Dunstan FD, Luzio SD et al. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. *Br J Ophthalmol* 2015; 99: 64–68
- [12] Jampol LM, Glassman AR, Sun J. Evaluation and care of patients with diabetic retinopathy. *N Engl J Med* 2020; 382: 1629–1637
- [13] Xie J, Ikram MK, Cotch MF et al. Association of Diabetic Macular Edema and Proliferative Diabetic Retinopathy With Cardiovascular Disease: A systematic review and meta-analysis. *JAMA Ophthalmol* 2017; 135: 586–593
- [14] Weitz Jeffrey I, John Byrne, Patrick Claggett G. et al. Diagnosis and Treatment of Chronic Arterial Insufficiency of the Lower Extremities: A Critical Review. *Circulation* 1996; 94: 3026–3049
- [15] Marso SP, Hiatt WR. Peripheral Arterial Disease in Patients With Diabetes. *J Am Coll Cardiol* 2006; 47: 921–929
- [16] Hobzial KB, Wukich DK. Diabetic foot infections: Current concept review. *Diabet Foot Ankle* 2012; 3. doi: 10.3402/dfa.v3i0.18409
- [17] Koekkoek PS, Kappelle LJ, van den Berg E et al. Cognitive function in patients with diabetes mellitus: Guidance for daily care. *Lancet Neurol* 2015; 14: 329–340
- [18] Hazari MAH, Ram Reddy B, Uzma N et al. Cognitive impairment in type 2 diabetes mellitus. *Int J Diabetes Mellit* 2015; 3: 19–24
- [19] Kullmann S, Heni M, Veit R et al. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes Care* 2015; 38: 1044–1050
- [20] Nunley KA, Rosano C, Ryan CM et al. Clinically relevant cognitive impairment in middle-aged adults with childhood-onset type 1 diabetes. *Diabetes Care* 2015; 38: 1768–1776
- [21] Luchsinger JA, Reitz C, Patel B et al. Relation of Diabetes to Mild Cognitive Impairment. *Arch Neurol* 2007; 64: 570–575
- [22] Anderson RJ, Freedland KE, Clouse RE et al. The Prevalence of Comorbid Depression in Adults With Diabetes: A meta-analysis. *Diabetes Care* 2001; 24: 1069–1078
- [23] Darwish L, Beroncal E, Sison MV et al. Depression in people with type 2 diabetes: Current perspectives. *Diabetes Metab Syndr Obes Targets Ther* 2018; 11: 333–343
- [24] Sanz M, Ceriello A, Buysschaert M et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. *J Clin Periodontol* 2018; 45: 138–149
- [25] Löe H. Periodontal Disease: The sixth complication of diabetes mellitus. *Diabetes Care* 1993; 16: 329–334
- [26] Graves DT, Ding Z, Yang Y. The impact of diabetes on periodontal diseases. *Periodontol* 2000 2020; 82: 214–224
- [27] Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. *Lancet Diabetes Endocrinol* 2016; 4: 537–547
- [28] Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clin Diabetes* 2008; 26: 77–82
- [29] Bommer C, Sagalova V, Heesemann E et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. *Diabetes Care* 2018; 41: 963–970
- [30] Association AD. 2 Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018; 41: S13–S27.
- [31] Feldman EL, Stevens MJ, Thomas PK et al. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994; 17: 1281–1289
- [32] Herman WH, Pop-Busui R, Bruffett BH et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med J Br Diabet Assoc* 2012; 29: 937–944
- [33] Moghtaderi A, Bakhshipour A, Rashidi H. Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. *Clin Neurol Neurosurg* 2006; 108: 477–481
- [34] Ling CHY, de Craen AJM, Slagboom PE et al. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. *Clin Nutr* 2011; 30: 610–615
- [35] Xu D, Zou L, Xing Y et al. Diagnostic Value of ankle-brachial index in peripheral arterial disease: A meta-analysis. *Can J Cardiol* 2013; 29: 492–498

- [36] Victor Aboyans, Criqui Michael H, Pierre Abraham et al. Measurement and interpretation of the ankle-brachial index. *Circulation* 2012; 126: 2890–2909
- [37] Petersen C, Peçanha PB, Venneri L et al. The impact of carotid plaque presence and morphology on mortality outcome in cardiological patients. *Cardiovasc Ultrasound* 2006; 4: 16–16
- [38] Nathan DM. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. *Diabetes Care* 2014; 37: 9–16
- [39] Holle R, Happich M, Löwel H et al. KORA - A Research Platform for Population Based Health Research. *Gesundheitswesen* 2005; 67: 19–25
- [40] Riboli E, Kaaks R. The EPIC Project: Rationale and study design. *European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol* 1997; 26 Suppl 1: S 6–14
- [41] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet* 1998; 352: 837–853
- [42] Effects of Intensive Glucose Lowering in Type 2 Diabetes *N Engl J Med* 2008; 358: 2545–2559
- [43] ADVANCE Collaborative Group Patel A, MacMahon S et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358: 2560–2572
- [44] Völzke H, Alte D, Schmidt CO et al. Cohort Profile: The Study of Health in Pomerania. *Int J Epidemiol* 2011; 40: 294–307
- [45] Szendroedi J, Saxena A, Weber KS et al. Cohort profile: The German Diabetes Study (GDS). *Cardiovasc Diabetol* 2016; 15: 59
- [46] Nathan DM. Group for the DR. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. *Diabetes Care* 2014; 37: 9–16
- [47] Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545–2559
- [48] Bowton E, Field JR, Wang S et al. Biobanks and Electronic Medical Records: Enabling Cost-Effective Research. *Sci Transl Med* 2014; 6: 234cm3–234cm3
- [49] Sudlow C, Gallacher J, Allen N et al. UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLOS Med.* 2015; 12: e1001779
- [50] Yin P, Peter A, Franken H et al. Preanalytical aspects and sample quality assessment in metabolomics studies of human blood. *Clin Chem* 2013; 59: 833–845
- [51] Herzberg-Schäfer S, Heni M, Stefan N et al. Impairment of GLP1-induced insulin secretion: Role of genetic background, insulin resistance and hyperglycaemia. *Diabetes Obes Metab* 2012; 14: 85–90
- [52] Ahlqvist E, Storm P, Käräjämäki A et al. Novel subgroups of adult-onset diabetes and their association with outcomes: A data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018; 6: 361–369