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CGM-based metrics and CGM-derived hypoglycemia duration with once-weekly insulin icodec versus once daily insulin glargine U100 in insulin-naive T2D: ONWARDS 1 post hoc analyses

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Diabetes type 2 in the Berlin Aging Study II: Cross-sectional and longitudinal data on prevalence, incidence and severity over on average seven years of follow-up

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Abstract

Aims: Aim of the current study was to describe the prevalence, incidence, and severity of diabetes mellitus type 2 (T2D) in a cohort of older men and women aged 60 years and above over the course of on average 7 years, since longitudinal data on this topic are scarce for this age group in Germany.

Methods: Baseline data of 1671 participants of the Berlin Aging Study II (BASE-II; 68.8 ± 3.7 years) and follow-up data assessed 7.4 ± 1.5 years later were analysed. The BASE-II is an exploratory, observational study on cross-sectional and longitudinal data of an older population. T2D was diagnosed based on self-report, antidiabetic medication use and laboratory parameters. T2D severity was determined by the diabetes complications severity index (DCSI). Prognostic capacity of laboratory parameters was evaluated.

Results: The proportion of participants with T2D increased from 12.9% (37.3% women) at baseline to 17.1% (41.1% women) with 74 incident cases and 22.2% not being aware of the disease at follow-up. The incidence rate is 10.7 new T2D diagnoses per 1000 person-years. More than half of the 41 newly identified incident T2D cases were diagnosed solely by the 2 h-plasma glucose test (OGTT) and diagnosis based on OGTT as the only criterion among incident cases was found more frequently in women ($p = 0.028$). T2D severity expressed by the DCSI significantly increased from baseline to follow-up (mean DCSI 1.1 ± 1.2 vs. 2.0 ± 1.8; range 0–5 vs. 0–6). Cardiovascular complications had the highest impact (43.2% at baseline and 67.6% at follow-up).

Conclusions: A comprehensive picture of T2D with respect to prevalence, incidence, and severity in older people of the Berlin Aging Study II is provided.

KEYWORDS

BASE-II, Berlin Aging Study II, DCSI score, diabetes mellitus type 2, GendAge

1 | INTRODUCTION

The number of people diagnosed with diabetes has risen over the past decades, now reaching a prevalence of an estimated average of 10.5% worldwide.[1] In Germany this number has increased from <2% in the 1950s[2,3] to 9.2% in 2010, including 2% undiagnosed cases (21.7% of the T2D patients) as reported from the German Health Interview and Examination Survey for Adults (DEGS1, 2008–2011).[4] As the risk of being diagnosed with diabetes increases with age, the globally estimated prevalence is almost 20% in the 65–79 year olds.[5] Studies suggest that only 49.9% of patients worldwide and 59.3% of patients in Europe affected from diabetes mellitus are aware of their condition.[5]

Besides genetic and demographic factors the following lifestyle factors are associated in a significant way with diabetes mellitus type 2 (T2D): high body mass index (BMI) [S1], low physical activity [S2], smoking [S3], alcohol consumption [S4] and an unhealthy diet [S5]. Being affected by diabetes results in a higher risk for comorbidities and a growing burden for the healthcare system, given that people diagnosed with T2D have healthcare expenditures 1.7× higher than people without this diagnosis [S6, S7]. Early diagnosis and treatment of T2D are essential, as studies show that adequate glycaemic control in people who are affected by T2D lowers the risk for developing complications and improves the outcome for patients who had already developed them[6-10] [S8].

To quantify the severity of diabetic complications and to better predict the risk of adverse outcomes, Young et al. developed the diabetes complications severity index (DCSI).[11] The DCSI incorporates seven categories of diabetic micro- and macrovascular complications: *retinopathy*, *neuropathy*, *nephropathy*, *cardiovascular disease*, *cerebrovascular disease*, *peripheral vascular disease*, and *metabolic complication*.

The DCSI as well as its adapted version (aDCSI), which does not consider laboratory parameters [S9], have been used as predictors of mortality, hospitalization, and healthcare use and cost in datasets of primary care and health insurances[11-13] [S10, S11]. It has also been used as a valid measure for the severity of diabetes and its comorbidities in cross-sectional studies[14] [S12-13]. The change of the DCSI and the aDCSI over time has been investigated several times using claims data [15-17] [S14–S16]. To our knowledge, longitudinal prospective data on the DCSI change have not yet been reported so far in a comparable German age group.

Aim of the current study was to describe the prevalence, incidence, and severity (DCSI) of T2D in a cohort of older men and women aged 60 years and above over the course of on average 7 years, since longitudinal data on this topic are scarce for this age group in Germany.

What's new?

- Provides a comprehensive picture of T2D in olderpeople of the Berlin Aging Study II.
- Clinically relevant differences in the informationalvalue of commonly used T2D diagnostic laboratory parameters between the men andwomen are described.
- Provides a snapshot of the currently usedantidiabetic medication in older people.

The analyses additionally included the investigation of the criteria resulting in the T2D diagnoses, antidiabetic medication, and also the capacity of three parameters of the glucose status, fasting glucose, HbA1c and 2-h-glucose (oral glucose tolerance test [OGTT]), to predict incident T2D in both sexes.

2 | METHODS

2.1 | Berlin Aging Study II baseline assessments and follow-up as part of the GendAge study

Participants of the Berlin Aging Study II (BASE-II) were recruited through an existing participant pool at the Max Planck Institute for Human Development and public advertisements from the Berlin metropolitan area. Baseline medical assessments took place between 2009 and 2014 and included 1671 participants aged 60 years and older (range: 60–84 years, older BASE-II group). Follow-up data on 1083 participants were assessed on average 7.4 ± 1.5 years later (range 3.91–10.37 years) as part of the GendAge study. For further details on BASE-II and GendAge see Bertram et al.[18] and Demuth et al.[19]

Loss of follow-up between the two assessments was $N = 588$ participants and is addressed in the limitation section (for details see Table S1).

In the current study we included a total of 209 participants with a T2D diagnosis at baseline. One hundred and eighty five participants had the diagnosis at follow-up. Of these 185, 111 had this diagnosis already at baseline or were newly diagnosed on this occasion (prevalent cases). Seventy-four were newly diagnosed after baseline assessment (incident cases), of which 41 were diagnosed for the first time at follow-up.

While determining T2D duration for incident cases in order to count person-years at risk for the incidence rate, there were 17 incident cases for which only the year of

being diagnosed with diabetes was known. In these cases, we set the 2nd July of the given year as date of the diagnosis. To calculate T2D duration in years we subtracted this date from the date of the follow-up assessment. For 16 participants who reported to be diagnosed between the first and second assessment, there was no date of diagnosis given. In these cases, we determined the time in years between the two assessments divided by two as T2D duration.

The T2D diagnosis of 15 participants at baseline could not be confirmed at follow-up. Six of them had reached the cut-off for at least one of the diagnostic laboratory values (see below) at baseline, which was then close to the cut-off but not reaching it at follow-up. The remaining nine participants were considered to have T2D at baseline based on the medical history provided, which was differently reported at follow-up.

2.2 | Diabetes mellitus type 2

Diabetes mellitus type 2 was diagnosed based on American Diabetes Association (ADA) guidelines[20] when applying at least one of the following criteria:

- Anamnestic history of T2D (self-report)
- Antidiabetic medication
- Fasting plasma glucose ≥126 mg/dL
- 2 h plasma glucose during 75 g-OGTT ≥200 mg/dL
- HbA1c ≥ 48 mmol/mol [6.5%]

Prediabetes was diagnosed applying fasting glucose (100–125 mg/dL) and/or HbA1c (39–46 mmol/mol) [5.7%–6.4%] and/or 2 h plasma glucose during 75 g-OGTT (140–199 mg/dL) according to ADA guidelines.[20]

2.3 | Diabetes complications severity index

The DCSI is a score developed by Young et al. to evaluate whether the complications of diabetes and the degree of its severity determine mortality and risk of hospitalization.[11] The score incorporates seven categories of complications deriving from diabetes, encoded according to the International Classification of Diseases, Ninth Revision (ICD-9-CM): *Retinopathy*, *nephropathy*, *neuropathy*, *cerebrovascular disease*, *cardiovascular disease*, *peripheral vascular disease*, and *metabolic complication*. A detailed description can be found in Supplementary Methods and Table S2. We included all 111 datasets of participants diagnosed with T2D at baseline and follow-up.

2.4 | Assessment of characteristics in the context of T2D

We evaluated physical activity using the rapid assessment of physical activity questionnaire.[21] Body weight was measured to the nearest 0.1 kg and height was determined to the nearest 0.1 cm by using an electronic weighing and measuring station (seca 764; seca). The BMI was calculated using the standard formula (weight in kilograms divided by height in metres squared). We used a modified version of the morbidity index originally described by Charlson,[22] for details see Meyer et al.[23]

2.5 | Statistical analysis

Statistical analysis was performed with SPSS version 26. Prevalence and incidence of T2D were determined, the latter in form of incident cases and incidence rate per person-years. Person-years, meaning the time under risk to develop T2D, were calculated from baseline to date of T2D diagnosis or to follow-up. If there was no date of diagnosis, follow-up time was divided by two ($N = 16$). If the date of diagnosis did only contain the year, the 2nd July was determined as accurate date ($N = 17$).

At baseline T2D data for 1625 participants and at follow-up T2D data for 1081 were available. Participants with none of the five criteria to diagnose T2D available were excluded (baseline $N = 46$, follow-up $N = 2$).

To test for differences between participants with T2D at baseline and follow-up, *t*-test or Wilcoxon rang test were performed. Normal distribution was tested visually using graphs showing the distribution and by Kolmogorov–Smirnov- and Shapiro–Wilk-test.

The 'UpSet' plots were produced with R 3.6.2 [S17] and the "UpSetR" package [S18]. To analyse the intersection between the individual diagnostic categories or medication, we formed separate datasets that contained only participants who met the regarding criteria. Subsequently, the intersections between the individual datasets were analysed and visualized as 'UpSet' plot. The bars on top of the columns represent the intersection size and the rows represent the individual datasets. All intersections are displayed and sorted by frequency.

Receiver operating characteristics (ROC) and areas under the curve (AUCs) and its confidence intervals were calculated with the "pROC" package [S19] in R. Logistic regression models were calculated by R's "glm" function.

3 | RESULTS

In the current study, we used data from two waves of medical assessments of the older subsample of BASE-II

participants, which represent up to 10.4 years of follow-up (mean follow up at 7.4 ± 1.5 years). Data were available for 1671 (mean age 68.8 ± 3.7 years, 51.6% women) and 1083 (mean age 75.6 ± 3.8 years, 52.0% women) participants of baseline and follow-up assessments, respectively. Detailed characteristics are shown in Table 1.

Two hundred and nine participants were diagnosed with T2D at baseline out of 1625 for whom T2D data were available (12.9%, 68.7 ± 3.7 years, 37.3% women), 52 of them were newly diagnosed (24.9%). One hundred and eighty-five participants (out of 1081 for whom sufficient data were available) had this diagnosis at the time of follow-up (17.1%, 75.6 ± 4.2 years, 41.1% women), including 111 prevalent and 74 incident cases (Figure 1). The incidence rate is 10.7 new T2D diagnoses per 1000 person-years with 6909.1 person-years at risk. Of the 185 T2D cases at follow-up, 41 participants (22.2%, women $N = 21$) were not aware of the disease, which resembles the proportion observed at baseline. At baseline, men had a T2D prevalence of 16.2% and women of 9.0% which increased at follow-up to 21.0% and 13.5%, respectively. Baseline and follow-up characteristics of participants with T2D are displayed in Table S5. Details of the analytical sample of 111 participants diagnosed with T2D at baseline *and* follow-up, the prevalent cases, are displayed in Table 2.

At baseline 38.9% of the participants had prediabetes. When focussing on the 74 incident T2D cases, for which 64 full laboratory datasets were available, 61 of 64 (95.3%) had prediabetes at baseline, and as expected they had significantly higher fasting blood glucose and HbA1c values at baseline when compared to the participants who had not developed T2D at the time of follow-up (both $p < 0.05$, Welch's *t*-test).

We next evaluated baseline HbA1c and fasting blood glucose in the 41 participants with incident T2D who were diagnosed at follow-up for the first time. This revealed that the mean baseline HbA1c was within the pre-diabetic range for both, men and women (39 mmol/mol ± 3; 40 mmol/mol ± 4) [5.8% ± 0.3, both in men and women], whereas this was the case for fasting glucose only in men (101.9 mg/dL ± 8.7) and not in women (97.7 mg/dL ± 9.3).

3.1 | Diabetes diagnostic criteria and antidiabetic medication at follow-up

We next focused on the diagnostic criteria and their combinations leading to the T2D diagnosis in the 185 participants with T2D at follow-up (Figure 2). A total of 143 participants were diagnosed based on at least one laboratory parameter, fasting glucose, 2 h-glucose (OGTT) or

TABLE 1 Characteristics of BASE-II baseline ($N = 1671$) and follow-up ($N = 1083$) samples (older group).

	Baseline		Follow-up	
Variables	**Mean ± SD or %**	**Number of observations**	**Mean ± SD or %**	**Number of observations**
Women	51.6	862	52.0	563
Age (years)	68.8 ± 3.7	1671	75.6 ± 3.8	1083
Diabetes mellitus type 2	12.9	209	17.1	185
Diabetes mellitus type 2; new diagnosis[a]	3.2	52	3.8	41
Prediabetes	38.9	623	44.4	478
Fasting glucose (mg/dL)	96.3 ± 20.2	1570	102.2 ± 22.3	1070
2 h-OGTT (mg/dL)	108.6 ± 36.0	1382	117.3 ± 36.0	822
HbA1c (mmol/mol) [%]	38 ± 6 [5.6 ± 0.6]	1568	39 ± 6 [5.7 ± 0.5]	1072
Anamnestic history of T2D (self-report)	9.3	150	12.1	131
Antidiabetic medication	6.9	111	9.2	100
Smoking (packyears)	10.4 ± 17.6	1611	9.9 ± 17.7	1003
Alcohol (four times a week or more)	27.6	459	20.6	223
RAPA score	5.1 ± 1.5	1588	4.8 ± 1.3	1080
BMI	26.8 ± 4.2	1638	26.9 ± 4.2	1081
Morbidity index[b]	0.9 ± 1.1	1495	1.2 ± 1.3	940

Note: 2 h-OGTT = oral glucose tolerance test (OGTT was only performed when T2D was not known).

Abbreviations: BMI, body mass index; RAPA, rapid assessment of physical activity; T2D, diabetes mellitus type 2.

[a]Diagnosed during the course of the study either at baseline or follow-up.

[b]Modified version of the morbidity index originally described by Charlson,[22] for details see Meyer et al.[23]

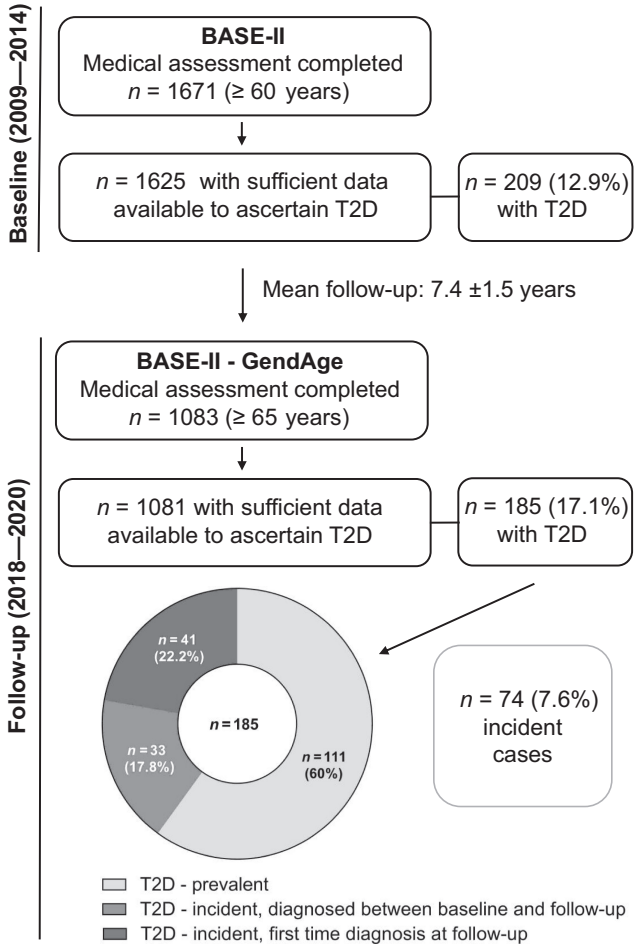

FIGURE 1 Diabetes mellitus type 2 at baseline (BASE-II) and follow-up (GendAge). The flow-chart shows the T2D prevalence among BASE-II participants at baseline and the number/proportion of prevalent and incident cases at follow-up 7.4 ± 1.5 years later. BASE-II, Berlin Aging Study II; T2D, diabetes mellitus type 2.

HbA1c, and 46 participants fulfilled the maximum of four diagnostic criteria (OGTT was only performed when T2D was not known): anamnestic information, antidiabetic medication, fasting glucose and HbA1c. In 42 participants the T2D diagnosis was based solely on anamnestic information on an existing T2D diagnosis and/or antidiabetic medication use without any of the laboratory parameters reaching the diagnostic cut-off. With 24 out of the 41 incident T2D cases at follow-up more than half of the newly diagnosed participants were diagnosed solely by the 2 h-OGTT. Interestingly, the T2D diagnosis based on impaired glucose tolerance (OGTT) as the only criterion among the incident cases was found more frequently in women ($N = 16$) than in men ($N = 8$), a difference which was statistically significant ($p = 0.028$, Fisher's exact test, Figures S1 and S2).

Logistic regression analyses revealed statistically significant ($p < 0.001$, Table S3) associations between baseline fasting glucose, HbA1c and 2 h-glucose (OGTT) and incident T2D after on average 7.4 years follow-up time ($n = 860$ provided information on all three parameters). This association remained significant in sex-stratified subgroup analyses (Table S4).

We next evaluated the capacity of these three laboratory parameters, as assessed at baseline to predict incident T2D at follow-up. The ROC curves from this analysis revealed that the AUCs for fasting glucose, HbA1c and 2 h-glucose were comparable with overlapping 95% confidence intervals (for details see Figure S3a). Stratification of this analysis by sex revealed that all three parameters of the glucose status tested are equally able to predict incident T2D with AUCs comparable to the values yielded from the not stratified analysis, with the exception of the 2 h-glucose (OGTT) in men which predicted incident T2D less accurate (Figure S3b,c).

Evaluating the antidiabetic medication of our sample in the follow-up dataset revealed that 100 out of the 185 participants diagnosed with T2D were treated with antidiabetic drugs. The majority ($N = 85$) used metformin, 47 of them as the only antidiabetic medication and 38 in combination with another oral antidiabetic drug or insulin; the most frequent combination being metformin and a dipeptidyl peptidase 4 inhibitor ($N = 15$). For details see Figure 3. There was no significant difference between women and men with respect to the antidiabetic medication, when considering each medication separately.

3.2 | DCSI at baseline and follow-up for prevalent cases

We computed the DCSI for both waves of assessments as a measure of T2D severity in prevalent cases and determined its change between the two assessments to evaluate T2D progression. The DCSI significantly increased in the 7.4 ± 1.5 years between baseline and follow-up (mean DCSI 1.1 ± 1.2 vs. 2.0 ± 1.8; range 0–5 vs. 0–6). The mean DCSI in women ($N = 40$) increased from 0.7 ± 0.8 to 1.8 ± 1.7 and in men ($N = 71$) from 1.3 ± 1.4 to 2.1 ± 1.8 (all $p < 0.01$, Wilcoxon signed rank test). Thus, while the DCSI was higher in men at both time points, the increase of T2D severity as assessed with the DCSI was higher in women, but not statistically significant. The DCSI change per year was 0.12 in men and 0.14 in women. Results are displayed in Figure 4.

In a next step we compared the different DCSI constituting categories (Table S6) with respect to their impact among the participants with prevalent T2D at both time points of assessment. This revealed that *cardiovascular* complications were the complications with the highest impact of 43.2% at baseline, and a steep increase to 67.6%

TABLE 2 Characteristics of the prevalent T2D cases in BASE-II ($N = 111$).

Variables	Baseline		Follow-up		
	Mean ± SD or %	Number of observations	Mean ± SD or %	Number of observations	*p*-value
Women	36.0	40	36.0	40	N/A
Age (years)	68.1 ± 3.7	111	75.4 ± 4.1	111	<0.001
T2D new diagnosis (unaware of disease)	20.7	23	N/A	N/A	N/A
DCSI	1.1 ± 1.2	111	2.0 ± 1.8	111	<0.001
Fasting glucose (mg/dL)	127.1 ± 31.2	106	143.6 ± 34.5	111	<0.001
2 h-OGTT (mg/dL)	218.8 ± 60.1	21	N/A	N/A	N/A
HbA1c (mmol/mol) [%]	48 ± 8 [6.6 ± 0.7]	105	50 ± 9 [6.7 ± 0.8]	111	<0.001
Medical history of T2D (self-report)	77.1	84	91.0	101	<0.002
Antidiabetic medication	56.4	62	76.6	85	<0.001
Smoking (packyears)	14.7 ± 18.4	103	15.3 ± 21.4	100	0.574
Alcohol (four times a week or more)	31.6	31	23.4	26	<0.001
RAPA score	4.8 ± 1.5	109	4.5 ± 1.2	111	0.056
BMI	29.6 ± 4.4	110	29.3 ± 4.2	111	0.099
Morbidity index[a]	1.0 ± 1.2	104	1.9 ± 1.7	85	<0.001

Note: 2 h-OGTT = oral glucose tolerance test (OGTT was only performed when T2D was not known).

Abbreviations: BMI, body mass index; DCSI, diabetes complications severity index; RAPA, rapid assessment of physical activity; T2D, diabetes mellitus type 2.

[a]Modified version of the morbidity index originally described by Charlson,[22] for details see Meyer et al.[23]; statistical analysis was performed by *t*-test or Wilcoxon signed test, as appropriate.

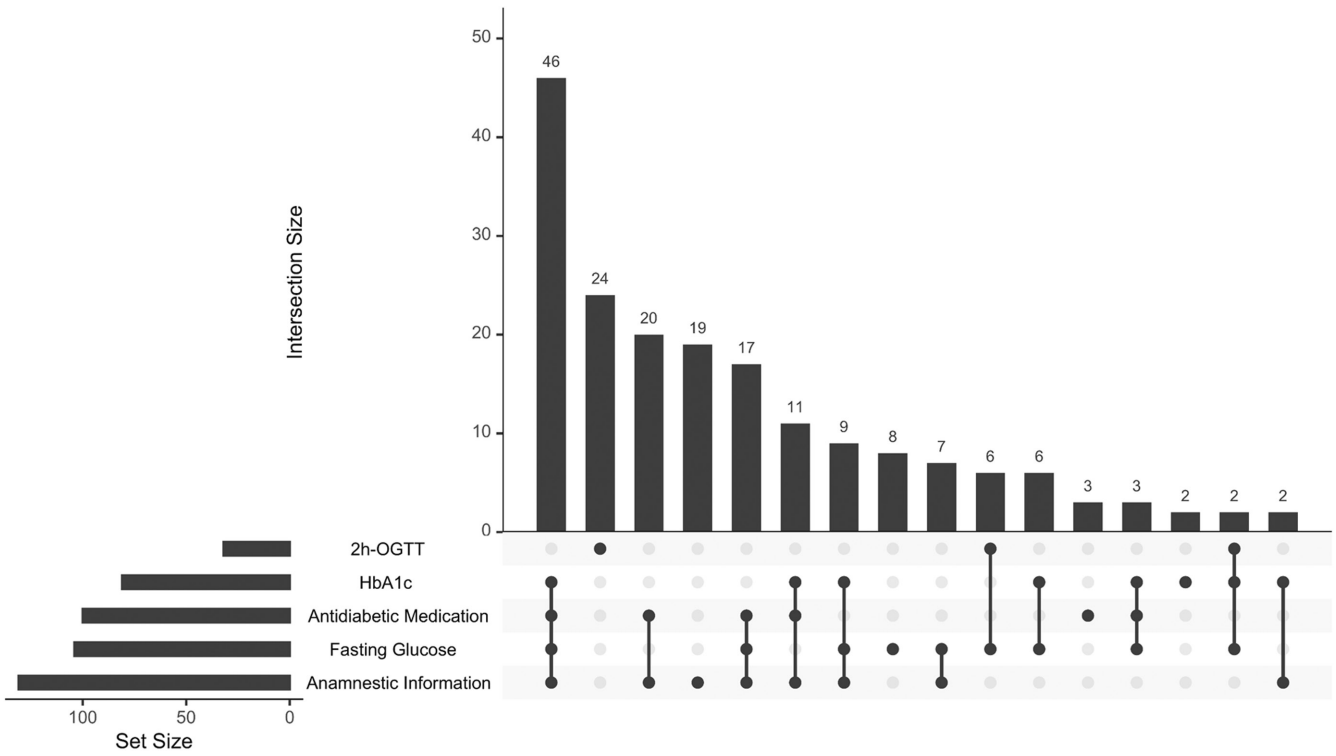

FIGURE 2 Type 2 diabetes diagnosis at follow-up ($N = 185$). Diabetes diagnosis criteria at follow-up and their combinations are indicated with the number of cases above the bars (OGTT was only performed when T2D was not known). OGTT, oral glucose tolerance test; T2D, diabetes mellitus type 2.

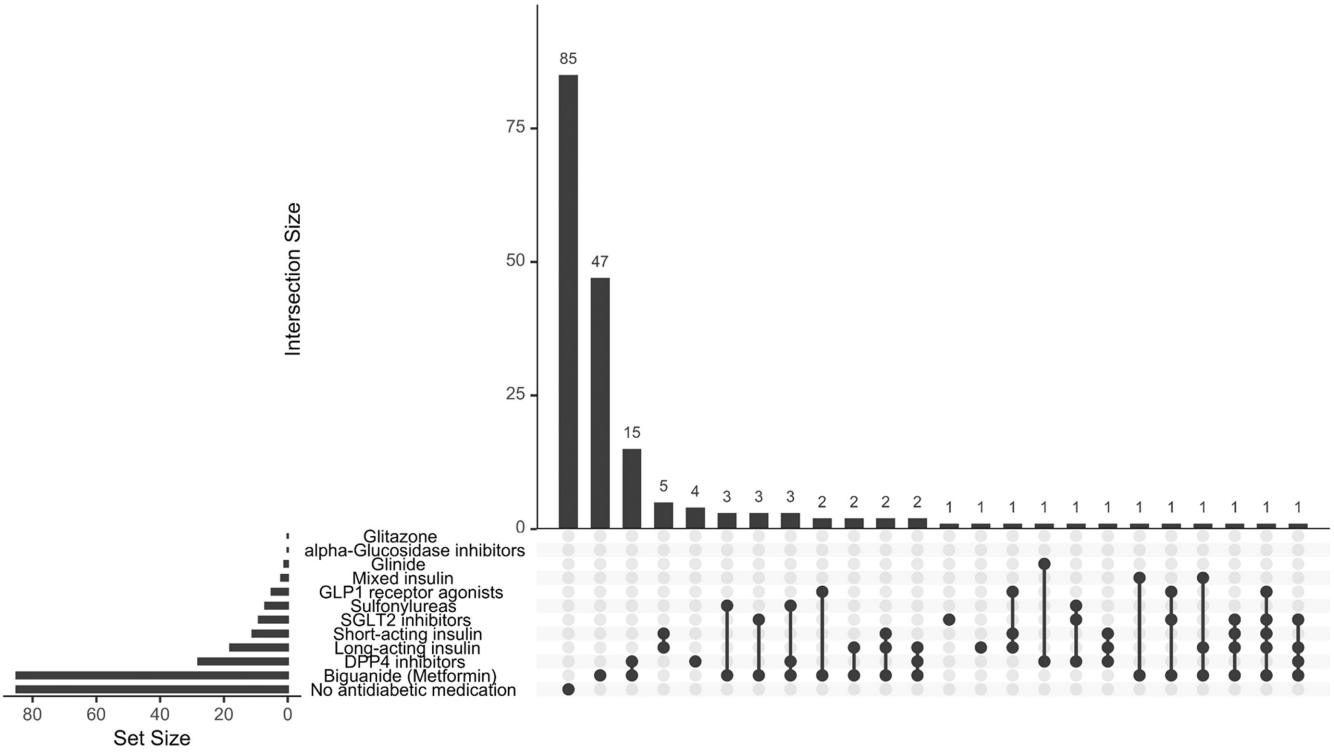

FIGURE 3 Antidiabetic medication at follow-up ($N = 185$). Antidiabetic medication at follow-up and its combinations are indicated with the number of cases above the bars. 41 of 85 participants without medication were newly diagnosed incident cases. DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose cotransporter 2.

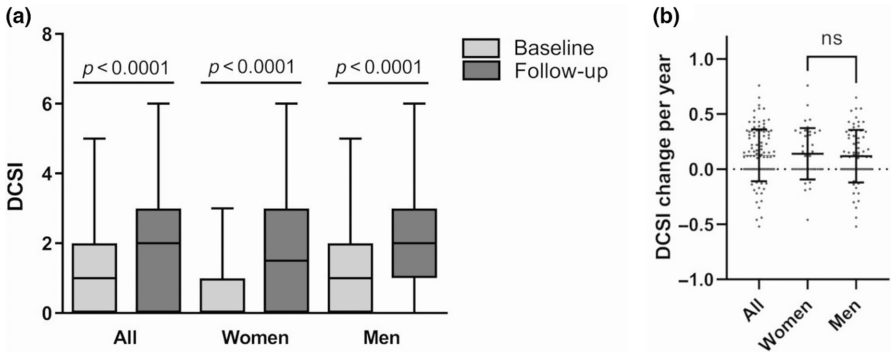

FIGURE 4 Severity of diabetes complications at baseline and follow-up as determined by the diabetes complications severity index (DCSI). (a) The mean DCSI at baseline and follow-up is shown for all prevalent T2D cases ($N = 111$) and separately for women ($N = 40$) and men ($N = 71$). Significant increase between baseline and follow-up for each group is indicated (Wilcoxon test). (b) The DCSI change per year over the 7.4 ± 1.5 years of follow-up is shown for the prevalent T2D cases. Mean and standard deviation is indicated. All: $N = 111$; females: $N = 40$; males: $N = 71$. No significant difference (ns) between mean DCSI of female and male participants were detected (*t*-test). T2D, diabetes mellitus type 2.

at follow-up. This was followed by the DCSI categories *nephropathy* (21.6% and 61.3%) and *peripheral vascular disease* (27.9% and 28.8%). When looking at sex differences, at baseline men were significantly more likely affected from cardiovascular diseases than women, but at follow-up this difference was not significant anymore ($p < 0.05$ and $p = 0.214$, Mann–Whitney-*U* test). At follow-up *nephropathy* had the highest impact (60.0%) in women, followed by *cardiovascular diseases* (52.5%), whereas for men it was the other way around (76.1% and 62.0% respectively). When comparing the progression of each category, there was no significant difference between the sexes ($p > 0.05$, Welch's test).

4 | DISCUSSION

In the current study, we assessed the course of T2D over on average 7 years in terms of prevalence, incidence, and disease severity as reflected by the DCSI, as well as diagnostic

criteria and antidiabetic medication. Epidemiological data on the prevalence and incidence of diagnosed, undiagnosed, and new-onset diabetes were lower, but basically in keeping with comparable nationwide data from the DEGS1 study.[4] The prevalence of T2D was lower in the current study (12.9% at baseline and 17.1% at follow-up) when compared to the nationwide reported 23.9% among 65–79 year olds. On average 23.6% (24.9% at baseline, 22.2% at follow-up) were undiagnosed cases compared to 17.6% when looking at 65–79 year-olds in Germany.[4] However, undiagnosed cases were only determined by HbA1c measurements in DEGS1, whereas we additionally considered fasting glucose and the OGTT. The incidence rate for diagnosed and undiagnosed diabetes in the current study was lower compared to nationwide data with 10.7 per 1000 person-years compared to 12.8.[24] On the one hand, these differences might be due to the fact that the nationwide data incorporate all types of diabetes and not only diabetes type 2, even though diabetes type 2 makes up over 90% of all diabetes diagnoses [S20]. On the other hand, the lower T2D prevalence in the current study might be explained by the observation of Berlin Aging Study II participants being overall healthier at baseline when compared to nationwide data as described earlier.[18]

Focussing on sex differences of diabetes prevalence in Germany, more men than women are affected by diabetes when considering the 18–79 year-olds (9.9% vs. 8.6%)[4] and also concerning 60–69 year-olds (14.5% vs. 10.0%) and 70–79 year-olds (21.9% vs. 16.9%); women "catch up" with and even overtake men when older than 90 years [S21]. The numbers reported here are comparable, with more men than women diagnosed with T2D (at baseline 16.2% vs. 9.0%; at follow-up 21.0% vs. 13.5%). As our cohort consists of participants that were on average younger than 80 years old, we could not determine conclusively whether women would overtake in terms of T2D prevalence in older age.

When investigating T2D severity, the mean DCSI value increased from 1.1 to 2.0 between the two assessments. Men had a higher baseline and follow-up DCSI, whereas women had a stronger DCSI increase within the observation period, even though the latter difference did not reach statistical significance.

Women generally get diagnosed with diabetes later than men and at a higher BMI.[25] Many studies have shown that natural menopause is not associated with a higher risk of T2D and that a higher post-menopausal diabetes incidence, if depicted, is rather due to chronological aging and physical inactivity than to the menopause per se [S21–S24]. However, this research remains controversial, since there are studies that showed higher risk of metabolic syndrome in post-menopausal women independent of age [S25, S26] and there is evidence that an early menopause increases the risk of T2D [S27–S29]. Multiple studies suggest that women affected by diabetes are at higher relative risk for CHD than men with this diagnosis, pre- and post-menopausal [S30–S32]. In our study, when looking at the absolute risk of the different DCSI categories on the subpopulation affected with T2D, *cardiovascular diseases* had the highest impact on DCSI progression. At baseline, men with T2D were significantly more likely affected from *cardiovascular diseases* than women, but at follow-up this was no longer the case.

The ROSSO study observed 3142 people with new-onset diabetes over a mean follow-up time of 6.5 years in Germany, focussing on diabetes mellitus complications and its treatment costs. Mean age of the participants recruited from primary care practices was 62.5 ± 9.6 years.[26] The complication rate increased linearly with time, coronary heart disease being the most common risk factor and complication, and neuropathy having the steepest increase after diagnosis. Men had more acute myocardial infarction events than women, whereas in numbers of strokes and mortality there was no difference. A longitudinal study by Weng et al. investigated 16,950 people with newly diagnosed diabetes from a US administrative claims database between 2006 and 2014, focusing on treatment and comorbidities of diabetes.[15] They found that men had higher DCSI scores and the DCSI progression was in general faster at higher age. In the age group above 65 years, cerebrovascular diseases were most prominent, followed by cardiovascular diseases. The data reported by Hazel-Fernandez et al. support our finding of more diabetic complications in men than in women.[13] In contradiction McCollum et al. found that women diagnosed with diabetes had significantly more comorbidities than men with this diagnosis (7.8 vs. 6.4 on average), but they did not distinguish between diabetes complications and comorbidities in general [S33].

The investigation of the diagnostic criteria resulting in the T2D diagnoses at follow-up ($N = 185$) showed that most of them are supported by four of the five criteria considered: anamnestic information, antidiabetic medication, fasting glucose and HbA1c (the 2 h-OGTT was performed only when T2D was not known). Focussing on the newly diagnosed participants, 58.5% were diagnosed by 2 h-OGTT only, of which 66.7% were women. These results are in line with earlier reports showing that women are more frequently affected from impaired glucose tolerance, whereas men more frequently show fasting glucose glycaemia (reviewed in[27]). With respect to the newly diagnosed participants at follow-up, only men's fasting blood glucose values (mean) at baseline were in the range indicating prediabetes, whereas the women's mean fasting glucose values were below the prediabetes cut-off. The HbA1c mean values, however, met the pre-diabetic range in both, women and men.

This underscores the particular importance of diagnostic laboratory test(s) applied with respect to the chance of an existing T2D being diagnosed and its difference between women and men. Thus, our data support the recommendations of the Deutsche Diabetes Gesellschaft (German Diabetes Society) of applying fasting blood glucose *and* HbA1c in combination when screening for T2D.[28] When choosing to apply only one test, our findings suggest a sex-specific approach: for men, both tests can be equally applied, whereas for women, one would recommend to measure HbA1c. A 2 h-glucose tolerance test (OGTT) should follow in case either of the two values, fasting glucose or HbA1c, were within the pre-diabetic range.[28]

A recent study on antidiabetic medication showed a lower risk of cardiovascular complications when combining metformin with a GLP-1 receptor agonist or a SGLT2 inhibitor, with GLP-1 receptor agonists having a greater effect in women than in men.[29] In our cohort these two antidiabetic drugs were only taken by a small proportion of the participants. With cardiovascular events being the most prevalent T2D complication, people diagnosed with T2D might benefit from these newer oral antidiabetic drug classes.[30]

The current study is subject to several limitations and strengths. As described above, participants of the BASE-II were healthier at baseline when compared to nationwide data.[18] Therefore, we are not able to generalise our results to the population level, which is reflected by our findings, e.g. when comparing T2D prevalence and incidence rates to nationwide data.

Furthermore, we cannot rule out an additional selection bias due to the loss of about one third of the participants during the follow-up period. However, a comparison of baseline data of participants with and without follow-up data revealed that even though older and less educated, there were no differences between these two groups with respect to gender or overall morbidity (for further details see Table S1 and Supplementary Methods), suggesting the potential bias to be rather low. Another limitation is that we have not assessed latent autoimmune diabetes in adults (LADA) among the participants diagnosed as having T2D. However, the prevalence of this type of diabetes is estimated to be comparatively small and ranges between 2% and 14% (overview in Hernández and Mauricio, 2021 [S34]). Finally, the analysed dataset is comparatively small, especially with respect to newly diagnosed cases at follow-up, which again might be the result of the above average health of our participants.

A strength of this study is the use of comprehensive laboratory diagnostics, including fasting glucose, HbA1c and the 2 h-glucose test (OGTT) which stands in contrast to many other health studies where only one or two parameters are available to identify unknown diabetes.[4,31] This not only allowed us to diagnose unknown diabetes according to established guidelines, but also to shed light on sex differences in the diagnostic value of these laboratory parameters. Finally, the extensive data collection of the current study enabled us to provide a comprehensive overview on various aspects of diabetes in older people, including prevalence, incidence, medication and diabetic complications.

5 | CONCLUSIONS

The data on the studied cohort available allowed us to describe a comprehensive picture of T2D with respect to its prevalence, incidence, and severity in older people in Germany. In addition, the combined use of cross-sectional and longitudinal data allowed us to detect clinically relevant differences in the informational value of the commonly used T2D diagnostic laboratory parameters between men and women. The study additionally provided a snapshot of the current antidiabetic medication use in older people, an area that can be expected to undergo greater changes in the future due to available newer classes of medication such as GLP-1 receptor agonists and SGLT2 inhibitors.

AUTHOR CONTRIBUTIONS

Nikolaus Buchmann, Ilja Demuth and Johanne Spieker conceived the study, discussed and interpreted data. Johanne Spieker analysed the data and wrote the first manuscript draft. Ilja Demuth, Johanne Spieker and Valentin Max Vetter have prepared the illustrations. Elisabeth Steinhagen-Thiessen, Ilja Demuth, Johanna Drewelies and Vera Regitz-Zagrosek provided data. Nikolaus Buchmann and Ilja Demuth supervised the study. All authors participated in drafting the paper or revising it critically, and provided final approval. Ilja Demuth 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 analyses.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Due to concerns for participant privacy, data are available only upon request. External scientists may apply to the Steering Committees of BASE-II and GendAge for data access. Please refer to the BASE-II website (https://www.base2.mpg.de/en/project-information/datadocumentation) for additional information. Please contact Ludmila Müller, scientific coordinator, at lmueller@mpib-berlin.mpg.de.

ETHICS APPROVAL

The medical assessments at baseline and follow-up were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (approval numbers EA2/029/09 and EA2/144/16) and were registered in the German Clinical Trials Registry as DRKS00009277 and DRKS00016157.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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