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Mortality patterns in Dutch diabetes outpatients

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Abstract

Aim: Diabetes mellitus is a major cause of death. Outpatients with diabetes have more complications than patients in general practice; mortality patterns have only been studied in the total diabetes population. This study aims to assess mortality, causes, and predictors in outpatients with diabetes.

Materials and Methods: A cohort study, included people with diabetes mellitus from the nationwide Dutch Paediatric and Adult Registry of Diabetes (DPARD) visiting diabetes outpatient clinics in 2016-2020. DPARD data were linked to Statistics Netherlands (CBS), comprising data on mortality, ethnicity and education. All-cause and cardiovascular mortality rates were estimated using Cox proportional hazard regression.

Results: During a median follow-up of 3.1 years among 12 992 people with diabetes, mortality rates per 10 000 person-years were 67.7 in adult type 1 diabetes and 324.2 in type 2 diabetes. The major cause of non-cardiovascular death was malignancy. During the pandemic years of influenza (2018) and COVID (2020), mortality rates peaked. Age, smoking and an estimated glomerular filtration rate of <60 ml/min were associated with all-cause mortality. In type 2 diabetes, additional factors were male sex, body mass index <20 kg/m^2, diabetes duration <1 year and hypertension.

Conclusions: Mortality among Dutch outpatients with diabetes is high. Smoking and renal failure were associated with mortality in both types. Further focus on early detection and treatment of mortality-associated factors may improve clinical outcomes.

KEYWORDS
database research, diabetes complications, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus is one of the most common long-term diseases, affecting 463 million adults worldwide; this number is expected to rise to a staggering 700 million by 2045 because of the ageing of the population and lifestyle leading to an increase in obesity.[1] The presence of diabetes mellitus dramatically increases the risk of microvascular and macrovascular complications and comorbidities and lowers life expectancy up to 17.7 life years in type 1 diabetes.[2,3]

Although underreported on death certificates, diabetes is ranked in the top 10 causes of death globally, accounting for 4.2 million deaths annually.[4,5] Cardiovascular diseases (CVDs) are the leading

cause of death among people with diabetes.[6] Adults with diabetes were shown to have a three- to fourfold higher all-cause and CV mortality compared with the general population.[7] Glucose-lowering treatment significantly reduced the risk of complications and premature mortality, yet excess diabetes-related mortality still exists.[8] Moreover, premature mortality in people with diabetes mellitus increased by 5% between 2000 and 2016 worldwide, while mortality from other causes of death declined.[4] In Europe, recent studies using registry data showed decreased yet persistent diabetes-related excess mortality.[8–10] A significant proportion of premature deaths from early diabetic complications such as ketoacidosis and hypoglycaemia were because of preventable causes.[11] A considerable part of acute and chronic diabetic complications, such as CVD or cancer, may be preventable or treatable.[12] Gaining insight into mortality in persons with diabetes mellitus can help us prevent premature deaths.[13] People with diabetes treated in outpatient clinics have more complications and comorbidities than their counterparts treated in primary care, which could contribute to excess premature death in outpatients with diabetes.[14] However, evidence is limited about mortality in persons with diabetes treated in outpatient diabetes care, and studies typically focus on people with type 2 diabetes.[15,16]

In 2017, the nationwide Dutch Paediatric and Adult Registry of Diabetes (DPARD) was launched.[17] DPARD includes people of all ages treated for diabetes mellitus in outpatient clinics in secondary and tertiary care across the Netherlands. Using DPARD, we aim to assess overall and cause-specific mortality rates in persons with diabetes treated in outpatient clinics compared with the general population. In addition, baseline characteristics of deceased persons with diabetes were collected.

2 | MATERIALS AND METHODS

2.1 | Participants

For this nationwide observational cohort study, data was retrieved from DPARD, a national quality registry of adults and children treated for diabetes mellitus in secondary and tertiary outpatient clinics across the Netherlands.[18] We included all persons who visited a Dutch outpatient clinic at least once between 1 January 2016 and 1 January 2021. Participants were included from the first outpatient visit within the inclusion period (irrespective of whether they had follow-up before 2016). Women with gestational diabetes and persons who received diabetes treatment in general practice are excluded. Data were collected from the electronic health records of participating hospitals and entered into a data series called batches. Batches were uploaded to our data processing company, Medical Research Data Management (MRDM),[19] which complies with all Dutch and European privacy laws.[20,21] Under Dutch and European Privacy Protection laws, no ethical approval or informed consent was required because DPARD is designed to assess and improve the quality of care; in addition, data were encrypted to prevent data from being traced back to individual participants.[22]

2.2 | Data collection

From DPARD, the date of birth, postal code, sex, diabetes type, diabetes duration, date of first outpatient visit (date of inclusion), date of last (most recent) outpatient visit, smoking status, body mass index (BMI), blood pressure, lipids, kidney function, glycated haemoglobin (HbA1c) and medication use were derived. The date of birth and postal code were blinded to the investigators. Diabetes mellitus was diagnosed according to American Diabetes Association (ADA) and International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines.[23,24] The diabetes type was derived from the clinical classification entered in to the electronic health records by medical professionals. BMI was calculated as weight in kilograms divided by height squared in metres (kg/m^2), using a cut-off value of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity in adults. HbA1c was expressed as mmol/mol and percentages. From Statistics Netherlands (CBS), data on ethnicity, socioeconomic status, vital status and cause of death were derived. CBS is an autonomous agency mandated to collect and process data, facilitating various databases covering the Netherlands' total population.[22] All records from DPARD were individually linked to the CBS' population-, death- and education records (n = 20 892 on the date of linkage, 5 November 2021). Successful linkage was established in 12 992 people (62.1%) using a unique personal identification number or a combination of date of birth, sex and zip code. Twelve participants (0.1%) were excluded as they were included in the dataset twice. In 7888 people (37.8%), linkage was not possible because of missing personal identification numbers or zip codes, as some hospitals chose not to provide these data. Characteristics of persons linked and not linked are shown in Table S1 of the Supporting Information. After successful linkage, a unique anonymous identifier was assigned to every registered person to allow for follow-up over time. From death records, the date and primary or secondary cause of death were obtained as stated on death certificates by the treating physician according to the 10th revision of the International Classification of Diseases (ICD-10).[23] The cause of death was defined as the illness, situation, or occurrence triggering a series of events, ultimately leading to death, and was categorized within the ICD-10 codes provided in Table S2A,B. In 98.4% of the CBS death records, a death certificate containing the cause of death could be linked.[24] Non-linkage could be partially explained by Dutch citizens who died outside the Netherlands, in which case death certificates are rarely provided. Linkage also provided migration background as an approximation of ethnic origin, defined as the country of origin based on the parents' or own country of birth. The migration background is distinguished between native Dutch, non-native Western [originating from a European country (excluding Turkey), North America, Oceania, Indonesia or Japan], and non-native non-Western [Africa, South America, Asia (excluding Indonesia and Japan), or Turkey]. Socioeconomic status was based on the highest educational level in the education records. Three education levels are distinguished according to the International Standard Classification of Education:[25] lower (elementary school or the first 3 years of secondary education); medium (upper secondary education and middle management and specialist education); and high (higher

education, associate degree, bachelor, master and doctoral degree programs). In children, their educational level was assumed to be equal to that of their parents. According to CBS guidelines, observations of less than five participants (including zero) were shown as not applicable to prevent data from being traced back to individual persons. Therefore, this study could not describe the characteristics of deceased children with diabetes because there were less than five fatalities.

2.3 | Outcomes

The primary outcome was mortality among people with diabetes treated in outpatient clinics, which was divided into all-cause mortality, mortality from CVD, and non-CV mortality. CV mortality included death from ischaemic heart disease, cerebrovascular diseases and other diseases of the circulatory system, such as hypertensive diseases and peripheral arterial disease (ICD-10 codes I00-I99). Non-CV deaths included all other causes within the following subcategories: malignant neoplasms, diabetes mellitus, respiratory/COVID-19, mental disorders and other causes, the ICD codes of which may be found in the supplementary addenda. Liver and kidney diseases as underlying causes of death were classified under other causes of death to conform to CBS guidelines, not disclosing less than five observations. Secondary outcomes are patient characteristics associated with mortality in outpatients with type 1 and type 2 diabetes, respectively.

2.4 | Statistical analysis

Descriptive statistics were used to assess patient characteristics. Because of the non-normal distribution of our continuous data, medians and ranges or interquartile ranges, were used for descriptive statistics. CBS guidelines required percentages approaching zero to be stated as not applicable because of their potential traceability to individuals. Because of the structure of the database, in the case of multiple measurements, the most recent one was used for analysis. Survival time was defined as the time from the date of inclusion (first outpatient visit during the study period) to the date of death or censoring at 1 January 2021, whichever came first, yielding a maximum follow-up of 5 years. Mortality rates are shown from 2017 onward to allow for a sufficient number of people with sufficient follow-up duration. The mortality rate was calculated by dividing the number of all-cause deaths during the study period by patient-years (the number of persons with diabetes at risk multiplied by their follow-up duration). Death rates in the general population were assessed by dividing the number of all-cause deaths of Dutch inhabitants during the study period by patient-years. Mortality rates were expressed as the number of deaths per 10 000 person-years (PY) using the SIR function in R (RStudio, version 1.4.1106). Mortality rates were stratified by age, using cut-off values of 18-35, 35-65 and ≥65 years. To study the effect of patient characteristics and clinical parameters measured at the outpatient visit on mortality, we performed a Cox proportional hazard regression with adjustment for age and, in a separate model, adjustment for age, gender, migration background, education level, diabetes duration, smoking status, BMI, systolic blood pressure, low-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR) and HbA1c. Results were summarized using hazard ratios with 95% confidence intervals (95% CI). The hazard ratio of CV mortality was assessed using a competing risk analysis following the cause-specific hazard approach, where non-CV mortality was considered a competing event. Rates of missing data were shown by variable in the tables or the results. Variables with missing values were used in the model as categorical variables, with missing values as a separate category. Continuous variables with missing values were converted into categorized variables. Mortality outcomes are reported only for adults because of the low death rates among children with diabetes ($n = 2$). Analyses are stratified by diabetes type 1 and type 2. Mortality data from 2017 up to 2019 and 2020 were compared by making mortality rates and causes of death insightful to discern the effect of the COVID pandemic on mortality. All statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, version 26.0) and R (RStudio, version 1.4.1106). A two-sided $p < .05$ was considered statistically significant.

3 | RESULTS

In total, 12 992 people with diabetes were included from the DPARD registry, comprising 11 641 adults (89.6%) and 1351 children (10.4%). Among persons of all ages, we identified 5241 individuals (40.3%) with type 1 diabetes, 6017 with type 2 (46.3%), 194 participants (1.5%) with secondary or other types of diabetes mellitus and 1520 persons (11.8%) with an unknown diabetes type. Patients were treated at seven medical centres (six secondary care hospitals and one independent diabetes treatment centre), covering 9% of all Dutch hospitals providing outpatient diabetes care.

Table 1 shows the characteristics of 4101 adult type 1 and 6012 people with type 2 diabetes by vital status, with a diabetes duration of 18.0 years [interquartile range (IQR) 10.0-29.0 years] and 16.0 years (IQR 9.0-22.0 years), respectively. The median follow-up duration of all adults was 3.1 years (IQR 2.1-3.7 years) and 3.1 years (IQR 1.7-3.7 years) in type 1 diabetes versus 3.3 years (IQR 2.1-3.9 years) in type 2 diabetes. From 2016 to 2021, a total of 717 adults with diabetes died (5.5%) during 32 822 PY of follow-up, rendering a mortality rate of 218.5 deaths per 10 000 PY. The median age at death was 73.0 years (range 18.0-95.0), and 64.7% were men. In total, 75 deaths (1.9%; 95% CI 1.4-2.2%) were observed in individuals with type 1 diabetes and 563 (9.4%; 95% CI 8.6-10.1%) in type 2. Mortality rates in type 2 diabetes were almost five times higher than in type 1 diabetes, with 67.7 per 10 000 PY in type 1 diabetes versus 324.2 per 10 000 PY in type 2. The median age of death in type 1 was 70.0 years (IQR 59.0-80.0) and 74.0 years in type 2 diabetes (IQR 67.0-80.0). Compared with persons with diabetes who stayed alive, individuals who died had a similar or lower BMI (23.8 vs. 25.4 kg/m^2 in type 1 diabetes, $p = .08$; 28.7 vs. 29.6 kg/m^2 in type

TABLE 1 Characteristics of adult outpatients with DM type 1 and DM type 2 included in the Dutch Paediatric and Adult Registry of Diabetes by vital status.

		DM type 1		DM type 2	
	Total	Alive	Deceased	Alive	Deceased
Characteristics	(n = 11 641)	(n = 4026)	(n = 75)	(n = 5449)	(n = 563)
Age, years	56.0 (38.0-68.0)	39.0 (25.0-54.0)	70.0 (59.0-80.0)	63.0 (54.0-71.0)	74.0 (67.0-80.0)
Male sex	52	54	65	53	64
Migration background					
Native Dutch	63	80	81	54	62
Non-native Western	4	4	8	4	4
Non-native non-Western	33	16	11	42	34
Education level					
Lower	21	16	NA	25	19
Medium	22	32	19	14	6
High	15	26	NA	8	3.
Unknown	42	26	65	53	72
Diabetes duration, years	15.0 (7.0-23.0)	17.0 (10.0-29.0)	33.0 (25.0-46.0)	15.0 (9.0-22.0)	18.0 (11.0-26.0)
Unknown	3	2	8	4	8
Smoking status					
Smoker	11	11	19	13	11
Non-smoker	57	54	67	66	54
Unknown	32	35	14	21	35
BMI, kg/m^2	27.7 (24.5-31.2)	25.4 (22.8-28.1)	23.8 (21.7-26.7)	29.6 (26.5-32.9)	28.7 (25.6-31.6)
<20	2	4	NA	1	2
20-24	17	25	32	11	10
25-29	26	25	24	28	22
≥30	22	9	NA	34	22
Unknown	33	37	35	26	44
Blood pressure					
Systolic, mmHg	134.0 (120.0-146.0)	130.0 (119.0-140.0)	138.0 (129.0-149.0)	136.0 (123.0-149.0)	135.5 (121.0-150.0)
Diastolic, mmHg	77.0 (70.0-83.0)	75.0 (69.0-83.0)	74.0 (69.0-80.0)	78.0 (70.0-84.0)	72.0 (65.0-80.0)
Unknown	35	50	19	19	26
Cholesterol					
HDL cholesterol, mmol/L	1.2 (1.0-1.5)	1.5 (1.2-1.8)	1.3 (1.0-1.8)	1.1 (0.9-1.3)	1.0 (0.8-1.2)
LDL cholesterol, mmol/L	2.4 (1.9-3.0)	2.6 (2.1-3.2)	2.3 (1.6-2.9)	2.3 (1.7-2.9)	2.2 (1.5-2.8)
Unknown	34	36	33	23	40
Kidney function					
eGFR, ml/min	77.0 (58.0-92.0)	89.0 (76.0-100.0)	65.0 (48.0-75.0)	71.0 (52.0-87.0)	46.0 (30.0-70.3)
Unknown	56	62	64	46	44
Albuminuria, mg/L	11.0 (4.0-46.0)	6.0 (3.0-15.0)	17.0 (5.8-51.0)	16.0 (5.0-67.0)	61.0 (16.3-294.0)
Unknown	58	59	67	49	62
HbA1c, mmol/mol	61.0 (53.0-72.0)	61.0 (53.0-69.4)	63.5 (54.8-75.3)	63.0 (54.0-74.0)	63.0 (53.0-74.0)
HbA1c	7.7 (7.0-8.7)	7.7 (7.0-8.5)	8.0 (7.2-9.0)	7.9 (7.1-8.9)	7.9 (7.0-8.9)
Unknown	9	4	NA	8	11
Diabetes treatment					
Insulin only	23	36	75	12	29
Oral agents only	8	NA	NA	14	9
Oral agents and insulin	23	NA	NA	39	41
Unknown	46	62	24	35	21

Note: Absolute numbers are presented as median (interquartile range) or percentages. Percentages reflecting absolute numbers of five people with diabetes or less (including zero) are stated as NA.

Abbreviations: BMI, body mass index; DM, diabetes; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.

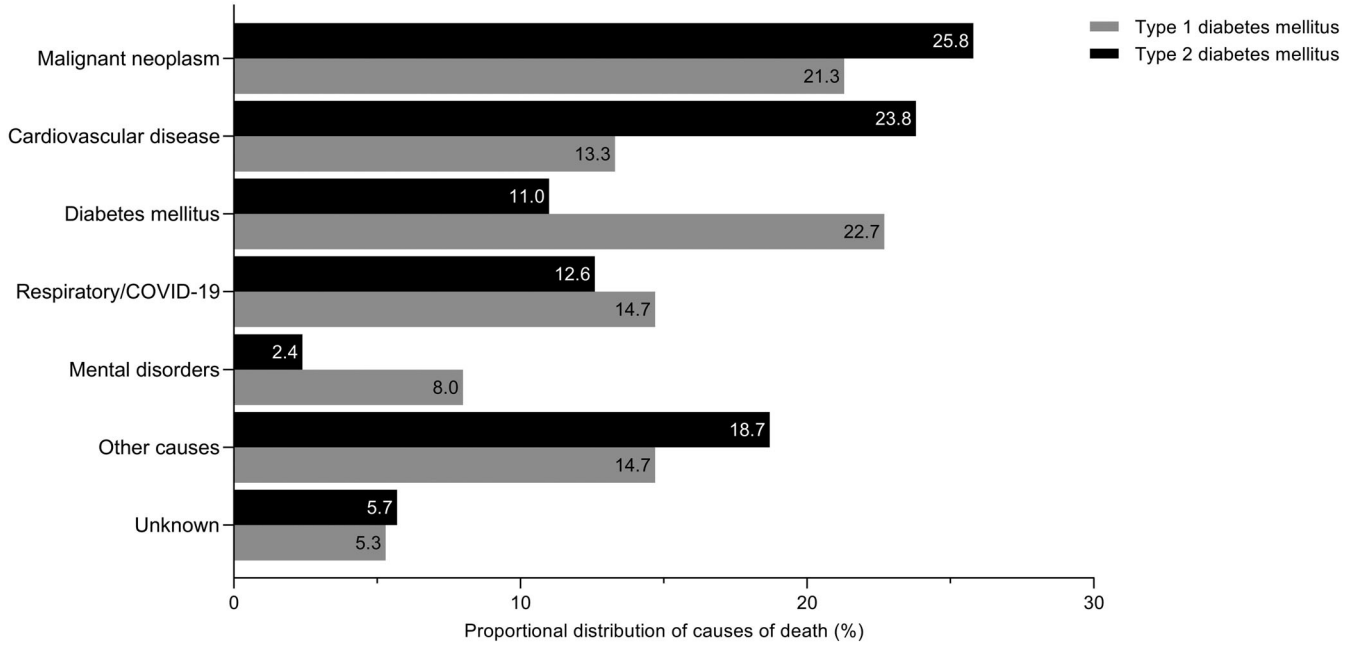

FIGURE 1 Proportional distribution of causes of death from 2016 to 2020 in adult individuals with type 1 and type 2 diabetes included in the Dutch Paediatric and Adult Registry of Diabetes.

2 diabetes, $p = .001$), a worse eGFR (65.0 vs. 89.0 ml/min in type 1; 46.0 vs. 71.0 ml/min in type 2 diabetes, $p < .001$), and higher albuminuria levels (17.0 vs. 6.0 mg/L in type 1 diabetes, $p = .001$ and 61.0 vs. 16.0 mg/L, $p < .001$). Among deceased people with type 1 and type 2 diabetes, persons with type 2 diabetes were older (74.0 vs. 70.0 years, $p = .02$), had a shorter diabetes duration (18.0 vs. 33.0 years, $p < .001$), had a non-native non-Western migration background more often (33.7% vs. 10.7%, $p < .001$), had a higher BMI (28.7 vs. 23.8 kg/m^2, $p < .001$), higher albuminuria levels (61.0 vs. 17.0 mg/L, $p = .03$) than individuals with type 1 diabetes, and had equal HbA1c levels compared with people with type 1 diabetes (63.0 vs. 63.5 mmol/mol, $p = .61$).

Among all 717 deceased adults with diabetes, CVD accounted for 153 deaths (21.3% of all deaths), comprising ischaemic heart disease (n = 46, 6.4%), cerebrovascular disease (n = 24, 3.3%) and other circulatory diseases (n = 83, 11.6%). Non-CV cause of death was recorded in 526 cases (73.6%), with cancer as the predominant cause of death (n = 206, 39.2%). The COVID-19 infection accounted for 9.3% (n = 49) of all non-CV deaths in individuals with diabetes. Only in 2020, the first year of the COVID-19 pandemic, coronavirus infection was recorded as the underlying cause. The distribution of causes of death in 2020 was similar to 2017-2019, except for malignancy, which was reported less in 2020 (21.6% vs. 32.4%, $p = .032$).

Figure 1 shows causes of death by type 1 (n = 75) and type 2 (n = 563) adults with diabetes. Among individuals with type 1 diabetes, 13% (n = 10) died of CVD, and 81.3% (n = 61) died of non-CVD. Diabetes mellitus (n = 17, 22.7%), malignant neoplasms (n = 16, 21.3%), and respiratory diseases, including COVID-19 (n = 6, 14.6%), were most frequently recorded as causes of death in type 1 diabetes. Up to 65 years of age, diabetes mellitus was the most frequent cause of death (n = 8, 25%), and >65 years, malignant disease (n = 10, 23.3%). Mental disorders were the underlying cause of death in six individuals with type 1 diabetes (8%). Among people with type 2 diabetes, CV death was reported in 134 participants (23.8%) and non-CV death in n = 397 (70.5%); the leading causes of death reported were malignancies (n = 145, 25.8%) and respiratory disease, including COVID-19 (n = 71, 12.6%). In persons with type 2 diabetes up to age 65 years, malignant neoplasms (n = 41, 34.2%), diabetes mellitus (n = 18, 15.0%) and CVD (n = 15, 12.5%) were the most common causes of death. Above 65 years of age, CVD (n = 119, 26.9%), malignancy (n = 104, 23.5%) and diabetes mellitus (n = 44, 9.9%) were the leading causes of death. Regarding COVID-19 as a cause of death, no differences were observed in the proportion of individuals deceased from COVID-19 between participants with type 1 and type 2 diabetes (8.0% vs. 7.1%, $p = .97$). In children, less than five deaths were observed from 2016 up to 2021 during 4514 PY of follow-up. The corresponding mortality rate was 4.4 per 10 000 PY.

Table 2 shows the association of patient characteristics and clinical parameters with all-cause mortality in adults with type 1 and type 2 diabetes. In persons with type 1 diabetes, age, smoking and an eGFR <60 ml/min are associated with all-cause mortality. Among people with type 2 diabetes, predictors for all-cause mortality were age, male sex, smoking, a diabetes duration <1 year, a BMI <20 kg/m^2, hypertension, an eGFR <60 ml/min and a HbA1c 53-64 mmol/mol (7-8%). Among 358 deceased males with type 2 diabetes, causes of death were predominantly malignancy (n = 95, 26.5%), CVD (n = 89, 24.9%) and diabetes mellitus (n = 47, 13.1%). In deceased women with type 2 diabetes (n = 205), the most common causes of death were malignancy (n = 50, 24.4%), CVD death (n = 45, 22.0%) and diabetes mellitus (n = 15, 7.3%).

TABLE 2 Hazard ratios of all-cause mortality by patient characteristics in adult outpatients with DM type 1 and type 2 included in the Dutch Paediatric and Adult Registry of Diabetes.

	DM type 1				DM type 2			
	Age-adjusted		Multivariable[a]		Age-adjusted		Multivariable[a]	
Characteristics	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	1.10 (1.08-1.11)	<.001	1.11 (1.08-1.13)	<.001	1.08 (1.08-1.09)	<.001	1.09 (1.08-1.10)	<.001
Male sex, %	1.66 (1.03-2.68)	.036	1.34 (0.80-2.25)	.262	1.55 (1.30-1.84)	<.001	1.37 (1.15-1.64)	<.001
Migration background								
Native Dutch, %	Ref	-	Ref	-	Ref	-	Ref	-
Non-native Western, %	1.78 (0.77-4.53)	.179	1.63 (0.67-3.96)	.284	0.88 (0.58-1.32)	.528	0.81 (0.54-1.22)	.314
Non-native non-Western, %	0.66 (0.31-1.37)	.264	1.06 (0.49-2.30)	.890	0.64 (0.54-0.77)	<.001	1.02 (0.85-1.23)	.830
Education level								
Low, %	0.58 (0.19-1.77)	.340	0.41 (0.13-1.29)	.127	1.67 (1.13-2.45)	.010	1.38 (0.94-2.05)	.103
Medium, %	Ref	-	Ref	-	Ref	-	Ref	-
High, %	0.72 (0.30-1.71)	.178	0.49 (0.20-1.20)	.118	0.97 (0.54-1.73)	.909	1.06 (0.59-1.90)	.847
Diabetes duration, years								
<1	2.59 (0.34-19.39)	.362	2.94 (0.36-24.22)	.315	2.38 (1.64-3.46)	<.001	2.44 (1.61-3.70)	<.001
1-5	0.43 (0.06-3.31)	.418	0.57 (0.07-4.51)	.595	0.97 (0.65-1.44)	.870	1.34 (0.89-2.02)	.159
5-10	0.18 (0.02-1.41)	.104	0.19 (0.02-1.47)	.112	0.91 (0.68-1.22)	.528	1.09 (0.81-1.47)	.563
10-20	Ref	-	Ref	-	Ref	-	Ref	-
>20	3.42 (1.83-6.39)	<.001	0.87 (0.46-1.64)	.663	1.40 (1.15-1.70)	.001	0.97 (0.79-1.18)	.737
Smoking status								
Smoker, %	1.37 (0.76-2.48)	.295	2.25 (1.19-4.25)	.013	1.00 (0.76-1.32)	.999	1.36 (1.03-1.81)	.033
Non-smoker, %	Ref	-	Ref	-	Ref	-	Ref	-
BMI, kg/m^2								
<20, %	1.66 (0.62-4.48)	.314	2.11 (0.73-6.07)	.165	3.60 (1.89-6.86)	<.001	3.02 (1.56-5.84)	.001
20-24, %	1.40 (0.76-2.59)	.278	1.72 (0.90-3.30)	.101	1.14 (0.83-1.57)	.421	1.04 (0.75-1.43)	.822
25-29, %	Ref	-	Ref	-	Ref	-	Ref	-
≥ 30, %	0.37 (0.09-1.58)	.179	0.53 (0.12-2.34)	.400	0.86 (0.67-1.10)	.234	1.02 (0.79-1.31)	.907
Systolic blood pressure, mmHg								
<135	Ref	-	Ref	-	Ref	-	Ref	-
≥135	2.42 (1.45-4.05)	.001	1.00 (0.58-1.70)	.988	0.97 (0.80-1.18)	.754	0.71 (0.58-0.86)	<.001
LDL cholesterol, mmol/L								
<2.6	Ref	-	Ref	-	Ref	-	Ref	-
≥2.6	0.37 (0.20-0.67)	.001	0.97 (0.42-1.48)	.462	0.85 (0.68-1.06)	.155	0.96 (0.77-1.21)	.739
eGFR, ml/min								
<60	7.15 (3.32-15.41)	<.001	3.01 (1.32-6.86)	.009	3.02 (2.41-3.79)	<.001	1.78 (1.40-2.25)	<.001
≥60	Ref	-	Ref	-	Ref	-	Ref	-
HbA1c, mmol/mol, %								
<53, <7.0%	0.82 (0.44-1.54)	.542	1.29 (0.65-2.53)	.466	1.26 (1.00-1.59)	.047	1.23 (0.97-1.55)	.088
53-64, 7.0-8.0%	0.71 (0.40-1.25)	.235	0.97 (0.54-1.75)	.916	0.91 (0.73-1.14)	.410	0.78 (0.62-0.98)	.031
64-86, 8.0-10.0%	Ref	-	Ref	-	Ref	-	Ref	-
≥86, ≥10.0%	1.19 (0.54-2.61)	.669	3.72 (1.58-8.73)	.003	0.97 (0.73-1.30)	.859	1.47 (0.60-1.18)	.319

Note: Both models are stratified for diabetes duration.

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; DM, diabetes; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; Inf, infinity; LDL, low-density lipoprotein; Ref, reference category.

[a]Additionally adjusted for age, gender, migration background, education level, diabetes duration, smoking status, BMI, systolic blood pressure, LDL cholesterol, eGFR and HbA1c.

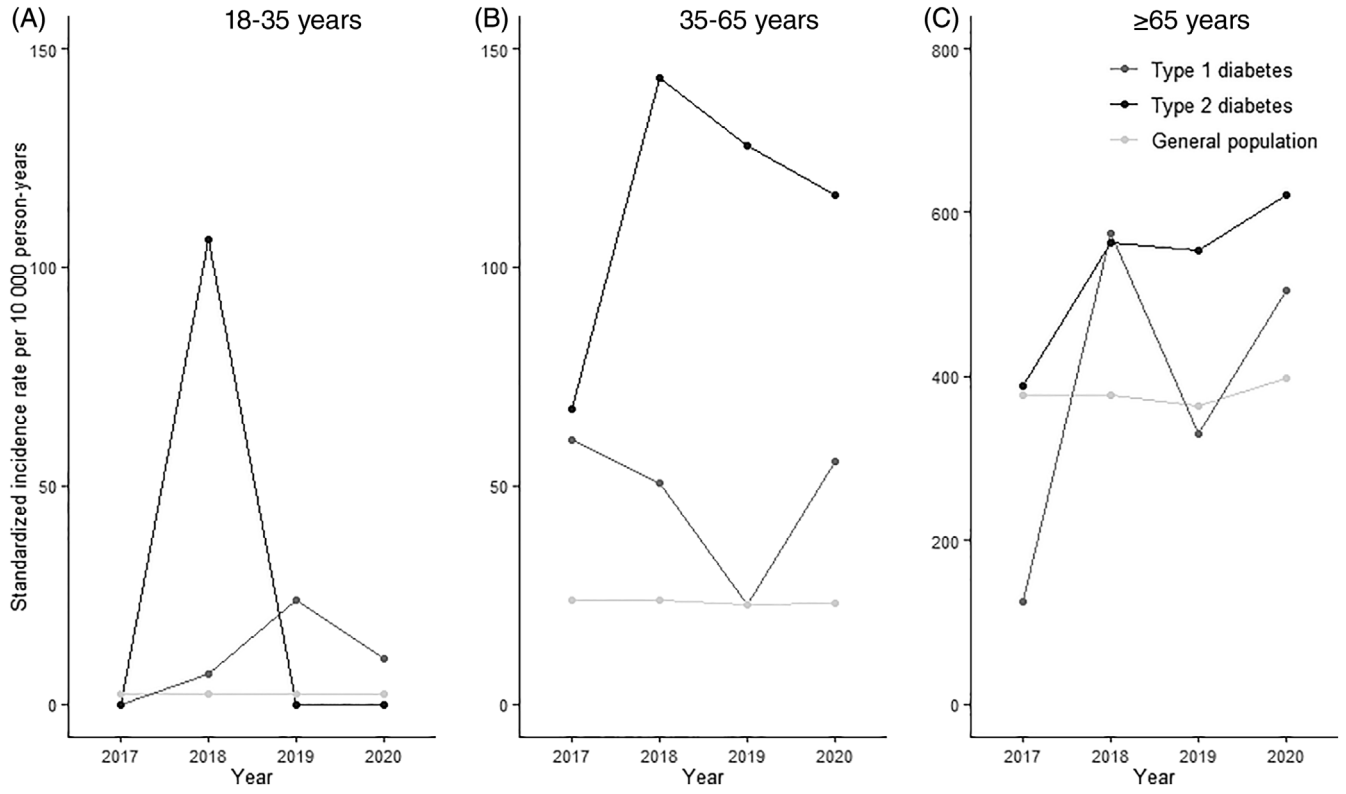

FIGURE 2 All-cause mortality rates by age category from 2017 to 2020 in adult outpatients with type 1 and type 2 diabetes were compared with the general population. A. Type 1: 95% CI 0.0 -35.6; Type 2: 95% CI 0.0 - 128.6; General population: 95% CI 0.3 – 8.0; B. Type 1: 95% CI 14.3- 77.9; Type 2: 95% CI 52.3 - 168.9; General population: 95% CI 14.5 – 35.7; C.Type 1: 95% CI 104.5- 624.2; Type 2: 95% CI 350.3 – 714.9; General population: 95% CI 328.5 – 438.0.

Figure 2 shows all-cause mortality rates per 10 000 PY from 2017 up to 2021 in individuals with type 1 and type 2 diabetes. The absolute increase of deaths between 2017 and 2020 was +38.8 deaths per 10 000 PY in type 1 and +156.9 deaths per 10 000 PY in type 2 diabetes, whereas the increase was +8.8 deaths per 10 000 PY in the general population. Mortality rates in people with type 1 diabetes ranged from 0.0 in persons between 18 and 35 years to 505.8 per 10 000 PY in individuals >65 years. In people with type 2 diabetes, mortality rates varied from 0.0 in individuals between 18 and 35 years to 662.5 per 10 000 PY in participants >65 years. In the general population, mortality varied from 2.3 in adults between 18 and 35 years of age to 397.0 per 10 000 PY in participants >65 years of age. Among persons with type 2 diabetes mellitus >65 years of age, the mortality rate in 2018 was 564.0 deaths per 10 000 PY, and in 2020, it was 622.5 deaths per 10 000 PY. In 2018, the most common causes of death in all adults with diabetes mellitus were malignancy (n = 61, 32.4%), CVD death (n = 52, 27.7%) and diabetes mellitus (n = 20, 10.6%). In 2020, among all adult participants with diabetes, malignancy (n = 53, 21.6%), COVID-19 infection (n = 49, 20.0%) and CVD (n = 41, 16.7%) were the leading causes of death. Kaplan-Meier curves of mortality in adults with type 1 and type 2 diabetes during follow-up at the diabetes outpatient clinic are shown in Figure S1.

Table 3 shows the association of patient and disease characteristics with CVD mortality in adults with type 1 and type 2 diabetes. In adult individuals with type 1 diabetes, there was no association between patient or disease characteristics and CVD mortality. Among adults with type 2 diabetes, a diabetes duration <1 year was associated with CVD mortality. The most common cause of death among 239 adult participants with type 2 diabetes with a diabetes duration <1 year (median age 54 years, range 18-86 years) was malignancy (n = 28, 84.8%).

Figure 3 shows CVD mortality per 10 000 PY from 2017 to 2020 in persons with type 1 and type 2 diabetes of ≥65 years. An increase in CVD mortality from, respectively, 123.3 deaths in type 1 and 105.4 deaths per 10 000 PY in type 2 diabetes was observed from 2017 to 2018. After 2018, mortality rates declined to 24.1 per 10 000 PY in individuals with type 1 diabetes and 117.2 per 10 000 PY in type 2 in 2020. The general population showed a similar mortality pattern, albeit attenuated, with a decrease in CVD deaths of 10.2 per 10 000 PY from 2017 to 2020.

4 | DISCUSSION

To our knowledge, this is the first study to assess mortality patterns in the Dutch diabetes outpatient population using nationwide data. Our results showed that the mortality rate in individuals with type 2 diabetes treated in an outpatient hospital setting was 324 per 10 000 PY,

TABLE 3 Hazard ratios of cardiovascular mortality by baseline characteristic in adult outpatients with DM type 1 and type 2 included in the Dutch Paediatric and Adult Registry of Diabetes.

	DM type 1				DM type 2			
	Age-adjusted		Multivariable[a]		Age-adjusted		Multivariable[a]	
Characteristics	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	0.99 (0.98-1.01)	.465	1.02 (0.98-1.06)	.229	0.99 (0.98-1.00)	.008	0.99 (0.98-1.01)	.254
Male sex, %	1.19 (0.71-1.99)	.507	0.76 (0.35-1.65)	.482	0.98 (0.80-1.19)	.822	0.94 (0.76-1.15)	.545
Migration background								
Native Dutch, %	Ref	-	Ref	-	Ref	-	Ref	-
Non-native Western, %	1.80 (0.76-4.27)	.182	1.52 (0.37-6.13)	.560	0.80 (0.50-1.27)	.336	0.91 (0.56-1.47)	.693
Non-native non-Western, %	1.87 (0.83-4.19)	.130	2.97 (0.81-10.92)	.100	1.01 (0.83-1.24)	.915	1.04 (0.83-1.31)	.723
Education level								
Low, %	1.19 (0.39-3.68)	.760	0.51 (0.07-3.64)	.506	1.13 (0.74-1.74)	.572	1.19 (0.75-1.89)	.459
Medium, %	Ref	-	Ref	-	Ref	-	Ref	-
High, %	0.96 (0.36-2.54)	.933	1.13 (0.26-4.89)	.866	0.95 (0.51-1.76)	.867	1.09 (0.56-2.12)	.796
Diabetes duration, years								
<1	5.14 (0.62-42.85)	.130	82.79 (3.37-2032.89)	.007	4.01 (2.70-5.95)	<.001	2.09 (1.30-3.38)	.003
1-5	10.86 (1.22-97.09)	.033	5.08 (0.33-79.16)	.246	1.44 (0.92-2.24)	.110	0.84 (0.52-1.36)	.485
5-10	0.0 (0.0-Inf)	.996	0.0 (0.0-Inf)	.997	1.13 (0.80-1.58)	.488	0.88 (0.61-1.26)	.481
10-20	Ref	-	Ref	-	Ref	-	Ref	-
>20	0.73 (0.38-1.38)	.329	1.14 (0.36-3.64)	.822	0.87 (0.70-1.10)	.250	0.83 (0.65-1.06)	.129
Smoking status								
Smoker, %	1.58 (0.84-2.96)	.155	2.93 (1.08-7.96)	.035	1.34 (0.98-1.84)	.063	1.22 (0.87-1.71)	.257
Non-smoker, %	Ref	-	Ref	-	Ref	-	Ref	-
BMI, kg/m^2								
<20, %	0.97 (0.32-2.93)	.953	0.75 (0.16-3.60)	.719	1.97 (0.99-3.91)	.055	1.77 (0.86-3.63)	.118
20-24, %	1.35 (0.70-2.62)	.317	0.86 (0.31-2.39)	.766	1.31 (0.90-1.91)	.155	1.43 (0.97-2.11)	.074
25-29, %	Ref	-	Ref	-	Ref	-	Ref	-
≥30, %	0.58 (0.08-4.46)	.604	0.89 (0.09-9.14)	.919	1.17 (0.88-1.57)	.285	1.23 (0.91-1.67)	.183
Systolic blood pressure, mmHg								
<135	ref	-	ref	-	ref	-	ref	-
≥135	1.40 (0.78-2.51)	.255	0.86 (0.35-2.16)	.753	0.90 (0.72-1.13)	.363	0.89 (0.70-1.13)	.323
LDL cholesterol, mmol/L								
<2.6	Ref	-	Ref	-	Ref	-	Ref	-
≥2.6	1.06 (0.55-2.02)	.869	1.17 (0.39-3.45)	.780	1.11 (0.86-1.44)	.409	1.20 (0.92-1.57)	.174
eGFR, ml/min								
<60	1.72 (0.74-3.96)	.205	1.35 (0.37-4.94)	.651	0.76 (0.58-0.99)	.042	0.94 (0.71-1.26)	.701
≥60	Ref	-	Ref	-	Ref	-	Ref	-
HbA1c, mmol/mol, %								
<53, <7.0%	1.33 (0.68-2.60)	.407	1.46 (0.54-3.95)	.451	1.01 (0.78-1.31)	.952	1.01 (0.77-1.34)	.932
53-64, 7.0-8.0%	1.18 (0.63-2.23)	.601	1.78 (0.74-4.25)	.197	0.89 (0.69-1.16)	.392	0.87 (0.66-1.15)	.324
64-86, 8.0-10.0%	Ref	-	Ref	-	Ref	-	Ref	-
≥86, ≥10.0%	0.62 (0.27-1.46)	.278	0.61 (0.18-2.05)	.421	1.00 (0.71-1.40)	.993	0.93 (0.64-1.33)	.675

Note: Both models are stratified for diabetes duration.

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; DM, diabetes; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; Inf, infinitive; LDL, low-density lipoprotein; Ref, reference category.

[a]Competing risk analysis. Additionally adjusted for age, gender, migration background, education level, diabetes duration, smoking status, BMI, systolic blood pressure, LDL cholesterol, eGFR and HbA1c.

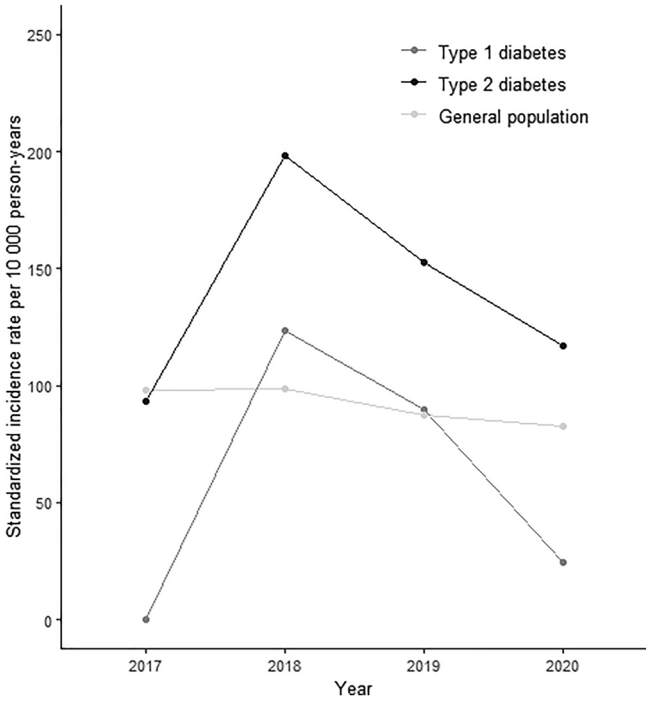

FIGURE 3 Cardiovascular disease mortality rates from 2017 to 2020 in individuals with type 1 and type 2 diabetes in the Dutch Paediatric and Adult Registry of Diabetes ≥65 years. Type 1: 95% CI 0.0 –147.1; Type 2: 95% CI 75.2 – 228.1; General population: 95% CI 65.8 – 110.1.

which was five times higher compared with a mortality rate of almost 68 per 10 000 PY in people with type 1 diabetes. All-cause mortality rates were the highest in participants aged ≥65 years, and new-onset type 2 diabetes mellitus was associated with all-cause and CV mortality. Malignancy was most frequently recorded as a non-CV cause of death. Moreover, influenza and the COVID-19 pandemic notably impacted mortality in Dutch individuals with diabetes between 2016 and 2021. As a result, malignancy was registered less often as the cause of death in persons with diabetes during the COVID-19 pandemic.

Our observed mortality rates of 324 per 10 000 PY were comparable with previous studies in people with type 2 diabetes from 11 high-income countries, with rates of 224.4-481.4 deaths per 10 000 PY.[8,26] However, most studies have assessed mortality rates in primary and secondary care combined, lacking focus on individuals primarily treated in outpatient diabetes care. In general, patients treated in hospitals will have more complex disease trajectories and intensified resource use, making the prognosis of this specific patient population an important focus. A single-centre study with people with complicated type 2 diabetes from Denmark observed a mortality rate of 407 per 10 000 PY. Mortality may be slightly higher in this study because of the specialized treatment setting and time period (2002-2010).[27] A single-centre study from Cameroon in outpatients with type 2 diabetes did observe all-cause mortality rates as high as 5400 per 10 000 PY.[15]

The mortality rate of 68 per 10 000 PY was almost five times lower in people with type 1 diabetes than in outpatients with type 2 diabetes, yet it still increased compared with the general population, which may partly be attributed to the older age of the latter group. A recent study from the National Diabetes Audit from England and Wales showed similar mortality at all age groups in type 1 and type 2 diabetes mellitus,[28] while our data still show a greater excess mortality in individuals with type 2 diabetes in lower age categories, exemplifying the distinct pathophysiological background of each diabetes type. While the vast majority of persons with type 2 diabetes are treated in primary care, accordingly, we focus on a selected group of people with type 2 diabetes bearing more comorbidities and complications. Nearly all individuals with type 1 diabetes in the Netherlands are treated in an outpatient setting, signifying that the mortality rate we found represents the entire type 1 diabetes population. In data from the Swedish National Diabetes Register, a lower all-cause mortality rate of 19.0 per 10 000 PY was observed in a relatively young type 1 diabetes population with a mean age at entry in the dataset of 35.3 years.[7] A recent study among people with type 1 diabetes in six high-income countries from 2000 to 2016 found 116.8 deaths per 10 000 PY, with outcomes similar to our findings in Spain and Australia, with 88.9 and 77.1 deaths per 10 000 PY, respectively.[29]

Many previous studies about mortality in diabetes mellitus are from earlier time periods up until 2016, when mortality rates in high-income settings were gradually declining. Since then, the COVID pandemic has severely influenced health care practices and death rates, so these earlier rates may not be representative of diabetes care during pandemic periods.[26,30] Indeed, our findings show two peaks in mortality rates of persons with diabetes >65 years old, possibly caused by an influenza epidemic in 2018 and the COVID-19 pandemic in 2020. Previous Dutch national reports have reported similar patterns in the general population.[31]

Likewise, we observed an increase in CV mortality among both type 1 and type 2 diabetes in 2018, with stabilization from 2020 onwards. Again, the influenza epidemic may have affected CV mortality, as influenza is associated with cardiac changes, CV hospitalizations and mortality.[32,33] Other studies have observed a stable decrease in CV mortality; however, these studies did not include the pandemic years of COVID-19.[7,32–36] Moreover, these studies included individuals with diabetes from all treatment settings, in contrast to our study population of hospital outpatient care only. This could have led to more comorbidity and complications at baseline and, therefore, a higher risk of CVD than persons treated in primary care.[37]

Our results show that malignancy was the most important non-CV cause of death, a finding that is in concordance with previous studies.[8,38,39] Likewise, recent studies have shown that malignancy-related mortality has increased in elderly people with type 2 diabetes in several high-income countries, despite a reduction in all-cause and CV mortality rates.[40,41] Compared with the general population, malignancy-related mortality rates in individuals with diabetes were also higher.[42,43] This may be explained by improved life expectancy

because of a reduction in CV events, the link between obesity and several cancer types, or the potential effects of long-term glycaemic dysregulation.[43] In contrast, during the COVID-19 pandemic, we observed a decrease in malignancy as a recorded cause of death, corresponding with the literature. COVID-19 may have resulted in reduced malignancy diagnoses and, consequently, malignancy-associated mortality. Because of COVID-related barriers to general practice, hospitals postponing diagnostic evaluation or having longer turnaround times, and national screening programmes for malignancies that were temporarily interrupted.[44] Of note, several COVID-19-related deaths may have been mediated by CV complications, potentially resulting in an underestimation of the CV mortality rate.

Several possible associations with all-cause and CV mortality were observed. The observed association between new-onset type 2 diabetes within the first year of diagnosis and all-cause and CV mortality concord with previous findings, and may reflect how our health care system has developed over the last decades, possibly leading to lower mortality risk because of diabetes treatment.[45,46] Previous studies suggest that there may be a different mechanism at play than long-term atherosclerotic changes. A state of impaired glucose tolerance, with insulin resistance and unmanaged CV risk factors, may have been present long before the diagnosis of diabetes mellitus. However, the diabetes diagnosis could have been registered when people first visited the hospital and not at the actual diagnosis in primary care, leading to falsely shorter diabetes durations. This may explain why most individuals with new-onset diabetes mellitus type 2 had malignancy as a cause of death. These persons were most likely diagnosed with type 2 diabetes in primary care and died of a malignant disease during treatment in secondary or tertiary care. Moreover, the association between all-cause mortality and BMI <20 kg/m^2 in type 2 diabetes has been reported in the literature. The obesity paradox states that people with an average weight at the diagnosis of diabetes or other chronic diseases have higher all-cause mortality rates than their obese counterparts.[47] Several mechanisms have been suggested, such as differences in body composition and muscle mass, diabetes disease profile, or the coexistence of severe illnesses.[48,49]

To our knowledge, our study is the first to give an extensive overview of mortality in individuals treated for diabetes in an outpatient hospital setting, including mortality rates, causes of death and patient-associated factors. Data from the nationwide DPARD on diabetes type and clinical characteristics provide unique information unavailable from other national data sources. Moreover, the linkage with CBS data provides high accuracy in mortality rates and the causes of death because CBS collects all national death records in the Netherlands by law. Furthermore, this study provides an in-depth analysis of recent mortality patterns, including the influence of the COVID-19 pandemic on mortality rates and competing causes of death, which is also generalizable to other high-income countries. Our study also had several limitations. First, at the time of analysis DPARD, had no nationwide coverage of all individuals with diabetes treated in Dutch hospitals yet. From 2022 onward, coverage has rapidly increased, with currently 89% of all Dutch treatment centres applied to DPARD, and we expect to achieve nationwide coverage in the near future. Although a proportionate reflection of all treatment centres across the Netherlands, the group of hospitals included in this study may have introduced selection bias in the included persons. Second, linkage to the CBS data was only possible in 62.2% of cases because not all hospitals provided personal identification data (personal identification number or zip code). As the linked participants had a longer diabetes duration, higher systolic blood pressure, worse kidney function and a higher median HbA1c (Table S1), it is unlikely that the mortality rate in our linked study population would have been higher. Third, 12.1% of individuals with a missing diabetes classification had to be excluded from the stratified type 1 and type 2 diabetes analyses, leaving a relatively small group of deceased people with type 1 diabetes for analysis (n = 75). Most likely, these missing data were at random because of registration errors, as no association between the recording of people with diabetes and diabetes type is expected. Fourth, data containing less than five observations could not be provided for privacy reasons; therefore, information on death in children could not be provided separately. Fifth, as ICD-10 codes were used to establish the cause of death, diagnoses may have been miscoded. Finally, because of the observational design of our study, the associations found between clinical variables and mortality do not necessarily imply a causal relationship.

Within the following decades, the comorbidity profile of individuals with diabetes will change because of improving CV outcomes and mortality rates. By 2030, malignancy may be the most important cause of death in persons with type 2 diabetes.[43] Clinicians treating the elderly with diabetes with cancers and consequent multimorbidity may face various challenges in care provision, which deserve specific attention. Expertise in cancer treatment in people with diabetes, specifically concerning glycaemic targets and advanced care planning, is warranted. Despite the changes in comorbidity patterns, our results underscore once more that vigilant CV screening and early treatment remain imperative. Furthermore, 8% of type 1 individuals with diabetes died of mental disorders, which once again emphasizes the importance of psychological guidance for people with diabetes. Moreover, this study shows the value of national diabetes registries, as DPARD was able to notice recent temporal changes in important outcomes of Dutch individuals with diabetes, substantiated by clinical and disease characteristics. The results confirm mortality outcomes previously found in other high-income countries and provide insight into more recent epidemiological trends in mortality. DPARD is a steadily growing nationwide diabetes registry that will continuously provide insights into the characteristics of the Dutch diabetes population, from which evidence-based and data-driven strategies transpire to improve resource allocation and the quality of diabetes care.[50] The influence of complications, comorbidity, hospitalizations and other factors, such as the effects of new interventions and policy changes, on the quality of care in the Dutch outpatient population may be studied in more detail in future years to further improve clinical outcomes such as mortality.

In conclusion, all-cause and CV mortality in individuals with type 1 and type 2 diabetes treated in outpatient settings in the Netherlands between 2016 and 2021 were high, similar to rates

previously reported in high-income countries and extensively exceeded mortality rates in the general population. Peaks in mortality rates, most likely caused by the COVID-19 pandemic and an influenza epidemic in 2018, were notable in the outcomes. Malignancy is the major cause of non-CVD mortality. Renal failure is the only factor associated with all-cause mortality in both diabetes types. In participants with type 2 diabetes, an association was observed between male sex, BMI <20 kg/m^2, diabetes duration <1 year, hypertension and all-cause mortality. Early detection, treatment and prevention of factors associated with mortality may improve clinical outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. The idea for the article was provided by CV and MK. Writing of the manuscript and statistical analysis were performed by JB, CV and SV. JB, CV, SV and ES drafted the article. Support regarding statistical analysis was provided by RG. CV, RG, SV, ES, MK, DM, TS and MN, commented on previous versions of the manuscript. All authors read and approved the final manuscript. MK and CV are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15750.

DATA AVAILABILITY STATEMENT

Carianne Verheugt 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. Data referenced in this study are available in the DPARD-dataset from 2021-09-06. Data are available on request from the corresponding author Carianne Verheugt. The data are not publicly available because hospitals delivering data remain ownership of their data. Furthermore, DPARD-data are containing information that could compromise research participant privacy.

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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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