Trends in cause-specific mortality among people with type 2 and type 1 diabetes from 2002 to 2019: a Danish population-based study

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Summary

Background Despite advances in primary and secondary prevention of cardiovascular disease, excess mortality persists within the diabetes population. This study explores the components of this excess mortality and their interaction with sex.

Methods Using Danish registries (2002–2019), we identified residents aged 18–99 years, their diabetes status, and recorded causes of death. Applying Lexis-based methods, we computed age-standardized mortality rates (asMRs), mortality relative risks (asMRRs), and log-linear trends for cause-specific mortality.

Findings From 2002 to 2019, 958,278 individuals died in Denmark (T2D: 148,620; T1D: 7830) during 84.4 M person-years. During the study period, overall asMRs declined, driven by reducing cardiovascular mortality, notably in men with T2D. Conversely, cancer mortality remained high, making cancer the leading cause of death in individuals with T2D. Individuals with T2D faced an elevated mortality risk from nearly all cancer types, ranging from 9% to 257% compared to their non-diabetic counterparts. Notably, obesity-related cancers exhibited the highest relative risks: liver cancer (Men: asMRR 3.58 (3.28; 3.91); Women: asMRR 2.49 (2.14; 2.89)), pancreatic cancer (Men: asMRR 3.50 (3.25; 3.77); Women: asMRR 3.57 (3.31; 3.85)), and kidney cancer (Men: asMRR 2.10 (1.84; 2.40); Women: asMRR 2.31 (1.92; 2.79)). In men with type 2 diabetes, excess mortality remained stable, except for dementia. In women, diabetes-related excess mortality increased by 6–17% per decade across all causes of death, except cardiovascular disease.

Interpretation In the last decade, cancer has emerged as the leading cause of death among individuals with T2D in Denmark, emphasizing the need for diabetes management strategies incorporating cancer prevention. A sex-specific approach is crucial to address persistently higher relative mortality in women with diabetes.

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Keywords: Diabetes; Cause-specific mortality; Trends; Population-based; Cancer mortality

Introduction

Elevated cardiovascular disease (CVD) risk and subsequent CVD-related mortality have predominantly shaped mortality patterns in individuals with diabetes. However, secular trends in cardiovascular risk factors and improved treatment of risk factors and CVD during the last two decades have decreased CVD mortality, both among individuals with and without diabetes.[1] This has contributed substantially to the decrease in overall mortality in individuals with either type 1 diabetes (T1D)

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Research in context

Evidence before this study

We searched PubMed for population-based papers published from database inception to July 1, 2023, which reported on associations of diabetes and sex with all-cause and cause-specific mortality. We used search terms related to exposure (diabetes, diabetes mellitus, diabetes type 1, diabetes type 2, sex, gender) and outcomes (mortality, cause of death, cause-specific mortality, survival, cancer mortality, cancer-specific mortality).

Prior research indicates a decline in overall mortality rates among people with diabetes, along with a shift in causes of death. Nevertheless, the specific patterns of this shift vary among countries. Cancer has been identified as a predominant cause of death among individuals with type 2 diabetes in some studies. However, the nuances of this association, encompassing cancer types and sex-specific influences, remain inadequately elucidated.

Added value of this study

We found that all-cause mortality declined from 2002 to 2019 in individuals with and without diabetes, primarily due to improved cardiovascular mortality, particularly among men. Despite this, cancer-related mortality remained considerable, ultimately surpassing cardiovascular disease as the leading cause of death in people with type 2 diabetes. Individuals with type 2 diabetes exhibited relatively high mortality for several cancer types, notably pronounced for obesity-related cancers such as liver, pancreatic, and kidney cancers.

Declines in cause-specific mortality rates were less pronounced among women with type 2 diabetes compared to their non-diabetic counterparts, leading to an expanding diabetes-associated mortality gap for nearly all causes of death, a phenomenon not observed in men.

Notably, dementia-related mortality rates consistently rose throughout the study period, with a significantly steeper increase observed among both men and women with type 2 diabetes compared to their non-diabetic counterparts.

Implications of all the available evidence

Cancer has surfaced as the foremost cause of mortality among those with type 2 diabetes in Denmark, underscoring the necessity for customized diabetes management protocols encompassing cancer prevention and treatment strategies. A sex-specific approach is essential to tackle the persistent mortality disparity linked to diabetes, particularly among women.

or with type 2 diabetes (T2D) observed across several countries.[2,3]

Despite this consistent pattern of declining mortality, individuals with diabetes continue to manifest a substantial excess mortality compared to the general population without diabetes.[2] Recent research has indicated a significant contribution of cancer to the surplus mortality associated with diabetes, with cancer overtaking CVD as the primary cause of death in individuals with T2D in the US, the UK, and Hong Kong.[3–7]

The association between diabetes and cancer incidence has been well-established in previous population-based studies.[8,9] This relationship is thought to operate through both direct mechanisms (such as hyperglycemia) and indirect mechanisms (shared risk factors, such as obesity).[8] Furthermore, emerging research underscores a more pronounced impact of diabetes on cancer incidence among women compared to men.[10]

However, the relationship between diabetes and cancer-related mortality is less evident, and there is a scarcity of data addressing how the type of cancer and sex influence this association. Moreover, little research has investigated the potential interaction between sex and diabetes in time trends in excess mortality associated with diabetes over the past two decades.

Employing the extensive Danish national registers and a validated algorithm distinguishing between type 1 and type 2 diabetes, we aimed to investigate the impact of diabetes and sex on trends in overall and cause-specific mortality, especially cancer-related mortality, from 2002 to 2019 in Denmark.

Methods

Study population and design

This population-based cohort study was conducted using the nationwide Danish registries to identify all residents living in Denmark aged 18–99 years in the study period 1 January 2002 to 31 December 2019. The Danish registries contain routinely, prospectively collected health data based on all contacts to the tax-funded universal healthcare system, and the validity and completeness of the Danish registries is generally considered to be high.[11]

The study population was identified using information from the national civil registration system, which contains complete individual information on immigrations and emigrations to and from Denmark, date of birth, sex, continuously updated information on vital status, as well as the encrypted unique personal identification number assigned to all residents of Denmark. This unique number permits accurate linkage of recorded information in the nationwide Danish registers at the individual level.

All-cause and cause-specific mortality

Information on date of death was obtained from the Danish Civil Registration System,[11] which was

established in 1968 and contains daily updated information on vital status.

Information on cause of death was obtained from the Danish Cause of Death Register,[11] which since 1994 contains information on the underlying cause of death using ICD-10 codes as registered by the doctor certifying the death.

We categorized cause of death into six non-overlapping groups according to the following ICD-10 codes for the primary cause of death: cardiovascular disease (I00-15, I20-25, I26-52, I60-69, I70-99), cancer (C00-C97), diabetes (E10-14), dementia (F00, F01, F03, G30, G31.8, G31.9), respiratory disease (J00-99), and all other causes (remaining ICD-10 codes).[7,12]

Furthermore, we subcategorized cancer deaths into deaths as due to non-obesity or obesity related cancer, where the latter was based on the definition used by the WHO.[13] Obesity related cancer included the following ICD10 codes: esophagus (C15), upper stomach (C16), colorectal (C18-20), liver (C22), gallbladder and biliary tract cancer (C23-24), pancreas (C25), kidney (C64), thyroid (C70), meningioma (C73), and multiple myeloma (C90). Uterine and ovarian cancer (C54-56) and breast cancer (C50, only if the cancer was diagnosed after age 50 years) were categorized as obesity related cancers in women. Non-obesity related cancers included all cancers excluding the aforementioned and non-melanoma skin cancers.

Exposure

Individuals with diabetes were identified using data from the Danish National Patient Register,[11] which contains information on all hospital contacts and diagnoses since 1977, the Danish National Prescription Registry,[11] which contains information on all redeemed prescriptions at Danish pharmacies since 1995, and the Danish National Health Service Register,[11] which contains information on contacts with primary health care (eg, general practice, dentists, and podiatrists) since 1990. The identification of the diabetes population and the classification of diabetes into type 1 and type 2 was performed using a validated algorithm,[14] although we had no information on HbA1c available on a national level. In brief, diabetes was defined at the second occurrence of any event across three inclusion events: 1) hospital diagnoses of diabetes, 2) diabetes-specific services received at a podiatrist, 3) purchases of glucose-lowering drugs (ignoring purchases of insulin during pregnancies as potential gestational diabetes and metformin purchases in women below 40 years of age as potential treatment for polycystic ovary syndrome, and ignoring information on purchases of drugs for weight loss). Individuals were classified as having T1D if they had received at least one prescription for insulin after diagnosis of diabetes combined with a diagnosis of T1D from a medical hospital department. Otherwise, individuals with diabetes were classified as having T2D.[14] Diabetes status was treated in a time-dependent manner, allowing individuals to change status from unexposed to exposed during follow-up.

Ethics approval

According to Danish law and the Committee on Health Research Ethics in the Central Denmark Region, studies based on registry data, such as this, requires no ethical approval, nor patient consent for use of their registered data. In accordance with Danish law, the study was approved by the Central Region Denmark (file no. 1-16-02-304-19).

Statistical analyses

We included all individuals from 1 January 2002 (start of follow-up), their 18th birthday, or immigration into Denmark, whichever came last. They were followed until 31 December 2019 (end of follow-up), death, or emigration, whichever came first. Follow-up time was classified according to diabetes status. Time after diabetes onset was classified as T1D or T2D depending on the classification algorithm.

We applied a Lexis-based methodology to determine cause-specific death counts and the total person-time at risk for each calendar and age year. Using these aggregates, we computed age-standardized mortality rates (asMRs) for 2002–2010 and 2011–2019, standardized according to the 2002 population. The asMRs were stratified by diabetes status (without diabetes, T1D, T2D), sex, and cause of death. To assess the diabetes-related excess mortality, age-standardized mortality rate ratios (asMRRs) were calculated by comparing asMRs among those with diabetes (T2D and T1D) to those without diabetes for 2002–2010 and 2011–2019, respectively, and stratified on sex and cause of death.

As rates decreased over the follow-up period, we also reported time trends in cause-specific mortality from 2002 to 2019. They were obtained using Poisson regression, with linear trends on the log-rate scale, indicating a constant relative change on the rate scale. In visual inspections of time trends, we did not see clear departures from linear trends on the log-rate scale. No formal testing was done, since the large sample size would lead to rejection of linearity with minor and unimportant deviations from linearity. Trends were stratified by diabetes status, sex, and cause of death and presented as change per decade (with ten years chosen for means of interpretation only). This means, for instance, that a trend estimate of 1.02 implies a 2% increase in rate per decade. Comparisons were made between trends in individuals with diabetes and those without diabetes to derive a trend ratio, indicating the relative change in excess mortality per decade for individuals with diabetes compared to their non-diabetic counterparts.

All estimates are reported with 95% confidence intervals (CI). Stata 17.0 was used for statistical analyses.

Role of the funding source
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Results
From 2002 to 2019, a total of 958,278 individuals died in Denmark (without diabetes: 801,828, T2D: 148,620; T1D: 7830) over a cumulative risk duration of 84.4 million person-years (without diabetes: 80,556,547; T2D: 3,579,037; T1D: 305,885) (Table 1). The corresponding unadjusted MRs were 10.0 deaths per 1000 person-years for individuals without diabetes, 41.5 for those with T2D, and 25.6 for those with T1D.

Trends in overall mortality
Age-standardized mortality rates declined over the study period among individuals with and without diabetes, for both men and women (Table 1, Supplementary Figure S1). Men had consistently higher mortality rates but more favorable mortality trends than women within each diabetes stratum over the study period. For instance, men with T2D experienced a 27% (95% CI: 26–28) decrease in overall mortality per decade during the study period, whereas women with T2D experienced a 21% (95% CI: 19–22) decrease in overall mortality per decade (Table 1).

Trends in cause-specific mortality
In individuals with T2D, declining mortality rates over time were observed for all causes of death, except for dementia in both men and women and respiratory disease in women (Fig. 1 and Table 1). Nevertheless, elevated mortality risk persisted, ranging from around 30%–75%, across nearly all causes of death in individuals with T2D when compared to those without diabetes (Table 2).

Among women with T2D, time trends in mortality were less favorable than for women without diabetes for all causes of death (excluding CVD) with trend ratios ranging from 1.06 to 1.17 (Table 2). In contrast, in men, time trends in mortality were similar regardless of diabetes, except for deaths attributable to dementia for which relative risks associated with diabetes increased over time.

The most marked decline over time in cause-specific mortality was observed in CVD-related deaths, particularly among men with T2D with asMRs per 1000 person-years declining from 94 (95% CI: 92–96) in 2002–10 to 59 (95% CI: 58–60) in 2011–19 (Table 1 and Fig. 1).

In contrast to the steep decline in CVD mortality, cancer mortality rates declined less during the study period, and cancer became the primary cause of death among women with T2D in 2008 and among men with T2D in 2012 (Fig. 1). Time trends in cancer mortality were similar in men without diabetes and in men with T2D (trend ratio: 1.02; 95% CI 0.99–1.04), however, women with T2D had an 8% (95% CI: 4–11) lower decline in cancer mortality per decade compared to women without diabetes (Table 2).

Notably, dementia was the only cause of death with increasing asMRs among individuals with T2D in the study period (Table 1 and Fig. 1), and the dementia mortality per decade increased 17% (95% CI: 9–26) more in women with T2D and 13% (95% CI: 3–24) more in men with T2D compared to their non-diabetic counterparts (Table 2).

In individuals with T1D, diabetes remained the largest single cause of death during the study period despite a decline in the diabetes-related mortality per 1000 person-years from 141 (95% CI: 131–152) in 2002–10 to 97 (95% CI: 88–106) in 2011–19 among men and from 115 (95% CI: 105–124) in 2002–10 to 83 (95% CI: 75–92) in 2011–19 among women (Fig. 1 and Table 1). The most notable adverse influence of T1D on mortality trends was evident in dementia-related mortality among women, as indicated by the trend ratio of 1.68 (95% CI: 1.03–2.75) (Table 2).

Cancer mortality due to obesity and non-obesity related cancer
When stratifying cancer mortality into non-obesity and obesity related cancers, the results varied with both diabetes status and sex (Fig. 2 and Table 3). However, the results were inconclusive in individuals with T1D due to small numbers of each cancer type, and the results from the T1D population is not further commented upon in this section.

Overall, individuals with T2D had an excess risk of dying from both obesity and non-obesity related cancers compared to individuals without diabetes (Fig. 2), with the excess risk ranging from 10% (men, prostate cancer) to 260% (women, pancreatic cancer) in 2011–19 (Table 3). Regardless of diabetes status, men exhibited higher asMRs from non-obesity related cancer than from obesity related cancer. Notably, women with T2D had higher asMRs from obesity related cancer than from non-obesity related cancer, whereas women without diabetes had similar asMRs for obesity and non-obesity related cancer (Fig. 2).

For obesity related cancers, individuals with T2D exhibited notably higher mortality rates compared to those without diabetes. This was particularly evident in liver, pancreatic, and kidney cancer, where individuals with T2D demonstrated approximately 2–3 times higher

Total follow-up, 2002–19	Without diabetes									Type 2 diabetes									Type 1 diabetes								
Death, numbers	801,828									148,620									7830								
Risk time, yrs	80,556,547									3,579,037									305,885								
Crude MR per 1000 yrs	10									42									26								
	2002–10			2011–19			2002–19			2002–10			2011–19			2002–19			2002–10			2011–19			2002–19		
	asMR	95% CI		asMR	95% CI		Trend[a]	95% CI		asMR	95% CI		asMR	95% CI		Trend[a]	95% CI		asMR	95% CI		asMR	95% CI		Trend[a]	95% CI	
Men																											
All-cause mortality	**169**	169	170	**135**	134	135	**0.77**	0.77	0.78	**310**	305	314	**234**	231	237	**0.73**	0.72	0.74	**412**	393	431	**301**	284	318	**0.62**	0.59	0.66
Cause-specific mortality																											
Cardiovascular	**55**	55	56	**34**	34	35	**0.58**	0.58	0.59	**94**	92	96	**59**	58	60	**0.57**	0.56	0.58	**90**	81	100	**63**	55	71	**0.59**	0.52	0.67
Cancer	**47**	47	48	**41**	41	41	**0.83**	0.82	0.84	**69**	68	71	**61**	59	62	**0.84**	0.82	0.86	**73**	66	80	**56**	50	62	**0.73**	0.64	0.82
Dementia	**5.9**	5.8	6.1	**8.3**	8.1	8.4	**1.42**	1.37	1.46	**6.0**	5.5	6.5	**8.8**	8.3	9.2	**1.60**	1.47	1.75	**6.1**	3.0	9.1	**6.8**	4.3	9.2	**1.69**	0.99	2.91
Diabetes	**n/a**			**n/a**						**49**	47	51	**31**	30	32	**0.58**	0.56	0.60	**141**	131	152	**97**	88	106	**0.56**	0.51	0.62
Respiratory	**19**	18	19	**16**	16	17	**0.85**	0.83	0.86	**24**	23	25	**22**	21	23	**0.87**	0.83	0.91	**23**	18	28	**25**	19	31	**0.82**	0.65	1.04
Others	**42**	41	42	**35**	34	35	**0.83**	0.82	0.84	**67**	65	69	**53**	51	54	**0.80**	0.78	0.83	**78**	70	86	**53**	46	60	**0.63**	0.55	0.71
Women																									**0.73**	0.64	0.82
All-cause mortality	**118**	118	119	**96**	95	96	**0.81**	0.80	0.81	**219**	215	222	**166**	164	168	**0.79**	0.78	0.81	**323**	308	339	**250**	235	264	**0.76**	0.71	0.82
Cause-specific mortality																											
Cardiovascular	**36**	35	36	**22**	22	22	**0.59**	0.58	0.60	**62**	61	64	**37**	36	38	**0.57**	0.56	0.59	**79**	71	86	**49**	43	55	**0.64**	0.55	0.74
Cancer	**35**	34	35	**30**	30	30	**0.86**	0.85	0.87	**53**	52	55	**46**	45	47	**0.92**	0.9	0.95	**60**	53	66	**46**	41	52	**0.83**	0.72	0.97
Dementia	**6.4**	6.3	6.6	**9.1**	8.9	9.2	**1.47**	1.44	1.51	**5.7**	5.4	6.1	**9.0**	8.6	9.4	**1.73**	1.61	1.85	**4.6**	2.5	6.8	**9.7**	6.7	13	**2.48**	1.52	4.04
Diabetes	**n/a**			**n/a**						**32**	31	33	**20**	19	20	**0.61**	0.58	0.63	**115**	105	124	**83**	75	92	**0.65**	0.58	0.73
Respiratory	**13**	13	13	**12**	12	12	**0.90**	0.89	0.92	**19**	18	20	**18**	18	19	**1.03**	0.98	1.08	**18**	14	22	**17**	13	21	**0.83**	0.63	1.10
Others	**28**	28	28	**23**	23	23	**0.83**	0.82	0.84	**46**	45	48	**36**	35	36	**0.89**	0.86	0.92	**48**	42	54	**44**	39	50	**1.00**	0.85	1.18

yrs, years; asMR, age-standardized (to the 2002 population) mortality rate; CI, confidence interval. [a]Trend in mortality per 10 years. A value of 0.84 implies a 16% decrease in mortality per 10 years.

Table 1: **Total number of deaths, risk time (years), and crude mortality rates per 1000 person years (MR) from 2002 to 2019 stratified by diabetes status (without diabetes, type 2 diabetes, and type 1 diabetes) as well as age-standardized (to 2002 population) mortality rates per 1000 person years (asMR) for 2002–10 and 2011–19, respectively, and trend in mortality per 10 years for 2002–2019, stratified by diabetes status, sex, and cause of death in Denmark.**

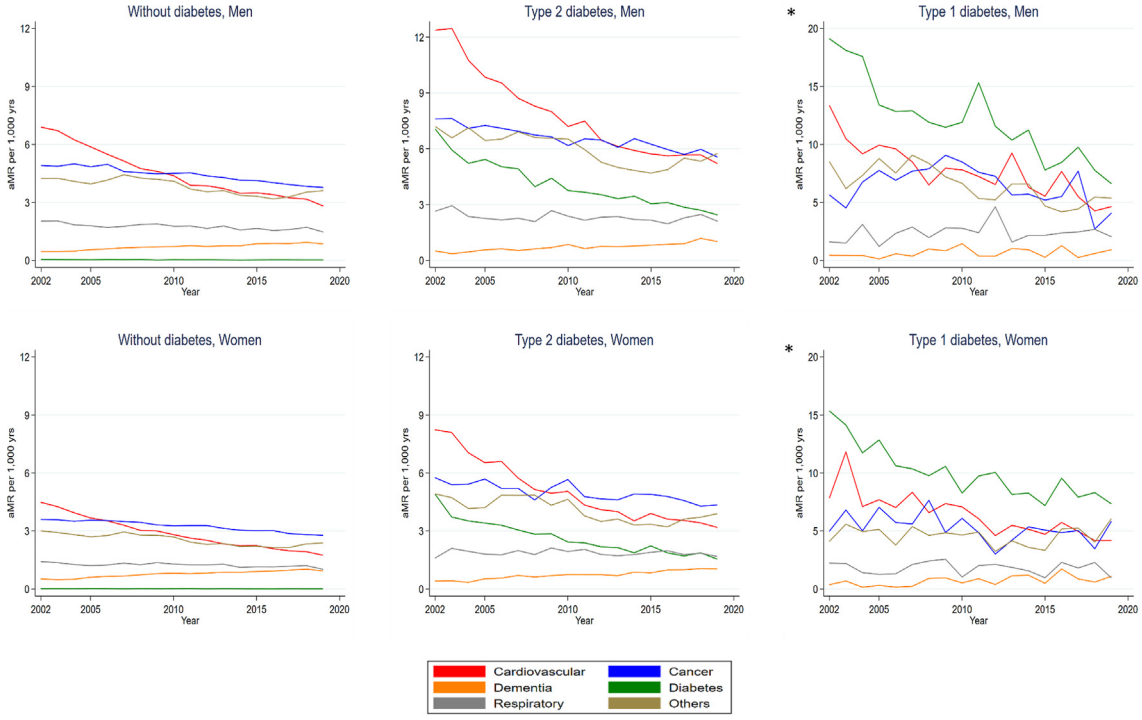

Fig. 1: **Age-standardized cause-specific mortality rates per 1000 person years (asMR) stratified by diabetes status (without diabetes, type 2 diabetes, and type 1 diabetes) and sex**. *Indicating change in the y-axis interval.

mortality rates than individuals without diabetes (Table 3). Furthermore, T2D was associated with a 30–40% higher risk of death from colorectal cancer (CRC), and a 40% higher risk of death from breast cancer among women above 50 years at breast cancer diagnosis.

For non-obesity related cancers, individuals with T2D also experienced elevated mortality rates compared to those without diabetes, particularly for central nervous system (CNS) cancer in both men and women, as well as breast cancer in women diagnosed at below 50 years of age. Furthermore, the highest cause-specific mortality rate was observed in men with T2D who died from lung cancer, and diabetes appeared to worsen the trend in lung cancer mortality during the study period for both men and women (Table 3).

Discussion

Our study is the most comprehensive study yet to explore the effect of diabetes and sex on trends in cause-specific mortality, with a focus on site-specific cancer deaths, during the past two decades in a nationwide cohort.

In this study, we found declining overall mortality rates (2002–19) in individuals with and without diabetes, primarily due to reductions in cardiovascular mortality, particularly among men. However, cancer mortality decreased only slightly over the study period, making it the most common cause of death in individuals with T2D and without diabetes, surpassing cardiovascular disease.

Unlike men, women experienced a widening diabetes-associated mortality gap across all causes of death (excluding CVD) during the study period.

Among individuals with T2D, there was an elevated mortality risk compared to individuals without diabetes for several cancer types, and this was particularly marked for obesity-related cancers like liver, pancreatic, and kidney cancers. For non-obesity-related cancers, the most notable association with diabetes was for lung cancer mortality. Lastly, we observed increasing dementia-related mortality, contrasting with other causes of death, and this trend was higher in T2D individuals than those without diabetes.

Our findings are similar to findings of previous studies in other countries, identifying an overall decline in mortality during the past two decades for both individuals with and without diabetes.[3,6,7] The decline in overall mortality among individuals with T2D was primarily due to a reduction in cardiovascular mortality, which has also been reported in previous studies.[6,7] This improvement can be attributed to secular trends in risk factors and improvements in treatment in the past three decades.[4,15]

Despite these advances, individuals with T2D still exhibited a significant excess mortality compared to their non-diabetic counterparts. Sex-dependent

	Type 2 diabetes vs without diabetes									Type 1 diabetes vs without diabetes								
	2002–10			2011–19			2002–19			2002–10			2011–19			2002–19		
	asMRR	95% CI		asMRR	95% CI		Trend ratio[a]	95% CI		asMRR	95% CI		asMRR	95% CI		Trend ratio[a]	95% CI	
Men																		
Cause-specific mortality																		
Cardiovascular	**1.70**	1.66	1.74	**1.72**	1.68	1.76	**0.98**	0.95	1.00	**1.63**	1.47	1.81	**1.84**	1.62	2.09	**1.01**	0.89	1.14
Cancer	**1.47**	1.42	1.51	**1.48**	1.45	1.52	**1.02**	0.99	1.04	**1.54**	1.40	1.71	**1.37**	1.23	1.53	**0.88**	0.78	0.99
Obesity cancer	*1.84*	*1.77*	*1.92*	*1.91*	*1.85*	*1.98*	*1.02*	*0.97*	*1.07*	*1.87*	*1.60*	*2.18*	*1.90*	*1.62*	*2.23*	*0.96*	*0.79*	*1.16*
Non-obesity cancer	*1.27*	*1.22*	*1.32*	*1.27*	*1.23*	*1.31*	*1.02*	*0.98*	*1.06*	*1.35*	*1.17*	*1.55*	*1.07*	*0.91*	*1.27*	*0.80*	*0.67*	*0.95*
Dementia	**1.01**	0.93	1.1	**1.06**	1.01	1.12	**1.13**	1.03	1.24	**1.03**	0.59	1.78	**0.82**	0.56	1.20	**1.19**	0.69	2.05
Diabetes																		
Respiratory	**1.30**	1.24	1.35	**1.36**	1.31	1.41	**1.02**	0.98	1.08	**1.25**	1.01	1.55	**1.53**	1.21	1.94	**0.97**	0.77	1.23
Others	**1.60**	1.54	1.66	**1.51**	1.46	1.57	**0.97**	0.94	1.00	**1.87**	1.69	2.07	**1.53**	1.34	1.75	**0.76**	0.67	0.86
Women																		
Cause-specific mortality																		
Cardiovascular	**1.75**	1.71	1.79	**1.70**	1.66	1.74	**0.98**	0.95	1.01	**2.21**	2.00	2.45	**2.25**	1.97	2.57	**1.08**	0.93	1.26
Cancer	**1.53**	1.48	1.58	**1.54**	1.5	1.58	**1.08**	1.04	1.11	**1.72**	1.54	1.92	**1.53**	1.36	1.73	**0.97**	0.84	1.13
Obesity cancer	*1.67*	*1.60*	*1.74*	*1.70*	*1.64*	*1.76*	*1.08*	*1.03*	*1.13*	*1.96*	*1.69*	*2.27*	*1.82*	*1.54*	*2.15*	*1.05*	*0.85*	*1.29*
Non-obesity cancer	*1.39*	*1.32*	*1.47*	*1.38*	*1.33*	*1.44*	*1.10*	*1.04*	*1.16*	*1.54*	*1.30*	*1.83*	*1.24*	*1.02*	*1.50*	*0.87*	*0.69*	*1.11*
Dementia	**0.89**	0.83	0.95	**0.99**	0.95	1.03	**1.17**	1.09	1.26	**0.72**	0.44	1.18	**1.06**	0.78	1.46	**1.68**	1.03	2.75
Diabetes																		
Respiratory	**1.46**	1.39	1.52	**1.56**	1.51	1.62	**1.14**	1.08	1.20	**1.39**	1.12	1.71	**1.44**	1.14	1.82	**0.92**	0.69	1.21
Others	**1.64**	1.58	1.70	**1.56**	1.51	1.60	**1.06**	1.03	1.10	**1.69**	1.49	1.92	**1.95**	1.71	2.23	**1.20**	1.02	1.42

asMRR, age-standardized mortality rate ratio; CI, confidence interval. [a]Mortality trend ratio per 10 years. A trend ratio of 1.13 implies a 13% increase in the diabetes-associated excess mortality per 10 years.

Table 2: **Cause-specific age-standardized mortality rate ratios (asMRRs) for 2002–10 and 2011–2019, respectively, and trend ratio per 10 years (indicating the relative change in excess mortality) for individuals with diabetes (type 2 or type 1 diabetes) compared to individuals without diabetes, stratified by sex.**

variations were observed, with men experiencing stable diabetes-related excess mortality over the study period, except for dementia. In contrast, women consistently faced widening diabetes-related mortality gaps for all causes of death, excluding cardiovascular disease. Steeper declines in all-cause mortality in men compared to women with T2D have previously been reported in the US.[3] Initial improvements in overall and cardiovascular mortality among individuals with diabetes in the latter part of the last century have mainly enhanced survival in men, without similar benefits being observed in women.[16] Hence, it is disconcerting that our results suggest a persistent and widening adverse impact of diabetes on mortality in women, while the mortality trend among men with T2D mirrors that of men without diabetes.

The transition to cancer as the predominant cause of death in those with T2D aligns with earlier population-

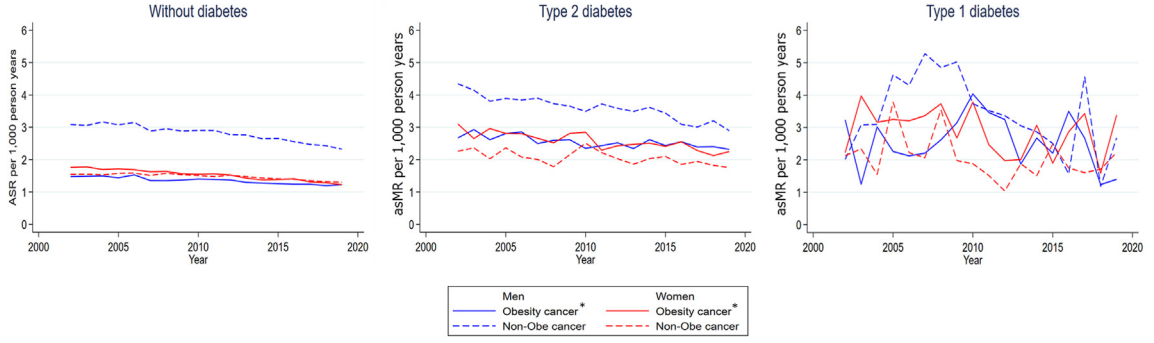

Fig. 2: **Age-standardized mortality rates per 1000 person-years (asMR) for obesity related and non-obesity related cancer in individuals without diabetes, with type 2 diabetes, and type 1 diabetes, stratified by sex**. *Obesity related cancer was defined as cancer in the following organs: Esophagus, upper stomach, colorectal, liver, gallbladder/biliary tract, pancreas, breast cancer (diagnosed >50 years), uterus, ovary, kidney, thyroid, multiple myeloma, and meningioma.

	Without diabetes									Type 2 diabetes										Type 2 diabetes vs without diabetes								
	2002–10			2011–19			2002–19			2002–10			2011–19			2002–19				2002–10			2011–19			2002–19		
	asMR	95% CI		asMR	95% CI		Trend[a]	95% CI		asMR	95% CI		asMR	95% CI		Trend[a]	95% CI			asMRR	95% CI		asMRR	95% CI		Trend ratio[b]	95% CI	
Men																												
Obesity related																												
Esophagus cancer	**1.66**	1.59	1.73	**1.57**	1.51	1.64	**0.90**	0.86	0.96	**2.13**	1.79	2.48	**1.99**	1.76	2.22	**0.95**	0.81	1.10	**1.29**	1.09	1.52	**1.26**	1.12	1.43	**1.05**	0.89	1.23
Stomach cancer	**1.48**	1.41	1.55	**1.32**	1.26	1.38	**0.91**	0.86	0.97	**1.92**	1.66	2.19	**1.81**	1.59	2.03	**0.93**	0.79	1.09	**1.30**	1.12	1.51	**1.37**	1.20	1.56	**1.02**	0.86	1.21
Colorectal cancer	**6.20**	6.05	6.34	**4.85**	4.74	4.97	**0.75**	0.73	0.78	**8.01**	7.49	8.53	**6.74**	6.3	7.18	**0.74**	0.69	0.80	**1.29**	1.21	1.39	**1.39**	1.30	1.49	**0.99**	0.91	1.08
Liver cancer	**0.86**	0.81	0.91	**1.07**	1.02	1.12	**1.20**	1.12	1.29	**3.56**	3.21	3.91	**3.83**	3.55	4.11	**1.05**	0.94	1.17	**4.13**	3.68	4.63	**3.58**	3.28	3.91	**0.87**	0.76	0.99
Gallbladder/biliary tract	**0.27**	0.24	0.30	**0.28**	0.26	0.31	**1.02**	0.89	1.17	**0.61**	0.44	0.79	**0.49**	0.37	0.6	**0.81**	0.61	1.09	**2.26**	1.66	3.07	**1.72**	1.33	2.22	**0.79**	0.57	1.10
Pancreatic cancer	**2.00**	1.92	2.08	**1.98**	1.90	2.05	**0.97**	0.93	1.02	**7.17**	6.62	7.71	**6.92**	6.47	7.37	**0.95**	0.88	1.03	**3.58**	3.29	3.90	**3.50**	3.25	3.77	**0.98**	0.89	1.08
Kidney cancer	**1.05**	1.00	1.11	**0.82**	0.78	0.87	**0.75**	0.7	0.81	**1.86**	1.59	2.12	**1.73**	1.52	1.93	**0.93**	0.79	1.09	**1.77**	1.51	2.06	**2.10**	1.84	2.40	**1.24**	1.04	1.48
Multiple myeloma	**0.68**	0.63	0.72	**0.72**	0.68	0.77	**1.00**	0.92	1.09	**0.94**	0.75	1.13	**0.77**	0.65	0.9	**0.81**	0.64	1.01	**1.38**	1.11	1.71	**1.07**	0.89	1.27	**0.80**	0.63	1.02
Non-obesity related																												
Oral/Pharyngeal cancer	**1.31**	1.25	1.37	**1.25**	1.20	1.31	**0.95**	0.89	1.00	**1.49**	1.05	1.93	**1.17**	1.00	1.33	**0.96**	0.79	1.18	**1.14**	0.84	1.55	**0.93**	0.8	1.08	**1.02**	0.83	1.26
Lung cancer	**11.6**	11.4	11.8	**9.19**	9.03	9.35	**0.75**	0.73	0.76	**14.7**	14.0	15.5	**12.7**	12.2	13.2	**0.81**	0.76	0.85	**1.27**	1.20	1.34	**1.38**	1.32	1.45	**1.08**	1.02	1.15
Urinary tract cancer	**2.55**	2.46	2.65	**1.97**	1.90	2.05	**0.73**	0.70	0.77	**2.86**	2.55	3.17	**2.51**	2.29	2.73	**0.78**	0.68	0.88	**1.12**	1.00	1.26	**1.27**	1.15	1.4	**1.06**	0.93	1.21
Malignt melanoma	**0.77**	0.72	0.82	**0.83**	0.78	0.87	**1.01**	0.93	1.09	**0.97**	0.69	1.25	**1.04**	0.89	1.19	**1.14**	0.91	1.42	**1.26**	0.93	1.7	**1.26**	1.08	1.48	**1.13**	0.89	1.42
Sarcoma	**0.64**	0.59	0.68	**0.70**	0.65	0.74	**1.04**	0.95	1.13	**0.75**	0.58	0.92	**0.74**	0.60	0.89	**1.05**	0.82	1.35	**1.18**	0.93	1.5	**1.07**	0.87	1.31	**1.01**	0.78	1.32
CNS cancer	**1.12**	1.07	1.18	**1.20**	1.14	1.25	**1.06**	0.99	1.13	**3.02**	2.24	3.79	**2.17**	1.87	2.46	**0.89**	0.76	1.04	**2.69**	2.05	3.51	**1.81**	1.57	2.09	**0.85**	0.72	1.00
Non-Hodgkin lymphoma	**1.16**	1.10	1.22	**1.01**	0.95	1.06	**0.81**	0.76	0.87	**1.90**	1.45	2.34	**1.19**	0.98	1.39	**0.67**	0.56	0.80	**1.63**	1.28	2.09	**1.18**	0.98	1.41	**0.82**	0.68	0.99
Leukemia	**1.58**	1.51	1.66	**1.47**	1.41	1.54	**0.88**	0.83	0.93	**1.84**	1.57	2.12	**1.65**	1.34	1.96	**0.81**	0.69	0.95	**1.16**	1.00	1.36	**1.12**	0.92	1.36	**0.92**	0.77	1.09
Prostate cancer	**7.89**	7.73	8.06	**6.95**	6.80	7.09	**0.83**	0.81	0.85	**8.47**	7.93	9.00	**7.55**	7.18	7.92	**0.83**	0.78	0.90	**1.07**	1.00	1.15	**1.09**	1.03	1.15	**1.00**	0.93	1.09
Ill-defined cancer	**2.90**	2.81	3.00	**2.21**	2.13	2.29	**0.71**	0.68	0.74	**4.71**	4.27	5.15	**3.31**	2.98	3.64	**0.65**	0.59	0.72	**1.62**	1.47	1.79	**1.50**	1.35	1.67	**0.92**	0.82	1.03
Other cancer	**1.03**	0.97	1.08	**1.20**	1.14	1.25	**0.94**	0.89	0.99	**1.74**	1.29	2.19	**2.02**	1.68	2.36	**1.02**	0.88	1.18	**1.70**	1.29	2.23	**1.69**	1.42	2.02	**1.08**	0.93	1.27
Women																												
Obesity related																												
Esophagus cancer	**0.53**	0.50	0.57	**0.46**	0.43	0.49	**0.86**	0.79	0.94	**0.44**	0.31	0.57	**0.51**	0.40	0.61	**1.11**	0.81	1.51	**0.82**	0.6	1.12	**1.10**	0.88	1.37	**1.29**	0.94	1.78
Stomach cancer	**0.70**	0.66	0.74	**0.58**	0.55	0.62	**0.81**	0.75	0.88	**1.14**	0.84	1.43	**0.93**	0.75	1.11	**0.84**	0.67	1.06	**1.63**	1.24	2.14	**1.59**	1.30	1.95	**1.04**	0.82	1.32
Colorectal cancer	**4.42**	4.32	4.52	**3.50**	3.42	3.59	**0.77**	0.75	0.80	**5.69**	5.23	6.16	**4.38**	4.07	4.70	**0.77**	0.70	0.84	**1.29**	1.18	1.40	**1.25**	1.16	1.35	**1.00**	0.90	1.10
Lever cancer	**0.45**	0.42	0.48	**0.57**	0.53	0.60	**1.26**	1.16	1.38	**1.12**	0.9	1.34	**1.41**	1.22	1.61	**1.25**	1.03	1.52	**2.48**	2.01	3.07	**2.49**	2.14	2.89	**0.99**	0.80	1.23
Gallbladder/biliary tract	**0.32**	0.29	0.34	**0.31**	0.29	0.34	**0.97**	0.87	1.09	**0.58**	0.43	0.73	**0.58**	0.46	0.70	**1.05**	0.79	1.39	**1.84**	1.4	2.41	**1.84**	1.47	2.3	**1.08**	0.79	1.46
Pancreatic cancer	**1.77**	1.70	1.83	**1.71**	1.65	1.77	**0.99**	0.94	1.04	**6.11**	5.56	6.66	**6.10**	5.7	6.51	**1.10**	1.00	1.20	**3.46**	3.14	3.81	**3.57**	3.31	3.85	**1.11**	1.00	1.23
Kidney cancer	**0.53**	0.50	0.57	**0.38**	0.36	0.41	**0.72**	0.65	0.79	**1.34**	1.07	1.60	**0.89**	0.74	1.04	**0.71**	0.57	0.87	**2.52**	2.04	3.11	**2.31**	1.92	2.79	**0.98**	0.78	1.24
Multiple myeloma	**0.46**	0.42	0.49	**0.43**	0.40	0.46	**0.95**	0.86	1.04	**0.49**	0.36	0.62	**0.49**	0.39	0.60	**1.07**	0.79	1.44	**1.07**	0.80	1.43	**1.15**	0.91	1.44	**1.13**	0.83	1.54
Breast cancer >50 yrs	**4.65**	4.55	4.75	**3.60**	3.52	3.69	**0.75**	0.73	0.77	**6.97**	6.46	7.47	**5.13**	4.81	5.46	**0.77**	0.71	0.84	**1.50**	1.39	1.62	**1.43**	1.33	1.52	**1.03**	0.94	1.13
Uterus cancer	**0.77**	0.73	0.81	**0.64**	0.61	0.68	**0.81**	0.75	0.87	**1.52**	1.27	1.77	**1.35**	1.16	1.54	**0.86**	0.72	1.03	**1.99**	1.67	2.36	**2.10**	1.80	2.45	**1.07**	0.88	1.29
Ovary cancer	**1.95**	1.88	2.02	**1.55**	1.49	1.61	**0.76**	0.72	0.80	**2.24**	1.88	2.6	**1.69**	1.46	1.92	**0.80**	0.68	0.94	**1.15**	0.97	1.36	**1.09**	0.95	1.25	**1.05**	0.89	1.25
Non-obesity related																												
Oral/Pharyngeal cancer	**0.52**	0.49	0.56	**0.46**	0.43	0.50	**0.86**	0.79	0.93	**0.62**	0.45	0.79	**0.58**	0.44	0.72	**0.96**	0.71	1.29	**1.18**	0.89	1.57	**1.25**	0.97	1.61	**1.09**	0.80	1.49
Lung cancer	**8.01**	7.88	8.15	**7.44**	7.31	7.56	**0.93**	0.91	0.95	**9.88**	9.20	10.3	**9.84**	9.34	10.6	**1.07**	1.00	1.15	**1.23**	1.15	1.32	**1.32**	1.25	1.39	**1.16**	1.08	1.25
Urinary tract cancer	**0.86**	0.82	0.90	**0.70**	0.66	0.74	**0.80**	0.74	0.85	**1.08**	0.89	1.27	**0.83**	0.71	0.96	**0.74**	0.60	0.91	**1.26**	1.05	1.51	**1.19**	1.01	1.40	**0.93**	0.75	1.15
Malignt melanoma	**0.50**	0.47	0.54	**0.51**	0.47	0.54	**0.97**	0.88	1.05	**0.62**	0.38	0.85	**0.54**	0.41	0.67	**1.28**	0.94	1.75	**1.23**	0.82	1.85	**1.07**	0.83	1.37	**1.33**	0.96	1.83
Sarcoma	**0.29**	0.27	0.32	**0.30**	0.28	0.33	**1.15**	1.02	1.29	**0.55**	0.34	0.76	**0.35**	0.25	0.46	**0.84**	0.59	1.19	**1.89**	1.26	2.85	**1.17**	0.85	1.60	**0.73**	0.51	1.06

(Table 3 continues on next page)

	Without diabetes							Type 2 diabetes							Type 2 diabetes vs without diabetes						
	2002-10		2011-19		2002-19			2002-10		2011-19		2002-19			2002-10		2011-19		2002-19		
	asMR	95% CI	asMR	95% CI	Trend[a]	95% CI		asMR	95% CI	asMR	95% CI	Trend[a]	95% CI		asMRR	95% CI	asMRR	95% CI	Trend ratio[b]	95% CI	
(Continued from previous page)																					
CNS cancer	**0.80**	0.76	0.84	**0.80**	0.76	0.85	**1.02**	0.95	1.10	**1.81**	1.40	2.21	**1.49**	1.24	1.74	**0.97**	0.79	1.18	**2.25**	1.78	2.85	**1.85**	1.55	2.21	**0.94**	0.76	1.17
Non-Hodgkin lymphoma	**0.74**	0.70	0.78	**0.58**	0.55	0.61	**0.77**	0.71	0.83	**1.23**	0.95	1.51	**0.73**	0.61	0.84	**0.75**	0.60	0.93	**1.66**	1.31	2.10	**1.26**	1.06	1.49	**0.97**	0.77	1.23
Leukemia	**0.91**	0.86	0.95	**0.80**	0.76	0.84	**0.87**	0.81	0.93	**1.05**	0.84	1.25	**1.20**	1.02	1.38	**1.09**	0.89	1.32	**1.15**	0.94	1.41	**1.50**	1.28	1.76	**1.25**	1.02	1.54
Breast cancer <50 yrs	**1.26**	1.21	1.32	**1.03**	0.98	1.08	**0.81**	0.76	0.86	**2.31**	1.76	2.86	**1.87**	1.52	2.22	**0.80**	0.62	1.02	**1.83**	1.43	2.34	**1.81**	1.49	2.20	**0.98**	0.76	1.27
Cervix cancer	**0.58**	0.54	0.62	**0.43**	0.40	0.46	**0.70**	0.64	0.77	**0.89**	0.62	1.17	**0.59**	0.43	0.75	**0.69**	0.51	0.92	**1.54**	1.11	2.12	**1.36**	1.02	1.81	**0.98**	0.72	1.34
Ill-defined cancer	**2.59**	2.52	2.67	**2.20**	2.13	2.27	**0.83**	0.80	0.87	**3.85**	3.46	4.24	**3.26**	2.98	3.55	**0.88**	0.79	0.98	**1.48**	1.34	1.65	**1.48**	1.35	1.62	**1.06**	0.94	1.19
Other cancer	**0.91**	0.87	0.96	**0.96**	0.91	1.00	**1.04**	0.99	1.11	**1.24**	1.00	1.49	**1.28**	1.10	1.45	**1.06**	0.90	1.25	**1.56**	1.26	1.94	**1.43**	1.24	1.64	**1.02**	0.85	1.21

asMR, age-standardized (to the 2002 population) mortality rate. CI, confidence interval. CNS, central nervous system. [a]Trend in mortality per 10 years. A value of 1.02. means that a (relative) trend increase 2% in rate per ten years. [b]Mortality trend ratio per 10 years. A trend ratio of 1.13 implies a 13% increase in the diabetes-associated excess mortality per 10 years.

Table 3: **Cancer-specific age-standardized (to 2002 population) mortality rates per 1000 person years (asMR) for 2002–10 and 2011–19, respectively, along with trends in mortality per 10 years for 2002–2019, stratified by diabetes status and sex. Also includes comparisons of mortality rate ratios and trend ratios between those with type 2 diabetes and those without diabetes.**

based studies.[4,7] However, this pattern was not observed in cohort studies of NHANES participants in the US.[17]

Higher cancer mortality could be attributed to a combination of higher cancer incidence and poorer prognosis in individuals with diabetes. Diabetes is strongly associated with higher cancer incidence due to shared risk factors like aging, obesity, and physical inactivity, as well as biological pathways involving hyperinsulinemia, hyperglycemia, and inflammation.[8,9,18,19] Given the known correlation between obesity, T2D, and specific cancers,[18] we expected the observed higher mortality from obesity-related cancers in those with T2D. The rise of GLP-1 receptor agonists for weight loss in Denmark post-study suggests the need for future research on their impact on obesity-related cancer incidence and fatality rates.

However, we also found that diabetes was associated with an increased mortality risk for non-obesity-related cancers. Several common risk factors are shared between diabetes and specific non-obesity-related cancers. For instance, smoking is an important risk factor for lung cancer, which displayed the highest cancer-related asMR for both men and women with T2D in our study, as well as being a risk factor for diabetes.[20]

Regarding cancer mortality, the excess risk of dying from cancer linked with diabetes is well established,[5] including an excess cancer-related mortality risk linked to obesity.[21] The heightened likelihood of a fatal cancer outcome in individuals with diabetes may stem from a broad variety of underlying mechanisms such as a lower uptake of cancer screening including later stage cancer diagnoses,[22] risk factors for diabetes complicating cancer treatment (eg, smoking, overweight, physical inactivity), more comorbidities,[23] and potential biological mechanisms, such as hyperglycemia and chronic inflammation, which may increase the risk of a worse cancer outcome.[19]

The notable increase in dementia-associated asMRs for both men and women with T2D aligns with prior findings in England by Pearson-Stuttard et al.[7] This trend was anticipated considering the reduced risk of death from other causes, typically occurring earlier in life, and the shared risk factors between diabetes and dementia.[24] Although dementia-related asMRs also rose for those without diabetes, our study revealed a 15% higher increase per decade in individuals with T2D compared to those without diabetes. Given the escalating prevalence of both diabetes and dementia, this holds potential public health implications.

The study's strengths lie in its nationwide cohort, virtually eliminating selection bias, and a register-based approach, ensuring minimal loss to follow-up. The extensive cohort facilitated investigating cause-specific deaths in both T2D and T1D populations, especially cancer-related mortality in T2D. Utilizing a time-dependent exposure approach for diabetes allowed a dynamic cohort study design. Validated algorithms

effectively distinguished between T1D and T2D. Additionally, comparing estimates to a diabetes-free reference group enhanced the study compared to those comparing diabetes mortality rates to those of the entire population.

The study faced some limitations. Using administrative databases for research purposes involves known challenges of coding variation and misclassification. The low autopsy rate in Denmark (around 2.5%) can contribute to potential misclassifications in the registered cause of death.[25] However, cancer coding accuracy in Denmark remains high (positive predictive values of 98–100%),[26] and concordance with autopsy-confirmed cases is substantial at 81%.[27] While coding practices for individual causes of death may have changed over our nearly 20 years study period, this is unlikely to be associated with diabetes status.

During the study period, Denmark introduced the use of a HbA1c cut-point as a diagnostic criterion for diabetes. Increases in screening activity, because a fasting blood sample was no longer needed, might result in decreasing mortality in the diabetes population due to earlier diagnosis of diabetes, thus introducing lead-time bias.[2] However, mortality among newly diagnosed individuals with T2D in Denmark increased after adoption of the HbA1c criterion, suggesting delayed diagnosis at a more advanced disease stage.[28]

The study carries a risk of reverse causality, given the uncertainty about diabetes duration before death. For example, a notable excess risk of CNS cancer-related mortality was evident in individuals with T2D in this study, however, a direct link between T2D and increased CNS cancer incidence has not been identified.[29] Therefore, the diabetes-related excess mortality might reflect the presence of diabetes secondary to high dose steroid treatment in patients with CNS cancer. Further studies using an incident diabetes cohort and excluding cancers diagnosed in the first years after inclusion, may elucidate this issue.

Lastly, sex-specific mortality risks and the association between T2D and cancer mortality may be influenced by socioeconomic status,[30] however, socioeconomic data were not accessible for this study, and investigating the causal pathways driving the observed trends was beyond the scope of this paper. Further research incorporating causal interference is warranted to elucidate the underlying mechanisms driving these trends in mortality.

Implications

The ascendance of cancer as the predominant cause of death among individuals with T2D in Denmark emphasizes the necessity of diabetes management strategies integrating cancer prevention. A sex-specific approach is crucial to address the expanding diabetes-related mortality gap in women across various causes of death.

Contributors

Authors TL and SG performed the literature search. Authors TL, SG, and HS performed the data management (all three authors had access to the underlying data reported in the manuscript), the data analysis, and made the first draft of the manuscript. All authors contributed to the study design, data interpretation, and writing of the manuscript.

Data sharing statement

The data that support the findings of this study are available from The Danish Health Data Authority's Research Services but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Access to data may be obtained with permission of The Danish Health Data Authority through a collaboration with a Danish research institution.

Declaration of interests

HS has received personal consulting fees from Novartis, Pfizer, Neumirna and Merck Sharpe & Dome within the last 36 months unrelated to the present study. The remaining authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100909.

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