Duration of type 2 diabetes and incidence of cancer: an observational study in England

Running title: Age, diabetes duration, and risk of cancer

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ABSTRACT

Objective

To investigate the association between duration of type 2 diabetes and cancer incidence.

Research Design and Methods

In the Clinical Practice Research Datalink database, we identified 130,764 individuals with type 2 diabetes aged ≥35 years at diagnosis linked to hospital and mortality records. We used sex-stratified Royston-Parmar models with two time scales to estimate incidence rates of all cancers, the four commonest cancers in the UK (colorectal, lung, prostate, breast), and the obesity-related cancers (e.g., liver, ovary) between 1/1/1998 and 14/1/2019, by age and diabetes duration.

Results

During 1,089,923 person-years, 18,977 incident cancers occurred. At the same age, in men and women rates of all cancers did not vary across durations ranging from diagnosis to 20 years; conversely, for any duration, there was a strong, positive association between age and cancer rates. In men, the rate ratio comparing 20 to 5 years of duration was 1.18 (95% CI: 0.82, 1.69) at 60 years of age and 0.90 (0.75, 1.08) at 80 years; corresponding ratios in women were 1.07 (0.71, 1.63) and 0.84 (0.66, 1.05). This pattern was observed also for the four commonest cancers. For obesity-related cancers, although rates were generally higher in individuals with a higher body mass index, there was no association with duration at any level of body mass index.

Conclusions

In this study, we did not find evidence of an association between duration of type 2 diabetes and risk of cancer, with the higher risk observed for longer durations related to ageing.

ARTICLE HIGHLIGHTS

- While a longer duration of type 2 diabetes has been associated with a higher risk of vascular events, the relationship with the risk of cancer is less clear.

- Is duration of type 2 diabetes associated with a higher risk of cancer incidence?

- The greater risk of several cancers, including obesity-related cancers, for longer diabetes durations is an epiphenomenon of the parallel ageing: chronological age, not duration *per se*, is associated with the risk of cancer.

- Strategies to prevent cancer in individuals with diabetes should be guided by individual's age and not diabetes duration.

Improvements in the risk stratification and personalised strategies for early identification and treatment of cardiovascular risk factors have contributed to the reducing morality trends and rising life expectancies in people with type 2 diabetes during the last two decades.(1-6) These epi-demographic changes have likely contributed to the phenotypical shift in the trajectories of morbidities and causes of death in people with type 2 diabetes: growing evidence has indeed shown that non-cardiovascular diseases represent an increasingly more frequent cluster of complications in individuals with type 2 diabetes, particularly in older individuals.(7; 8) Among these complications, cancer is emerging as an important morbidity,(9) possibly overtaking cardiovascular disease as the leading cause of excess deaths in individuals with diabetes.(8) While a robust and extensive observational literature has reported increased risks of several cancers in people with type 2 diabetes,(10; 11) the strength of associations is higher for some (e.g., pancreatic, liver) than other (e.g., lung) cancers.(10) In line with pre-clinical studies,(9; 12) a higher body mass index (BMI) – one of the strongest risk factors for type 2 diabetes(13) – results in an insulin resistance/hyperinsulinemia milieu which could enhance mitogenesis and risk of oncogenesis.(12)

A longer life expectancy in individuals with type 2 diabetes may also contribute to a longer disease duration and a prolonged exposure to insulin resistance/hyperinsulinemia, potentially explaining the higher risk of cancer incidence and mortality observed in older individuals with diabetes.(7; 14) However, as a longer disease duration necessarily results in an older age, which is a risk factor for cancer, a higher risk in individuals with a longer duration may simply reflect ageing. Therefore, to investigate whether diabetes duration is a risk factor for cancer, both the duration itself and the (isochronous) increase in chronological age should be accounted for.

There is some evidence on the association between diabetes duration and risk of cardiorenal diseases or all-cause/cause-specific mortality – with longer durations generally linked to higher risks.(15-19) However, the available evidence about diabetes duration and cancer incidence remains sparse;(20-27) this information is important for developing and optimising the design of early detection strategies for cancer. In this study, we aimed to disentangle the association of age and diabetes duration with the risk of incident cancer in people with type 2 diabetes. To corroborate our results, we also detailed associations with cancers that are currently considered causally linked to a higher body fat, given the

postulated role of insulin resistance/hyperinsulinemia in the risk of cancer in people with type 2 diabetes.(9)

RESEARCH DESIGN AND METHODS

This study followed a pre-registered protocol, approved by the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (No. 19_120Mn) before data were made available, and has been reported in line with the RECORD guidelines (Supplementary Material).

Data sources

We identified a cohort of individuals with type 2 diabetes in the UK within the CPRD GOLD database, which routinely collects de-identified primary care patient data; CPRD is representative of the national population in terms of age, sex, and ethnicity.(28) Individual-level information is linked to the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) death registrations data to extract details on hospitalisations and date and cause of death, respectively, based on the International Classification of Diseases (ICD) codes. Linkages are available only for patients in England.

Study design and participants

The flowchart of the cohort definition is shown in Supplementary Figure S1. In CPRD, we first extracted data on all individuals with a first-ever diagnosis code of type 2 diabetes between 1/Jan/1998 and 30/Nov/2018 (i.e., the date of type 2 diabetes diagnosis - index date), aged ≥35 years and registered with an up-to-standard practice for a minimum of 1 year at the index date, and with linkages to HES and ONS. We then excluded individuals with a CPRD diagnosis code of type 2 diabetes after death, on the same day of death, or on the last day of the CPRD cohort definition (30/Nov/2018), as well as those who had a code of type 2 diabetes in HES and were younger than 35 years at the time of coding. To rule out potential diabetes misclassification by clinical coding, we further excluded individuals with a code of type 1 diabetes any time in either CPRD or HES. Lastly, as the main outcome was cancer incidence, we excluded individuals with a cancer diagnosis in HES before the first-ever diagnosis code of type 2 diabetes in CPRD or HES, leaving 130,764 individuals for the analyses.

Exposures and outcomes

Information on the two main exposures, age at type 2 diabetes diagnosis and BMI, were extracted from CPRD. Age at diagnosis was estimated as the difference between the calendar date at type 2 diabetes diagnosis and the date of birth. Data on BMI were extracted using the values of the closest date before the index date; BMIs were categorised as underweight (BMI <18.5 kg/m^2), healthy weight (≥18.5 to <25 kg/m^2), overweight (≥25 to <30 kg/m^2), and obesity class 1 (≥30 to <35 kg/m^2), class 2 (≥35 to <40 kg/m^2), or class 3 (≥40 kg/m^2).

To identify incident cancers following index date, we used the first ever ICD codes (C00-C97, except non-melanoma skin cancer [C44]) in any position in hospital (HES) or death (ONS) records. We investigated cancer incidence rates for all cancers, the four commonest cancers in the UK (lung [C34], colorectal [C18-C20], breast [C50], and prostate [C61]), and for cancers which are considered causally linked to higher body fat (breast, colorectal, endometrial, gallbladder, gastric cardia, kidney, liver, multiple myeloma, oesophagus, ovary, pancreas, thyroid; Supplementary Table S1).(29) Individuals were followed from the index date until the occurrence of cancer, death, or the end of study (linkage date of HES data, 30/Nov/2018), whichever occurred first.

Statistical analysis

We reported the baseline characteristics at index date, stratified by sex and age at type 2 diabetes diagnosis (<40, ≥40 to <50, … , ≥70 to <80, and ≥80 years), as median and interquartile range (IQR) for continuous variables and numbers and proportions for categorical ones; similarly, we estimated cancer incidence rates by sex and age at diagnosis.

During the follow-up from diabetes diagnosis until cancer incidence or right-censoring, both duration of diabetes and age increase by the same amount: for example, in an individual diagnosed at 40.5 years, the attained age (i.e., the current/chronological age whilst the individual is followed up in the study) after 5.5 years of follow-up (or, equivalently, after 5.5 years of diabetes duration) is 46 years; similarly, the attained age is also 46 years in another subject diagnosed at 39 years with 7 years of diabetes duration. As the follow-up occurs across two time scales, we modelled both scales to disentangle the association of age and diabetes duration with cancer incidence:(30) we employed a Royston-Parmar survival model with a continuous, nonlinear main effect for both time scales using a restricted cubic

spline with five knots and a two-way interaction between the timescales. This approach allowed us to investigate the (time-varying) association of diabetes duration (from diagnosis until 20 years) on the cancer incidence rates by attained age (50 to 100-year-old) and age at diagnosis (50 to 80-year-old), thus separating the role of each of these three factors on the risk of cancer. In the analyses of obesity-related cancers, we estimated incidence rates in all BMI groups except <18.5 kg/m^2 (given the very small number of events/individuals in this group) and included an interaction between BMI and each of the two time scales, allowing for the association of BMI to vary across diabetes duration and attained age.

In sensitivity analyses, we re-estimated the incidence rates: (1) for all and the four commonest cancers, after excluding individuals with a BMI <18.5 kg/m^2 (to reduce the risk of diabetes misclassification) and a follow-up shorter than 2 years (to reduce the risk of reverse causation and detection bias);(27) (2) for and obesity-related cancers, after excluding individuals with follow-up shorter than 2 years.

All analyses, conducted in Stata (18.0 MP, SPECTRE High Performance Computing Facility, University of Leicester), were stratified by sex; results are reported with 95% confidence interval (CI).

RESULTS

Population characteristics

The characteristics at type 2 diabetes diagnosis of the 130,764 individuals included in our study are summarised in Table 1: women accounted for 44.3% and the median age was 61.8 (IQR: 52.8-70.6) years in men and 65.6 (55.2-75.0) in women. At diagnosis, the BMI was slightly higher in women (31.2 kg/m^2) than men (30.2 kg/m^2), with values of BMI ≥30 kg/m^2 in 51.9% and 57.9% of men and women, respectively. Regardless of sex, there was an inverse relationship between age at diagnosis and BMI, ranging from a median of 32.5 kg/m^2 in men younger than 40 years to 27.3 kg/m^2 in those aged 80 years or more; corresponding figures in women were 36.4 and 27.4 kg/m^2.

Cancer incidence

During a median follow-up of 8.0 (IQR: 4.6-11.9) years and a total of 1,089,923 person-years of observation, 18,977 (14.5%) incident cancers were recorded: 11,146 (15.3%) in men and 7,831 (13.5%) in women. The crude incidence rate was 17.4 (95% CI: 17.2, 17.7) per 1,000 person-years, slightly higher in men (18.3) than women (16.3). Table S2 reports the numbers of all cancers and cancer-specific incident events and rates stratified by sex and age at diabetes diagnosis: in both men and women, incidence rates of all cancers were progressively higher in individuals diagnosed at older ages, increasing from 1.9 (95% CI: 1.4, 2.6) per 1,000 person-years in men younger than 40 years at diagnosis to 49.4 (46.7, 52.3) in those aged 80 years or more; corresponding estimates in women were 3.5 (2.6, 4.5) and 28.7 (27.1, 30.3). This pattern was also observed for obesity-related and the four commonest cancers, albeit the absolute rates varied (generally higher for the two sex-specific cancers; Table S2).

All cancers

For all cancers, incidence rates decreased within the first one or two years from type 2 diabetes and progressively increased thereafter, particularly in individuals diagnosed at younger age, in both men (Figure 1A) and women (Figure 2A). Rates were also: (i) higher for older attained age but largely overlapping across varying diabetes duration (men, Figure 1B; women, Figure 2B); (ii) higher for older

attained age and for age at diagnosis (Figure 1D and 2D); (iii) for the same attained age, virtually identical across varying diabetes duration (Figure 1C and 2C).

In men, incidence rates of all cancers at an attained age of 50 years were 2.9 (95% CI: 2.5, 3.3) and 1.7 (0.4, 7.5) per 1,000 person-years for diabetes durations of 5 and 20 years, respectively; at 60 years, 8.1 (7.6, 8.7) and 9.5 (6.7, 13.7); at 70 years, 20.0 (19.0, 21.0) and 18.4 (15.0, 22.5); at 80 years, 37.3 (35.3, 39.4) and 33.6 (28.0, 40.2); at 90 years, 50.5 (45.7, 55.7) and 48.3 (36.9, 63.2); and at 100 years, 59.6 (42.8, 83.0) and 45.9 (18.9, 111.6) (Figure S2). These estimates translated into incidence rate ratios, comparing 20 to 5 years of diabetes duration, of 0.60 (95% CI: 0.14, 2.63) at an attained age of 50 years; 1.18 (0.82, 1.69) at 60 years; 0.92 (0.75, 1.13) at 70 years; 0.90 (0.75, 1.08) at 80 years; 0.96 (0.73, 1.26) at 90 years; and 0.77 (0.31, 1.92) at 100 years (Figure 3).

Although the absolute rates differed, the pattern was mirrored in women, with rates largely related to the attained age (increasing in older individuals) but similar for the same attained age and varying durations. Incidence rates of all cancers at an attained age of 50 years were 4.3 (95% CI: 3.8, 5.0) and 10.4 (3.1, 34.8) per 1,000 person-years for diabetes durations of 5 and 20 years, respectively; at 60 years, 9.9 (9.1, 10.7) and 10.6 (7.1, 16.0); at 70 years, 16.2 (15.2, 17.1) and 14.6 (11.3, 18.8); at 80 years, 21.3 (20.1, 22.6) and 17.8 (14.2, 22.2); at 90 years, 27.3 (25.0, 29.8) and 20.3 (15.2, 27.1); and at 100 years, 35.3 (26.3, 47.4) and 26.3 (10.3, 66.7) (Figure S2). These estimates translated into incidence rate ratios, comparing 20 to 5 years of diabetes duration, of 2.40 (95% CI: 0.70, 8.25) at an attained age of 50 years; 1.07 (0.71, 1.63) at 60 years; 0.90 (0.69, 1.18) at 70 years; 0.84 (0.66, 1.05) at 80 years; 0.74 (0.55, 1.00) at 90 years; and 0.74 (0.28, 1.95) at 100 years (Figure 3).

Four commonest cancers

As for all cancers, incidence rates of the four commonest cancers in the UK were greater in older individuals but overlapped across diabetes durations, for the same attained age (Figure S2). In men, there was no evidence of higher incidence rates at 20 compared to 5 years of diabetes duration for colorectal, lung, and prostate cancer (i.e., all confidence intervals of the rate ratios crossed 1; Figure 3), regardless of the attained age. Likewise, incidence rates of the four commonest cancers in women were similar across diabetes duration (Figure S2), with no differences comparing 20 to 5 years of diabetes

duration, except: (i) for colorectal cancer, as at an attained age of 80 years the incidence rate was higher at 5 [3.3 (95% CI: 2.8, 3.9) per 1,000 person-years] than 20 years [0.8 (0.3, 1.7); Figure S2] of duration, equating to a rate ratio – comparing 20 to 5 years – of 0.24 (0.11, 0.54; Figure 3); (ii) for lung cancer, as at an attained age of 90 years corresponding figures were: 3.1 (2.4, 4.1), 1.1 (0.4, 3.0), and 0.34 (0.12, 0.95) (Figure S2 and Figure 3).

Obesity-related cancers

The pattern found for all and the four commonest cancers was also observed for obesity-related cancers: while the incidence rates were generally higher in individuals with a higher BMI and greater by attained age (men, Figure S3; women, Figure S4), for the same BMI and attained age rates were overlapping across varying diabetes duration (Figure S5). Nominal statistically significant associations, with wide confidence intervals, were observed (Figure S6): (i) in the BMI group ≥18.5 to <25 kg/m^2, incidence rates were higher at 5 than 20 years of diabetes duration, in men (rate ratio comparing 20 to 5 years: 0.34 [95% CI: 0.13, 0.90] and 0.33 [0.13, 0.84] at an attained age of 70 and 80 years, respectively) and in women (0.42 [0.18, 0.97] and 0.40 [0.17, 0.91] at 70 and 90 years, respectively); (ii) in the BMI group ≥35 to <40 kg/m^2, incidence rates were conversely lower at 5 than 20 years in women at an attained age of 50 years (rate ratio comparing 20 to 5 years: 4.89 [1.01, 23.80]).

Sensitivity analysis

After the exclusion of individuals with a BMI <18.5 kg/m^2 and a follow-up shorter than 2 years (n=12,705), the results were virtually identical to those of the main analysis for all cancers (Figure S7) and the four commonest cancers (Figure S8). Similarly, the exclusion of individuals with a follow-up shorter than 2 years (n=11,029) resulted in no difference in the incidence rates of obesity-related cancers (Figure S9).

CONCLUSIONS

In this study of around 130,000 individuals with newly-diagnosed type 2 diabetes, we did not find evidence of an association between diabetes duration and risk of all cancers, the four commonest cancers (colorectal, lung, prostate, breast), and obesity-related cancers; conversely, we observed a strong, positive association between age and cancer incidence irrespective of the diabetes duration. Together, these findings suggest that the previously reported higher risk of cancer in individuals with a longer diabetes duration is likely explained by the older age associated with the longer duration. Whilst in contrast with previous studies showing associations between longer diabetes durations and higher risks of vascular diseases and death, our results have important implications for cancer risk stratification and possibly screening or new early detection strategies in relation to age and diabetes duration, and contribute to elucidate the mechanisms underpinning the temporal associations between type 2 diabetes and certain cancers.

The declining trends in CVD morbidity and mortality occurred during the last 20 years have contributed to the increased life expectancy in individuals with type 2 diabetes,(1-6) who therefore spend longer periods of their life with the condition. This longer duration results in a prolonged exposure to the metabolic abnormalities of type 2 diabetes, including insulin resistance/hyperinsulinemia, which could enhance the risk of carcinogenesis.(9; 12) Yet, a longer disease duration is necessarily associated with an older age; as such, other co-occurring, ageing-related pathophysiological changes can contribute to the higher risk of cancer in individuals with a longer duration. Separating the association of diabetes duration from that of age is therefore essential to disentangle their relative impact. We therefore employed an incident diabetes study design, which has been recommended when the aim is to investigate the role of diabetes duration on the incidence of cancer: this design results in a cohort of individuals followed from their diagnosis, allowing to examine associations for a wide range of ages at diagnosis and diabetes durations.(31) Moreover, we modelled a time-varying association of age and duration using two time scales: this approach has been advocated as the methodology of choice, if not necessary,(30-32) when the aim is specifically to explore the (time-varying) association of continuous age and disease duration with the risk of outcomes, particularly when the evidence suggests that the risk

is expected to be related to both age and duration of the disease, a well-established notion in clinical diabetes.(31-33)

Likely due to the heterogenous designs and analyses, published studies have described associations between diabetes duration and cancer incidence of variable directions and magnitudes;(21-24) this limits the possibility of a comparison with our study. Conversely, our findings can be compared to previous investigations employing the same study design, with follow-up starting from diagnosis. In an incident cohort of people with type 2 diabetes in Canada (1994 to 2006) and in two cohorts with both type 1 and type 2 diabetes in Denmark (1995 to 2009) and Australia (1997 to 2008),(25-27) the investigators reported increased risks of several cancers around the diagnosis of diabetes followed by a reduction and more stable risks thereafter. Notably, these patterns were identical to those observed in our study, with higher rates soon after the diagnosis and a subsequent reduction followed by a plateau until 20 years of diabetes duration, possibly related to a detection bias whereby the suspicion of a cancer would trigger clinical investigations resulting in the diagnosis of diabetes or the diagnosis of diabetes could increase the clinical investigations resulting in a cancer diagnosis.(31) By showing consonant results in a different geographical region (spatial validation) and in a more contemporary cohort (temporal validation, particularly relevant in view of the shift in the long-term complications in individuals with type 2 diabetes during more recent years(7; 8)), our findings further clarify and corroborate the current evidence about the role of age and diabetes duration on the risk of cancer.

Our findings, which indicated the absence of an association between the duration of type 2 diabetes and the risk of incident cancers, are not contradictory to the numerous previous investigations that have shown an increased risk of several cancers in individuals with type 2 diabetes compared to those without.(10; 11) Instead, our results suggested that the elevation in cancer risk may occur earlier in the trajectory of metabolic abnormalities that ultimately lead to (the clinical diagnosis of) type 2 diabetes. In this respect, the results of the analyses examining the impact of obesity on the relationship of age and diabetes duration with the risk of cancer are informative. If an excess in body fat (and, in turn, a greater insulin resistance) is among the potential mechanisms linking type 2 diabetes to cancer,(12) higher incidence rates should be expected in individuals with higher BMIs. While this was generally observed in our study, we did not find evidence of a greater association with a longer diabetes duration

in individuals with higher BMIs, as rates were rather constant up to 20 years of duration within each clinically-relevant BMI group. This observation points towards a different comparative role of insulin resistance and hyperglycaemia on the temporal relationship between diabetes duration and its complications and aligns with the current knowledge on the pathophysiological changes occurring before and after the clinical diagnosis of type 2 diabetes.(34) The lack of an overall association with cancer incidence – and of a differential impact of duration across BMI levels – would indeed indicate that the insulin resistance-related mechanisms enhancing cancer risk would develop earlier in the continuum of the metabolic abnormalities in type 2 diabetes and exert most of their effects well before the clinical, glycaemia-based diagnosis of type 2 diabetes, with a modest or null effect over the course of diabetes after its diagnosis. This would also suggest that the potential "actionable window" to reduce the legacy effects of an excess in body fat/higher insulin resistance occurs earlier than the interventional timeframe to reduce the long-term effects of an uncontrolled hyperglycaemia,(35) with important implications in the research and policy area of cancer prevention and early detection.

Our study has some limitations and strengths. As CPRD data are not primarily collected for research, the quality of diabetes recording has changed over time.(36) To establish the diagnosis date of type 2 diabetes, we relied on the date of the first-ever code associated with the condition; while free testing to evaluate the risk of type 2 diabetes is available for individuals aged 40-74 years in the UK, there may still be instances where gaps exist between the actual diagnosis and the recording of the diagnostic code. We also identified incident cancers in hospital and death records; information from cancer registry – which was not available in our study – may further improve ascertainment for some cancers.(37) Associations are also representative of primary care patients in England who were aged ≥35 years at type 2 diabetes diagnosis: caution should be exercised when generalising these results to other countries or younger individuals. Although unlikely to fully explain the associations between diabetes and cancer and notwithstanding the consistent results in the sensitivity analyses excluding the first 2 years of follow-up, an underlying subclinical cancer may cause in hyperglycaemia (reverse causality), probably driving some of the early increase in the cancer incidence rates around the diagnosis of diabetes.(31) The heterogeneity of cancer biology would also suggest that directions and magnitudes of the observed associations could vary across cancers of different sites. We focused on cancer incidence; the pattern

for cancer mortality may be different, as several factors following cancer diagnosis (e.g., treatment) could have a relatively greater impact than diabetes duration on the risk of all-cause/cancer-specific mortality. Lastly, we did not explore the role of other risk factors (e.g., smoking, socioeconomic status, HbA1c, glucose-lowering medications) which could have confounded the association between duration and cancer. Strengths of our study include: modelling relative and absolute differences, the latter being easier to interpret for the individual patient and more relevant from a public health perspective;(38) the incident cohort design, with follow-up since diabetes diagnosis;(31) the simultaneous use of two time scales;(31) and the linkage to HES and ONS to identify incident cancers.(39)

In conclusion, using a large cohort of individuals with type 2 diabetes we did not find evidence of an association between diabetes duration and incidence of cancer; the higher incidence rates observed in individuals with a longer disease duration are likely an epiphenomenon of ageing.

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Data availability

Data access is through permission from the CPRD only (Protocol No. 19_120Mn); enquiries should be addressed to enquiries@cprd.com. The electronic health record codes are either reported in the manuscript or, alongside the statistical analysis underpinning this study, available at https://github.com/frazac82/.

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Authors' relationships and activities

KK has acted as a consultant, speaker or received grants for investigator-initiated studies for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim and Bayer.

MJD has acted as consultant, advisory board member and speaker for Boehringer Ingelheim, Lilly, Novo Nordisk and Sanofi, an advisory board member and speaker for AstraZeneca, an advisory board member for Janssen, Lexicon, Pfizer, Medtronic and ShouTi Pharma Inc and as a speaker for Napp Pharmaceuticals, Novartis and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca and Janssen.

All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement

FZ designed the study. KB and KK acquired research funding. FZ defined the clinical codes. SL extracted and cleaned the data; FZ analysed the data and drafted the article. All authors contributed to

the interpretation of the data, critically revised the article, and approved the final version. SL and FZ had full access to all the data. FZ 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.

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Table 1: Population characteristics at type 2 diabetes diagnosis by age at diagnosis

	Age at diabetes diagnosis group (years)						
	<40	**≥40 to <50**	**≥50 to <60**	**≥60 to <70**	**≥70 to <80**	**≥80**	**Total**
Men							
No. of individuals	2,230 (3.1)	11,022 (15.1)	19,178 (26.3)	21,100 (29.0)	14,288 (19.6)	4,971 (6.8)	72,789
Age at diabetes diagnosis (years)	37.9 (36.6, 39.0)	46.0 (43.5, 48.1)	55.3 (52.7, 57.7)	64.8 (62.4, 67.3)	74.2 (72.0, 76.7)	83.4 (81.5, 86.2)	61.8 (52.8, 70.6)
Body mass index (kg/m^2)	32.5 (28.3, 37.7)	32.1 (28.4, 36.6)	31.3 (28.0, 35.2)	30.1 (27.2, 33.6)	28.8 (26.1, 31.8)	27.3 (24.8, 30.2)	30.2 (27.1, 34.0)
Body mass index category (kg/m^2)							
<18.5	3 (0.2)	18 (0.2)	26 (0.1)	33 (0.2)	37 (0.3)	31 (0.7)	148 (0.2)
≥18.5 to <25	198 (10.2)	750 (7.6)	1,316 (7.5)	1,866 (9.6)	2,049 (15.6)	1,154 (26.1)	7,333 (11.0)
≥25 to <30	474 (24.3)	2,761 (27.8)	5,635 (32.3)	7,586 (38.9)	5,905 (45.0)	2,069 (46.7)	24,430 (36.8)
≥30 to <35	558 (28.7)	3,065 (30.9)	5,861 (33.6)	6,448 (33.0)	3,813 (29.0)	943 (21.3)	20,688 (31.2)
≥35 to <40	377 (19.4)	2,004 (20.2)	2,938 (16.9)	2,516 (12.9)	1,038 (7.9)	191 (4.3)	9,064 (13.7)
≥40	337 (17.3)	1,317 (13.3)	1,656 (9.5)	1,061 (5.4)	291 (2.2)	38 (0.9)	4,700 (7.1)
Missing	283	1,107	1,746	1,590	1,155	545	6,426
Women							
No. of individuals	1,645 (2.8)	7,040 (12.1)	12,076 (20.8)	15,183 (26.2)	14,063 (24.3)	7,968 (13.7)	57,975
Age at diabetes diagnosis (years)	38.0 (36.6, 39.0)	46.0 (43.4, 48.1)	55.4 (52.9, 57.8)	65.1 (62.6, 67.6)	74.6 (72.3, 77.1)	84.1 (81.9, 87.4)	65.6 (55.2, 75.0)
Body mass index (kg/m^2)	36.4 (30.8, 42.4)	35.2 (30.3, 41.1)	33.5 (29.1, 38.6)	31.3 (27.6, 35.8)	29.5 (26.2, 33.6)	27.4 (24.2, 30.8)	31.2 (27.2, 36.2)
Body mass index category (kg/m^2)							
<18.5	1 (0.1)	9 (0.1)	18 (0.2)	54 (0.4)	105 (0.8)	144 (2.1)	331 (0.6)
≥18.5 to <25	88 (5.7)	404 (6.1)	843 (7.4)	1,530 (10.7)	2,149 (16.7)	1,902 (28.3)	6,916 (12.9)
≥25 to <30	243 (15.6)	1,132 (17.0)	2,490 (21.9)	4,243 (29.8)	4,550 (35.3)	2,619 (39.0)	15,277 (28.6)
≥30 to <35	337 (21.6)	1,688 (25.3)	3,322 (29.2)	4,239 (29.8)	3,660 (28.4)	1,472 (21.9)	14,718 (27.5)
≥35 to <40	361 (23.2)	1,485 (22.3)	2,393 (21.0)	2,504 (17.6)	1,656 (12.8)	438 (6.5)	8,837 (16.5)
≥40	527 (33.8)	1,941 (29.1)	2,309 (20.3)	1,673 (11.7)	775 (6.0)	141 (2.1)	7,366 (13.8)
Missing	88	381	701	940	1,168	1,252	4,530

Shown are median (interquartile range) or number (%).

FIGURES LEGEND

Figure 1: Incidence rates of all cancers in men by age at diagnosis, diabetes duration, and attained age

Legend: Dotted lines indicate the 95% confidence interval. Please note the different y-axis scales.

Figure 2: Incidence rates of all cancers in women by age at diagnosis, diabetes duration, and attained age

Legend: Dotted lines indicate 95% confidence interval. Please note the different y-axis scales.

Figure 3: Rate ratios of all and four commonest cancers by attained age

Legend: Ratios, in men and women, between the incidence rate at 20 years of diabetes duration and the incidence rate at 5 years of diabetes duration, for attained age of 50, 60, 70, 80, 90, and 100 years.
Lines indicate the 95% confidence interval.