

## ORIGINAL ARTICLE

# All-cause and cardiorenal mortality in 6 million adults with and without type 2 diabetes: A comparative, trend analysis in Canada, Spain, and the UK

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## Abstract

**Aims:** To understand geographical and temporal patterns in the diabetes gap, the excess mortality risk associated with type 2 diabetes (T2D), in three high-income countries.

**Methods:** Using databases from Canada (Ontario), Spain (Catalonia) and the UK (England), we harmonized the study design and the analytical strategy to extract information on subjects aged over 35 years with incident T2D between 1998 and 2018 matched to up to five subjects without diabetes. We used Poisson models to estimate age-specific mortality trends by diabetes status and rate ratios and rate differences associated with T2D.

**Results:** In more than 6 million people, 694 454 deaths occurred during a follow-up of 52 million person-years. Trends in all-cause mortality rates differed between Ontario and England; yet, the diabetes gaps were very similar in recent years: in 2018, we estimated 1.3 (95% confidence interval: 0.8, 1.8) and 0.8 (0.2, 1.5) more deaths per 1000 person-years in 50-year-old men with diabetes in Ontario and England, respectively, and 8.9 (6.1, 11.7) and 12.1 (9.1, 15.1) in 80-year-old men; between-country differences were small also in women. In Catalonia, rate ratios comparing T2D with no diabetes in men in 2018 were 1.53 (1.11, 2.11) at 50 years old, 0.88 (0.72, 1.06) at 60 years old, 0.74 (0.60, 0.90) at 70 years old and 0.81 (0.66, 1.00) at 80 years old, indicating lower mortality rates in men with T2D from the age of 60 years; rates were similar in women with and without diabetes at all ages. The diabetes gaps in cardiorenal mortality mirrored those of all-cause mortality: we observed consistent reductions in the proportions of cardiorenal deaths in subjects

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aged 80 years but variations in subjects aged  $\leq 70$  years, regardless of the presence of diabetes.

**Conclusions:** By reducing the confounding impact of epidemiological and analytical differences, this study showed geographical similarities and differences in the diabetes gap: an excess risk of all-cause and cardiorenal mortality in subjects with T2D is still present in Ontario and England in recent years, particularly in elderly subjects. Conversely, there were very small gaps in young men with T2D or even lower mortality rates in older subjects with T2D in Catalonia.

#### KEYWORDS

all-cause mortality, cardiorenal mortality, electronic health records data, multinational study, trend analysis, type 2 diabetes

## 1 | INTRODUCTION

The increasing epidemic of overweight and obesity in children and young adults is leading to an earlier onset of type 2 diabetes (T2D), which, alongside a wider screening for glucose abnormalities, is determining a change in the epidemiology of T2D and contributing to the persistent global burden of diabetes<sup>1-3</sup>: in 2021, it was estimated that, globally, 10.5% of adults aged 20-79 years (537 million) lived with diabetes and the prevalence is projected to increase to 783 million by 2045.<sup>4</sup>

Individuals with T2D have a higher risk of premature death, predominantly attributed to an increased risk of cardiovascular (CVD) complications.<sup>5</sup> The last two decades witnessed remarkable improvements in the diagnosis and treatment of CVD and its risk factors in high-income countries, which resulted in downward trends in the rates of CVD events and CVD-related mortality in the general population and a parallel shift in the most prevalent comorbidities and causes of death.<sup>6-8</sup> Whether these recent trends similarly occurred in subjects with diabetes has been explored only in few studies, mainly from high-income countries<sup>9-15</sup>; although very variably, they generally report reductions in the mortality rates regardless of the diabetes status and confirm the presence of an excess mortality risk in subjects with diabetes (i.e. “diabetes gap”) also during the most recent years.

To disentangle “true” differences—potentially related to diverse screening strategies, guidelines implementation, access to the health care system, or diagnosis-treatment pathways—from variabilities related primarily to the design, analysis and aim of each study is difficult. This hampers the ability to understand geographical and temporal patterns in the burden of diabetes across countries,<sup>16</sup> confirm whether improvements in the diabetes gap have been lower in younger subjects with T2D<sup>12,15</sup> and clarify to what extent a diversi-

fication in the causes of deaths is contributing to the diabetes gap trends.<sup>14,17</sup>

In this study, we assembled data from electronic health records in three countries (Canada, Spain and the UK) following a harmonization of clinical codes to investigate trends in all-cause and cardiorenal mortality rates in subjects with T2D and without diabetes over the last two decades, within a shared epidemiological design and analytical strategy. We quantified the excess mortality risk associated to diabetes in terms of both absolute (rate difference) and relative (rate ratio) diabetes gap and combined CVD and kidney outcomes given the well-established pathophysiological, clinical, and therapeutic continuum between CVD and renal diseases.<sup>18-20</sup>

## 2 | METHODS

### 2.1 | Study design and participants

In this population-based cohort study, we used data from health care administrative databases in Ontario, Canada; the Information System for the development of Primary Care Research (SIDIAP) database in Catalonia, Spain; and the Clinical Practice Research Datalink (CPRD) GOLD in England, UK, to identify three cohorts of subjects with T2D and without diabetes between 1998 and 2018. The use of Ontario data in this study was authorised under section 45 of the *Personal Health Information Protection Act*, which does not require review by a research ethics board. The use of SIDIAP and CPRD data has been approved by the SIDIAP Jordi Gol Clinical Research Ethics Committee (protocol no. 19/029-P) and the CPRD Independent Scientific Advisory Committee (ISAC protocol no. 18\_196Mn), respectively. We followed the REporting of studies Conducted using Observational Routinely-collected health Data

(RECORD) guidelines in conducting and reporting this study (checklist in the Supplementary Material).<sup>21</sup>

### 2.1.1 | Ontario, Canada

All residents using the single-payer universal health care system in Ontario, Canada are recorded in administrative health care databases, including The Registered Persons Database for demographic information, Ontario Diabetes Database (ODD) for all non-gestational diabetes, Discharge Abstract Database for all hospital admissions, and the vital statistics registry for causes and dates of death. These datasets were linked using unique encoded identifiers and analysed at the Institute for Clinical Evaluative Sciences (ICES).

### 2.1.2 | SIDIAP, Spain

The SIDIAP database contains demographic and clinical information, laboratory test results, prescriptions and referrals recorded by about 3400 general practitioners since 2005 through a common software used by 370 primary care centres managed by the Catalan Health Institute.<sup>22</sup> The SIDIAP database has been extensively used for different epidemiological research and it is established as a well-validated Spanish primary care database for diabetes.<sup>23</sup> SIDIAP is linked to the National Statistics Institute in Spain for causes of death.

### 2.1.3 | CPRD, UK

The CPRD routinely collects primary care data on demographics, clinical diagnoses and medicine prescriptions, and it is broadly representative of the UK population in terms of age and sex.<sup>24</sup> We linked the CPRD to Hospital Episodes Statistics Admitted Patient Care (HES APC) and to the Office for National Statistics (ONS) Death Registration to obtain hospital admissions and causes and date of death, respectively.

In all datasets, the exposed group included all subjects with T2D aged  $\geq 35$  years at diagnosis: the index date was the date of T2D diagnosis. In Canada, all subjects registered in ODD between 1 January 1998 and 31 December 2017 with a minimum 1 year of health care coverage before the index date were included. When validated against primary care records, ODD has a specificity of 99.1% and sensitivity of 79.9% for diabetes; although types of diabetes cannot be distinguished in ODD, >90% of cases are T2D.<sup>25</sup> In Spain, all subjects with a diagnosis code of T2D in the SIDIAP database between 1 January 2006 and 31 December 2018 were included. In the UK, all subjects with a first ever diagnosis code of T2D in the CPRD GOLD database between 1 January 1998 and 31 November 2018 were included; subjects must have had linkages to HES and ONS and registered with an up-to-standard CPRD practice minimum 1 year before the index date.

## 2.2 | Exposure and outcome

To reduce misclassification of T2D, we excluded all participants with a diagnostic code of other types of diabetes any time in all three electronic databases. Up to five subjects without any type of diabetes were matched to those with T2D in each country. Exposed subjects were matched to those without diabetes (non-exposed) by year of birth and sex in Ontario; by year of birth, sex, and health care area in Catalonia; and by year of birth ( $\pm 1$  year), sex, and practice in England. Non-exposed subjects were followed-up from the same index date as their matched exposed one. Subjects with cardiorenal diseases or malignant neoplasms before or at the index date were excluded.

Outcomes included all-cause mortality and cardiorenal mortality. The date and underlying cause of death were ascertained via linkage to the vital statistics registries in three countries; subjects were followed-up until death or end of the study: 31 December 2017 for cardiorenal mortality and 31 March 2018 for all-cause mortality in Ontario, 31 December 2018 for both outcomes in Catalonia; and 14 January 2019 for both outcomes in England.

All clinical codes used in the study were reviewed by clinicians, harmonized across countries and reported at <https://github.com/supingling/diabetesmortalitytrend>.

## 2.3 | Statistical analysis

We presented the characteristics of subjects by diabetes status in each country: median and interquartile range (IQR) for age; number of subjects and percentage in each category of sex, index year and age group (<40, 40-49, 50-59, 60-69, 70-79 and  $\geq 80$  years old).

To estimate trends in all-cause and cardiorenal mortality rate in the three countries, we first split the risk time (follow-up) into 1-year intervals by attained age and calendar time (1998-2019)<sup>26,27</sup>; then, we modelled the outcomes with Poisson regressions, using log-person-time as offset and natural splines of attained age and calendar time. In both subjects with T2D and without diabetes, sex-stratified models included an interaction term between age and calendar time and were fitted separately for each outcome and country: this allowed to predict age- and calendar-time specific all-cause and cardiorenal mortality rates; we used these rates to estimate the rate ratios and the absolute rate differences comparing subjects with T2D with those without diabetes, as well as the proportion of cardiorenal deaths out of all-cause deaths. We estimated the rates for ages 50, 60, 70 and 80 years and, in line with the data availability in each database, for the following calendar periods: 1998-2018 for all-cause mortality and 1998-2017 for cardiorenal mortality in Ontario; 1998-2018 in England and 2006-2018 in Catalonia for both outcomes. We further conducted a sensitivity analysis by limiting the study period from 2006 onwards in Ontario and England, to have consistent calendar times among the databases. All analyses were conducted in R ([www.R-project.org](http://www.R-project.org); R Foundation for Statistical Computing, Vienna, Austria) with the “Epi” package;<sup>26</sup> graphs were generated in Stata/BE 17.0 (StataCorp, College Station, TX, USA).

**TABLE 1** Baseline characteristics of adults with and without type 2 diabetes in three countries

	Canada (Ontario)		Spain (Catalonia)		UK (England)	
	Type 2 diabetes (N = 828 113)	No diabetes (N = 3 499 128)	Type 2 diabetes (N = 217 650)	No diabetes (N = 965 351)	Type 2 diabetes (N = 102 023)	No diabetes (N = 465 774)
Index year						
1998	29 122 (3.5)	128 862 (3.7)	-	-	1429 (1.4)	6904 (1.5)
1999	31 024 (3.7)	135 549 (3.9)	-	-	1789 (1.8)	8513 (1.8)
2000	31 377 (3.8)	135 455 (3.9)	-	-	2807 (2.8)	13 036 (2.8)
2001	34 710 (4.2)	148 269 (4.2)	-	-	4210 (4.1)	19 278 (4.1)
2002	37 365 (4.5)	158 226 (4.5)	-	-	5277 (5.2)	24 028 (5.2)
2003	36 962 (4.5)	155 825 (4.5)	-	-	6485 (6.4)	29 351 (6.3)
2004	41 362 (5.0)	173 375 (5.0)	-	-	6587 (6.5)	29 975 (6.4)
2005	45 600 (5.5)	189 018 (5.4)	-	-	6669 (6.5)	30 292 (6.5)
2006	48 317 (5.8)	198 821 (5.7)	34 404 (15.8)	141 368 (14.6)	7922 (7.8)	35 714 (7.7)
2007	45 053 (5.4)	186 027 (5.3)	23 929 (11.0)	101 301 (10.5)	6582 (6.5)	30 096 (6.5)
2008	43 271 (5.2)	179 192 (5.1)	22 545 (10.4)	97 563 (10.1)	6692 (6.6)	30 562 (6.6)
2009	49 759 (6.0)	204 922 (5.9)	20 256 (9.3)	88 841 (9.2)	6819 (6.7)	31 088 (6.7)
2010	45 052 (5.4)	186 753 (5.3)	18 603 (8.6)	82 309 (8.5)	6459 (6.3)	29 482 (6.3)
2011	41 689 (5.0)	174 447 (5.0)	15 525 (7.1)	69 729 (7.2)	6110 (6.0)	27 950 (6.0)
2012	40 361 (4.9)	170 092 (4.9)	14 410 (6.6)	65 066 (6.7)	6283 (6.2)	28 713 (6.2)
2013	43 920 (5.3)	186 192 (5.3)	13 504 (6.2)	61 585 (6.4)	5970 (5.9)	27 108 (5.8)
2014	43 502 (5.3)	185 442 (5.3)	11 838 (5.4)	54 417 (5.6)	4409 (4.3)	20 168 (4.3)
2015	45 981 (5.6)	197 444 (5.6)	10 848 (5.0)	50 597 (5.2)	3533 (3.5)	16 102 (3.5)
2016	47 210 (5.7)	203 530 (5.8)	11 050 (5.1)	52 236 (5.4)	2698 (2.6)	12 327 (2.6)
2017	46 476 (5.6)	201 687 (5.8)	10 338 (4.8)	49 720 (5.2)	1797 (1.8)	8249 (1.8)
2018	-	-	10 400 (4.9)	50 619 (5.2)	1496 (1.5)	6838 (1.5)
Age at index date, years						
Median (IQR)	57.0 (49.0-66.0)	55.0 (47.0-64.0)	58.9 (50.3-69.5)	58.0 (49.5-68.2)	61.0 (52.0-71.0)	60.0 (51.0-69.0)
<40	49 019 (5.9)	241 037 (6.9)	10 291 (4.7)	50 198 (5.2)	4151 (4.1)	20 886 (4.5)
40-49	180 351 (21.8)	880 073 (25.2)	42 540 (19.5)	203 418 (21.1)	14 751 (14.5)	74 458 (16.0)
50-59	254 244 (30.7)	1 139 954 (32.6)	62 356 (28.6)	284 503 (29.5)	26 604 (26.1)	130 509 (28.0)
60-69	206 024 (24.9)	764 766 (21.9)	50 307 (23.1)	216 699 (22.4)	28 293 (27.7)	128 099 (27.5)
70-79	106 974 (12.9)	374 310 (10.7)	33 584 (15.4)	137 363 (14.2)	19 939 (19.5)	80 967 (17.4)
≥80	31 501 (3.8)	98 988 (2.8)	18 572 (8.5)	73 170 (7.6)	8285 (8.1)	30 855 (6.6)
Sex						
Women	390 686 (47.2)	1 748 853 (50.0)	109 249 (50.2)	481 960 (49.9)	46 303 (45.4)	213 688 (45.9)
Men	437 427 (52.8)	1 750 275 (50.0)	108 401 (49.8)	483 391 (50.1)	55 720 (54.6)	252 086 (54.1)

Note: Shown are n (%) and medians (interquartile range, IQR) for categorical and continuous variables, respectively. - indicates not available.

### 3 | RESULTS

#### 3.1 | Cohort characteristics

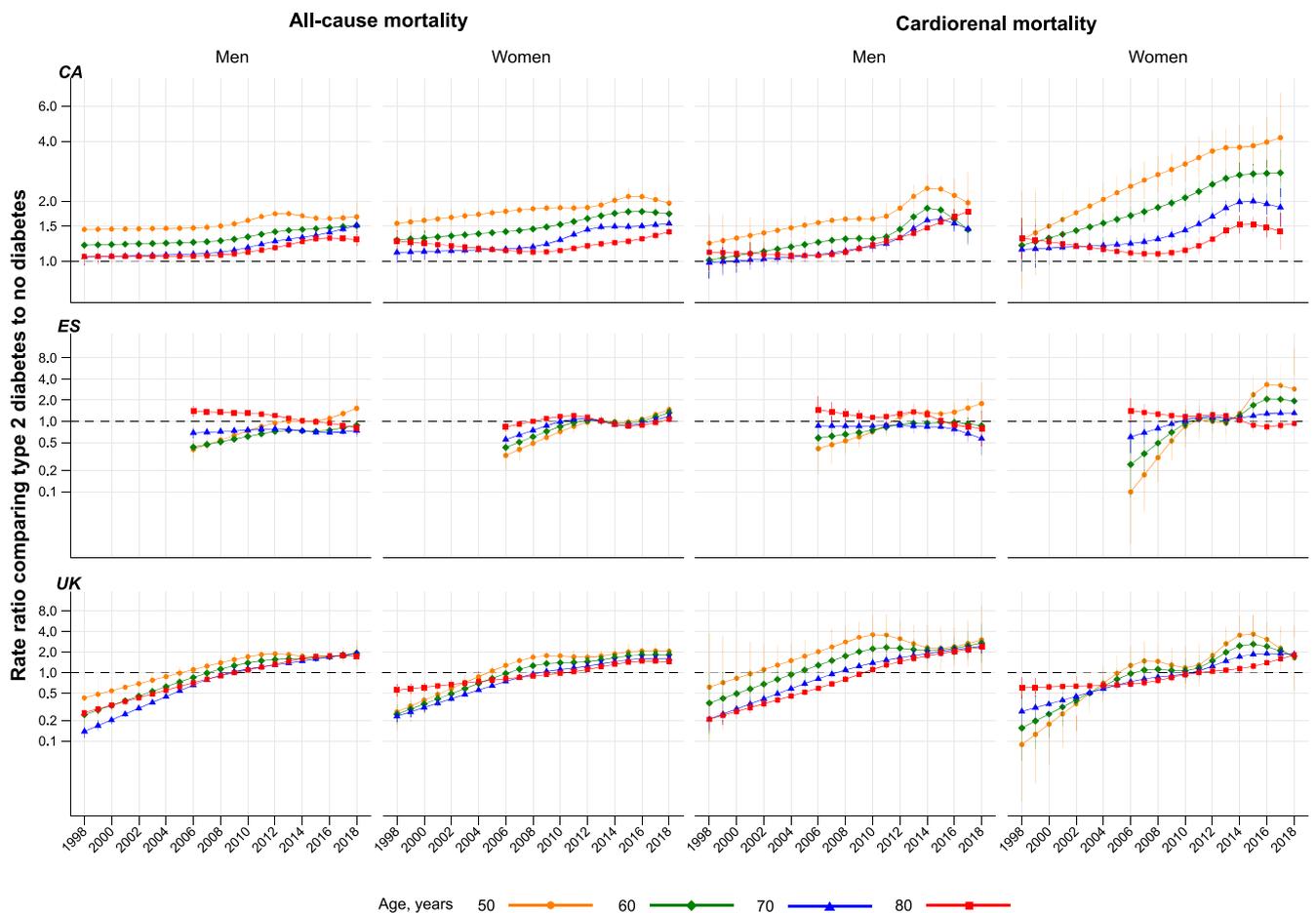
Overall, 6 078 039 subjects were included in this analysis: 828 113 incident T2D cases in Ontario, 217 650 in Catalonia and 102 023 in England; and 3 499 128, 965 351 and 465 774, matched subjects without diabetes, respectively. The flowcharts of participants' selection in three countries are presented in Figures S1-S3. Baseline characteristics by diabetes status in the three countries are presented in

Table 1: 390 686 (47.2%) subjects with T2D in Ontario, 109 249 (50.2%) in Catalonia and 46 303 (45.4%) in England were women; corresponding numbers of subjects without diabetes were 1 748 853 (50.0%), 481 960 (49.9%) and 213 688 (45.9%).

#### 3.2 | All-cause mortality

Table 2 reports the number of deaths and follow-up durations in the three countries: during 7 309 544 and 31 488 102 person-years of





**FIGURE 2** Age-specific trends in all-cause and cardiorenal mortality rate ratios comparing type 2 diabetes with no diabetes. CA, Canada (Ontario); ES, Spain (Catalonia); UK, United Kingdom (England). Spikes indicate 95% confidence interval.

Figure 2 depicts the rate ratios by diabetes, which are tabulated in Table S1. In both men and women, comparing subjects with T2D with those without diabetes, the mortality rate ratios increased over time in both Ontario and England, and rate ratios were constantly larger in younger than older ages across the 20-year period in both countries (Figure 2, Table S1, Figure S4). Such increasing rate ratios were also observed in both men and women from Catalonia, except in 80-year-old men where there was a progressive reduction, from 1.38 (1.18-1.63) in 2006 to 0.81 (0.66-1.00) in 2018. Notably, in this country the risk of death in subjects with T2D was not always higher than those without diabetes during the study period.

Figure 3 shows the rate differences by diabetes (tabulated in Table S2). These trends translated into increasing absolute risk differences in recent years in both men and women and for most ages in all three countries; the magnitude was, however, heterogeneous across ages and countries (Figure 3, Table S2, Figure S4). In Ontario, trends were similar in men and women but larger differences were observed in older than younger ages, e.g. 2.5 (1.9-3.0) more deaths per 1000 person-years in men in 2018 at 60 years old, 5.7 (4.5-6.8) at 70 years old and 8.9 (6.1, 11.7) at 80 years old. In Catalonia, there was a narrowed diabetes gap in men and no evidence of differences in women in recent years: all-cause mortality rate differences increased from -13.1

(-15.4 to -10.8) per 1000 person-years in 2006 (i.e. about 13 less deaths in men with T2D) to -0.9 (-2.2 to 0.4) in 2018 in 60-year-old men, and from 20.2 (9.1 to 31.3) more deaths per 1000 person-years in 2006 to -8.0 (-15.3 to -0.7) in 2018 in 80-year-old men. In England, with similar trends, the magnitude of differences was smaller in younger than older ages and in women than men at older ages, but similar between women and men at younger ages: from 1998 to 2018, -112.0 (-128.8 to -95.2) per 1000 person-years to 12.1 (9.1-15.1) in 80-year-old men; -42.9 (-55.7 to -30.1) to 11.1 (7.2 to 14.9) in 80-year-old women; -1.7 (-2.9 to -0.5) to 0.8 (0.2 to 1.5) in 50-year-old men; and -4.1 (-5.7 to -2.4) to 1.1 (0.4 to 1.9) in 50-year-old women.

### 3.3 | Cardiorenal mortality

In Ontario, during 7 131 779 person-years of follow-up, 24 361 (2.9%) cardiorenal deaths occurred in subjects with T2D; corresponding figures in those without diabetes were 30 708 772 and 73 026 (2.1%). During the same person-years of all-cause mortality, there were 4676 (2.1%) cardiorenal deaths in subjects with T2D and 18 617 (1.9%) in those without in Catalonia, and 5853 (5.7%) and 20 451 (4.4%) in England, respectively (Table 2).



**FIGURE 3** Age-specific trends in all-cause and cardiorenal mortality rate differences comparing type 2 diabetes with no diabetes. CA, Canada (Ontario); ES, Spain (Catalonia); UK, United Kingdom (England). Spikes indicate 95% confidence interval.

Figure 4 shows the trends in cardiorenal mortality rates, which mostly mirrored those in all-cause mortality in subjects with T2D and without diabetes in all three countries, with more evident declines in older than younger ages in Catalonia, and in subjects without diabetes than those with T2D in England (Supplemental Material “Additional results”).

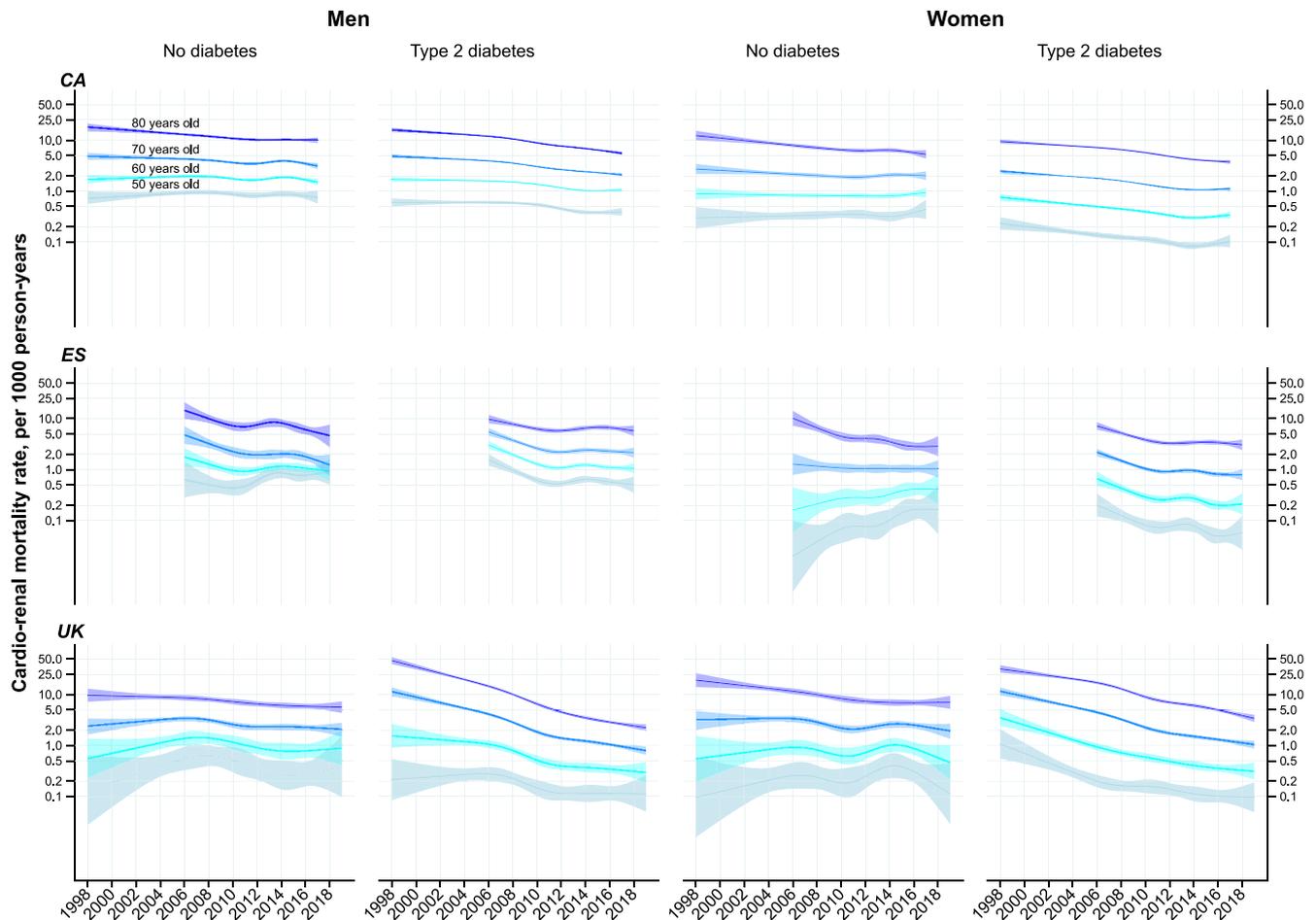
These rates translated into increasing rate ratios comparing subjects with T2D with those without diabetes in all three countries, except in women aged 80 years old in Ontario, where a U-shaped trend was observed; and in men and women at older ages in Catalonia, where it slightly decreased (Figure 2, Table S3, Figure S5).

These patterns were reflected in the rate differences (Figure 3, Table S4, Figure S5). In Ontario, the rate difference reduced from 2.9 (0.1-5.7) more deaths per 1000 person-years in 80-year-old women with T2D in 1998 to 0.6 (−0.0 to 1.2) in 2008, and increased again to 1.5 (0.5-2.6) in 2017; in Catalonia, from 4.6 (−1.2, 10.3) in 2006 to −1.2 (−4.0, 1.5) in 2018 in 80-year-old men and from −3.0 (−0.7, 6.7) to −0.2 (−1.7, 1.3) in 80-year-old women. Nevertheless, in these two countries the absolute cardiorenal mortality rates differences were overall small, being the largest in 80-year-old men with 4.4 (2.9-5.8) more deaths per 1000 person-years in 2017 in Ontario and 4.6 (−1.2, 10.3) in 2006 in Catalonia. In England, trends were similar to Ontario and Catalonia but absolute rate differences were

inconsistent: at 70 years, from −8.9 (−11.4 to −6.4) per 1000 person-years in 1998 to 1.2 (0.7-1.7) in 2018 in men, and from −8.4 (−10.9 to −5.9) to 1.0 (0.4-1.5) in women; corresponding estimates in men and women aged 80 years were −36.8 (−44.9 to −28.8) to 3.3 (2.2-4.4), and −12.8 (−20.9 to −4.6) to 3.1 (1.6-4.7), respectively.

Figures S6 and S7 show the trends in the proportions of cardiorenal deaths in women and men with or without diabetes. In all three countries, a clear downward trend was observed in people at older ages, irrespective of the presence of T2D. In Ontario, the proportion in 80-year-old men without diabetes decreased from 33.1% in 1998 to 17.3% in 2017, and from 34.8% to 23.7% in those with T2D; corresponding figures in 80-year-old women were 31.4% to 17.2% and 32.5% to 18.0%. Similar to Ontario, the proportion of cardiorenal deaths in subjects aged 80 years decreased from 30.8% in 1998 to 14.8% in 2018 in men without diabetes, and from 24.7% to 20.1% in those with T2D; corresponding figures in women were 33.4% to 15.4% and 36.3% to 19.3%. In Catalonia, the proportion decreased from 28.6% in 2006 to 15.1% in 2016 in 80-year-old women with T2D, and there was a decreasing trend in men with T2D at all ages except 50 years old.

The results from the sensitivity analysis limiting the study period from 2006 onwards in Ontario and England are shown in Figures S8



**FIGURE 4** Age-specific trends in cardio-renal mortality rate by diabetes, sex and country. CA, Canada (Ontario); ES, Spain (Catalonia); UK, United Kingdom (England). Areas indicate 95% confidence interval.

and S9. Overall, trends in rate ratios and rate differences of all-cause and cardio-renal mortality were similar to those observed using the whole study period in Ontario and England.

## 4 | DISCUSSION

We observed differences in the mortality rates and their trends over time between Ontario and England, but the all-cause and cardio-renal mortality gaps in the most recent years were very similar, in both men and women. In Catalonia, lower all-cause and cardio-renal mortality rates in men with T2D were observed from the age of 60 years; conversely, in women, mortality rates were similar in subjects with and without diabetes for all ages, except at the age of 80 years, in which cardio-renal mortality was lower in women with T2D than without diabetes. Overall, these findings indicate, particularly in older subjects, the persistence in Ontario and England of a “diabetes gap” in all-cause mortality and, albeit to a much smaller extent, cardio-renal mortality; in Catalonia, we conversely observed very small diabetes gaps or lower mortality rates in subjects with T2D.

Previous studies on all-cause and cause-specific mortality trends in subjects with and/or without diabetes have been conducted in few

high-income countries across four continents and vary substantially in their aims, designs, populations and outcomes (details of these studies are reported in the Supplemental Material). There are at least three overarching messages that can be distilled from them. First, there are remarkable differences in the all-cause mortality rates in subjects with diabetes, for which ascertainment biases should be virtually absent, suggesting that such variations are probably related to the combined effect of true and methodological differences (definition and ascertainment of diabetes and modelling approach, among others): it remains difficult to disentangle the relative contribution, potentially larger, of the latter on the former.<sup>28</sup> Secondly, detailed investigations across age groups are not common, yet more frequent in more recent studies: overall, the available evidence would suggest a differential improvement in the diabetes gap across different ages, with older subjects experiencing a greater absolute reduction in the diabetes gap. Thirdly, any understanding in the temporal changes in the diabetes gap cannot be interpreted without necessary considerations around the metric used to measure such gap (i.e. rate ratio, rate difference or standardized mortality ratio), and direct comparisons of these metrics, within and between studies, are possible only when mortality rates are available in subjects both with and without diabetes, an

information particularly important if the goal is to explore a possible differential improvement across ages, as age is strongly associated with the risk of death.

We aimed to limit the above drawbacks by consistently defining the populations, exposure and the outcomes through a harmonization of clinical codes; sharing a common epidemiological design and analytical strategy; and standardizing the outcome reporting with absolute and relative measures in both subjects with T2D and without diabetes. Conscious that other biases may still be present, nevertheless this approach reduced the impact of other factors when investigating trends of rates and gaps, enhancing a better comparison across countries. This may be one of the reasons behind the remarkable similarity between England and Ontario in all-cause and cardiorenal absolute mortality gap over the last years, yet the temporal trajectories of such gaps were quite heterogeneous. Of note, the study period was not harmonized because of the availability of data in Catalonia, but trends were not largely changed in our sensitivity analysis by limiting study period to 2006 onwards in Ontario and England, suggesting that different diabetes durations during follow-ups only partly contributes to the heterogeneous trends across countries.

Our findings regarding negligible absolute differences at younger ages in all three countries have implications for the ongoing discussion about the possible existence of a “young T2D” phenotype. When diagnosed at a younger age, T2D is associated with a worse control of cardiovascular risk factors and a more rapid deterioration of glucose control compared with diagnoses at middle or older ages<sup>1</sup>; yet, the implications of such differences are less well defined. Our results suggested one lens through which they should be interpreted: a 1.5-2.0-fold increase in the relative risk but very modest increases in the absolute mortality rates. This observation, alongside the increasing prevalence of subjects with young T2D, their longer life expectancy, and the possible diversification in the causes of deaths has implications in future cost-effectiveness evaluation of population-wide strategies for an earlier diagnosis of T2D to reduce the burden of complications and death.<sup>1,14,29</sup> Conversely, trends in all-cause rate ratios translated into more pronounced absolute gaps in the older groups, given their higher mortality rates.

Diabetes gaps increased as the reduction in all-cause mortality rates in subjects without diabetes were not paralleled by simultaneous improvements in subjects with T2D, particularly in England, suggesting that the excess risk associated with T2D has not been fully eliminated notwithstanding the improved management of diabetes and its (cardiorenal) complications in high-income countries. In this respect, it is worth noting that the mortality rates in subjects without diabetes should not be interpreted as, or directly compared with, country-specific nationwide life statistics: they are instead related to a cohort of subjects comparable with the diabetes cohort in terms of age, sex and regional (within each country) distribution; furthermore, when matched (at different ages), these subjects had no cardiorenal or cancer diseases. Nevertheless, the mortality rate reduction during the last 20 years in older people from the general population in England was larger compared with Catalonia and Ontario,<sup>30-32</sup> in line with our trends in subjects without T2D.

Previous studies have also variably investigated trends in mortality rates and gaps for several causes of death, as well as quantified the proportion of deaths attributable to specific causes.<sup>12,14,15,33-37</sup> Besides the methodological differences, comparisons among these studies and with our cardiorenal mortality results is further complicated by the heterogeneous definitions and grouping of these diseases. In our study, we combined cardiovascular and renal causes given their pathophysiological and clinical continuum,<sup>20</sup> confirmed by the results of several recent trials.<sup>18,19</sup> The results for cardiorenal mortality mirrored those of all-cause mortality, as we found only minor fluctuations in the proportions of cardiorenal deaths over time in subjects  $\leq 70$  years; however, in men and women aged 80 years, a consistent reduction in these proportion of cardiorenal deaths occurred in the last two decades in subjects with and without T2D, both in Ontario and England. Overall, the available evidence suggests a potential shift in the leading causes of death in subjects with diabetes, with a progressive decline in cardiovascular causes, particularly at older ages, and an increasing importance of other causes such as cancer, respiratory diseases and mental disorders (e.g. dementia),<sup>11</sup> as confirmed in our cohorts.

This study has some limitations. Although the clinical codes were harmonized in the three databases, the decision to use specific codes and the mechanisms by which coding was performed might vary across diverse health care systems, health care professionals, or over time. Miscoding is possible, and utilizing different combinations of diabetes codes results in inconsistent estimates for the same outcome<sup>38</sup>; in CPRD, frequency and quality of coding may have changed after 2004, following the introduction of the UK Quality and Outcomes Framework pay-for-performance scheme.<sup>39</sup> Furthermore, we have only included high-income countries and there was a shortened period of observation in Catalonia; therefore, the interpretations of the trends are only valid for subjects diagnosed during the respective study periods and the generalizability of our findings is only applied for the health care systems in these three high-income countries. We did not investigate other causes of deaths as the primary goal of our study was to conduct global comparisons in trends and the diabetes gap in all-cause mortality, the less biased among the outcomes; and, given the emerging evidence of a reduction of vascular events in subjects with diabetes,<sup>11,12,14,15,17,33,40</sup> to complement the main outcome by including cardiorenal events as the underlying cause of death, in view of the well-known increased risk of CVD and renal diseases in subjects with T2D. Lastly, the electronic health records underpinning the databases were primarily collected for administrative rather than research purposes.

Using harmonized data and analyses in over 6 million subjects with and without diabetes in Ontario, Catalonia and England, we observed differences in the absolute rates of all-cause and cardiorenal mortality over the last 20 years, which translated into heterogeneous relative and absolute differences in the diabetes gap. We found, however, a similar excess risk associated with diabetes in Ontario and England, which was still present in 2018; in Catalonia, there was conversely a reduced risk in people with diabetes at older ages but a similar risk in younger men and in women. Reducing epidemiological and

analytical differences across independent but coordinated studies in different countries is difficult and time-consuming: however, our study shows that a more global and possibly accurate understating of the diabetes gap is feasible. Reporting details on both relative and absolute differences is also essential, as they may diverge within the same context and their comparative relevance changes in different scenarios; furthermore, consistent analytical and coding procedures are even more relevant to confirm robustly the heterogeneous trends in the diabetes gap across ages or the temporal diversification in the causes of death.

### AUTHOR CONTRIBUTIONS

Suping Ling performed the study design, data extraction and preparation in the UK, statistical lead for all centres and analysis for the UK database, first draft. Francesco Zaccardi performed the study design, statistical analysis, coordination of clinical coding, first draft, interpretation and critical revision. Ping Li performed the statistical analysis in Canada and the critical revision. Bogdan Vlach, Manel Mata-Cases and Dídac Mauricio performed the study supervision in Spain and the critical revision. Jordi Real Gatus and Josep Franch-Nadal performed the statistical analysis in Spain and the critical revision. Baiju R. Shah performed the study supervision in Canada, interpretation and critical revision. Peter Fenici, Mikhail N. Kosiborod, Clare Gillies and Kamlesh Khunti conceived the study and design, interpreted the study and undertook the critical revision.

All authors have approved the final manuscript and accept responsibility to submit for publication; Ping Li had access to data in Canada; Jordi Real Gatus and Josep Franch-Nadal had access to data in Spain; Suping Ling and Francesco Zaccardi had access to data in the UK.

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### CONFLICT OF INTEREST

Francesco Zaccardi reports speakers' fees from Napp Pharmaceutical and Boehringer Ingelheim outside of the submitted work. Manel Mata-Cases has received an advisory and or speaking fees from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis,

Novo Nordisk and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk and Sanofi. Josep Franch-Nadal has received advisory and or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi and Boehringer. Mikhail N. Kosiborod has received grant payment to his institution from Boehringer Ingelheim; has received personal fees or fees to his institution, or both, for consultancy from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Merck, Novo Nordisk, Sanofi and Vifor Pharma; has received personal honoraria and honoraria to his institution for lectures from AstraZeneca, Boehringer Ingelheim and Novo Nordisk; has received personal honoraria and honoraria to his institution from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi and Vifor Pharma for participation on DSMB for advisory boards; and has received study drug for a clinical trial from AstraZeneca and Boehringer Ingelheim. Peter Fenici is employed by AstraZeneca. Dídac Mauricio has received advisory and/or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi and Boehringer. Kamlesh Khunti reports personal fees from Amgen, Bayer, NAPP, Roche, Berlin-Chemie AG/Menarini Group and Sanofi-Aventis; and grants and personal fees from Pfizer, Boehringer Ingelheim, AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme and Servier outside of the submitted work. The other authors declare that they have no competing interests.

### PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14856>.

### DATA AVAILABILITY STATEMENT

All clinical code lists, statistical codes and modelled outcomes are available on GitHub (link: <https://github.com/supingling/diabetesmortalitytrend>). Data access is through permission from each centre only: the Ontario dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at [www.ices.on.ca/DAS](http://www.ices.on.ca/DAS) (email: [das@ices.on.ca](mailto:das@ices.on.ca)); please send any enquiries to [didacmauricio@gmail.com](mailto:didacmauricio@gmail.com) for the Information System for the development of Primary Care Research (SIDIAP) database in Spain and enquiries@cpird.com for UK Clinical Practice Research Datalink.

### ETHICS STATEMENT

The use of Ontario data in this study was authorised under section 45 of the *Personal Health Information Protection Act*, which does not require review by a research ethics board. The use of SIDIAP data has been approved by the SIDIAP Jordi Gol Clinical Research Ethics



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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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