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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 harmonised 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; between-country differences were small also in women. In Catalonia, rate ratios comparing T2D to no diabetes in 2018 were 1.53 (1.11, 2.11) in 50-year-old men, 0.88 (0.72, 1.06) in 60-year-old, 0.74 (0.60, 0.90) in 70-year-old, and 0.81 (0.66, 1.00) in 80-year-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 aged 80 years but variations in subjects aged ≤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: type 2 diabetes; all-cause mortality; cardiorenal mortality; electronic health records data; trend analysis; multinational study

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:[1-3] 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.[4]

Individuals with T2D have a higher risk of premature death, predominantly attributed to an increased risk of cardiovascular (CVD) complications.[5] 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.[6-8] Whether these recent trends similarly occurred in subjects with diabetes has been explored only in few studies, mainly from high-income countries:[9-15] 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 in the most recent years.

To disentangle "true" differences – potentially related to diverse screening strategies, guidelines implementation, access to healthcare 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,[16] confirm whether improvements in the diabetes gap have been lower in younger subjects with T2D,[12,15] and clarify to what extent a diversification in the causes of deaths is contributing to the diabetes gap trends.[14,17]

In this study, we assembled data from electronic health records in three countries – Canada, Spain, and the UK – following a harmonisation 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 cardiovascular and renal diseases.[18-20]

METHODS

Study design and participants

In this population-based cohort study, we used data from healthcare 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**).[21]

Ontario, Canada*:* All residents using the single-payer universal healthcare system in Ontario, Canada are recorded in administrative healthcare 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).

SIDIAP, Spain*:* The SIDIAP database contains demographic and clinical information, laboratory test results, prescriptions, and referrals recorded by around 3,400 general practitioners since 2005 through a common software used by 370 primary care centres managed by the Catalan Health Institute.[22] SIDIAP database has been extensively used for different epidemiologic research and it is established as a well-validated Spanish primary care database for diabetes.[23] SIDIAP is linked to National Statistics Institute in Spain for causes of death.

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.[24] 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 35 years or over at diagnosis: the index date was the date of T2D diagnosis. In Canada, all subjects registered in ODD between 1st Jan 1998 and 31st Dec 2017 with minimum 1 year of healthcare coverage prior to the index date were

included. When validated against primary care records, ODD has 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.[25] In Spain, all subjects with a diagnosis code of T2D in the SIDIAP database between 1st Jan 2006 and 31st Dec 2018 were included. In the UK, all subjects with a first ever diagnosis code of T2D in the CPRD GOLD database between 1st Jan 1998 and 31st Nov 2018 were included; subjects must have had linkages to HES and ONS and registered with an up-to-standard CPRD practice minimum 1 year prior to the index date.

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 healthcare area in Catalonia; and by year of birth (±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: 31st Dec 2017 for cardiorenal mortality and 31st Mar 2018 for all-cause mortality in Ontario, 31st Dec 2018 for both outcomes in Catalonia; and 14th Jan 2019 for both outcomes in England.

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

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 gender, index year, and age group (<40, 40-49, 50-59, 60-69, 70-79 and ≥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's intervals by attained age and calendar time (1998-2019);[26,27] 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 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 to those without diabetes, as well as the proportion of cardiorenal deaths out of all-cause deaths. We estimated rates for age 50, 60, 70, and 80 years and, in line with the data availability in each database, for the following calendar periods: all-cause mortality, 1998-2018 for Ontario and England and 2006-2018 for Catalonia; cardiorenal mortality, 1998-2017 for Ontario and 1998-2018 for England. 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; R Foundation for Statistical Computing, Vienna, Austria) with the "Epi" package;[26] graphs were generated in Stata/BE 17.0 (StataCorp, College Station, TX).

RESULTS

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 **Figure 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%).

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 follow-up in people with and without T2D, 108,932 (13.2%) and 343,665 (9.8%) deaths, respectively, occurred in Ontario. Corresponding figures were 25,569 (11.7%) and 103,552 (10.7%) deaths during 1,516,692 and 6,375,516 person-years in Catalonia; and 23,698 (23.2%) and 89,038 (19.1%) deaths during 940,761 and 4,317,366 person-years in England, respectively.

Figure 1 shows the trends in all–cause mortality rates by diabetes status, sex, and country. In people with T2D, trends varied across age, gender, and countries: in Ontario, all-cause mortality rates constantly decreased in men while levelled off after 2010 in women at all ages; in Catalonia, a clear reduction was observed in both men and women at older ages (≥70 years) but there were slightly increasing trends in women at younger ages; in England, they were rather stable in both men and women at all ages. Conversely, all-cause mortality rates in men and women without diabetes decreased across all ages in all three countries during their respective study period, and absolute rates were higher in men than women (**"Additional results", Supplementary Material**).

Figure 2 depicts the rate ratios by diabetes, which are tabulated in **Table S1**. In both men and women, comparing subjects with T2D to 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 years 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 to 1.63) in 2006 to 0.81 (0.66 to 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 to 3.0) more deaths per 1000 person-years in 60-year-old, 5.7 (4.5 to 6.8) in 70-year-old, and 8.9 (6.1, 11.7) in 80-year-old men in 2018. 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., around 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 were 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 to 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.

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 4,676 (2.1%) cardiorenal deaths in subjects with T2D and 18,617 (1.9%) in those without in Catalonia, and 5,853 (5.7%) and 20,451 (4.4%) in England, respectively (**Table 2**).

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 (**"Additional results", Supplementary Material**).

These rates translated into increasing rate ratios comparing subjects with T2D to those without diabetes in all three countries, except in women aged 80 years 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 to 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 to 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 to 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 to 1.7) in 2018 in men, and from -8.4 (-10.9 to -5.9) to 1.0 (0.4 to 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 to 4.4), and -12.8 (-20.9 to -4.6) to 3.1 (1.6 to 4.7), respectively.

Figure S6-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 also a decreasing trend in men with T2D at all ages except 50-year-old.

The results from the sensitivity analysis limiting the study period from 2006 onwards in Ontario and England are shown in **Figure S8** and **S9**. Overall, trends in rate ratios and rate differences of all-cause and cardiorenal mortality were similar to those observed using the whole study period in Ontario and England.

DISCUSSION

We observed differences in the mortality rates and their trends over time between Ontario and England, but the all-cause and cardiorenal mortality gaps in the most recent years were very similar, in both men and women. In Catalonia, lower all-cause and cardiorenal 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 cardiorenal 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, cardiorenal mortality; in Catalonia, we conversely observed very small diabetes gaps or lower mortality rates in subjects with T2D.

Although 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 **Supplementary Material**), there are at least three overarching messages that can be distilled from them. Firstly, 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 likely 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.[28] 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 standardised 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 harmonisation of clinical codes; sharing a common epidemiological design and analytical strategy; and standardising 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 remarkably similarity

between England and Ontario in all-cause and cardiorenal absolute mortality gap in the last years, yet the temporal trajectories of such gaps were quite heterogeneous. Of note, the study period was not harmonised due to 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 on-going 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 to diagnoses at middle or older ages;[1] yet, the implications of such differences are less well defined. Our results suggested one lens through which they should be interpreted: a 1.5- to 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.[1,14,29] 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 morality 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 to 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 in the last 20 years in older people from the general population in England was comparatively larger to Catalonia and Ontario,[30-32] 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.[12,14,15,33-37] 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,[20] confirmed by the results of several recent trials.[18,19] 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 ≤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),[11] as confirmed in our cohorts.

This study has some limitations. Although the clinical codes were harmonised in the three databases, the decision to use specific codes and the mechanisms by which coding was performed might vary across diverse healthcare systems, healthcare professionals, or over time. Miscoding is possible, and utilising different combinations of diabetes codes results in inconsistent estimates for the same outcome;[38] 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.[39] 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 generalisability of our findings is only applied for the healthcare 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 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,[11,12,14,15,17,33,40] to complement the main outcome by including cardiorenal events as underlying cause of death, in view of the well-known increased risk of cardiovascular 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 harmonised 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 in the last twenty 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 robustly confirm the heterogeneous trends in the diabetes gap across ages or the temporal diversification in the causes of death.

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Contribution
SL: study design, data extraction and preparation in the UK, statistical lead for all centres and analysis for the UK database, first draft;
FZ: study design, statistical analysis, coordination of clinical coding, first draft, interpretation and critical revision;
PL: statistical analysis in Canada, critical revision;
BV, MMC, DM: study supervision in Spain, critical revision;
JRG, JFN: statistical analysis in Spain, critical revision;
BRS: study supervision in Canada, interpretation, critical revision;
PF, MNK, CG, KK: study concept and design, interpretation and critical revision.
All authors have approved the final manuscript and accept responsibility to submit for publication; PL had access to data in Canada; JRG and JFN had access to data in Spain; SL and FZ had access to data in the UK.

Conflict of interest
SL, PL, BV, JR, CL, BS have no conflict of interests to declare.

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Ethics committee approval
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 Committee (protocol No. 19/029-P).
The use of CPRD data has been approved by the CPRD Independent Scientific Advisory Committee (ISAC Protocol No: 18_196Mn).

Data sharing
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 (email: das@ices.on.ca); please send any enquiries to didacmauricio@gmail.com for the Information System for the development of Primary Care Research (SIDIAP) database in Spain and enquiries@cprd.com for UK Clinical Practice Research Datalink.

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FIGURE LEGEND

Figure 1. Age-specific trends in all-cause mortality rate by diabetes, sex, and country

Legend: CA: Canada (Ontario); ES: Spain (Catalonia); UK: United Kingdom (England). Areas indicate 95% confidence interval.

Figure 2. Age-specific trends in all-cause and cardiorenal mortality rate ratios comparing type 2 diabetes to no diabetes

Legend: CA: Canada (Ontario); ES: Spain (Catalonia); UK: United Kingdom (England). Spikes indicate 95% confidence interval.

Figure 3. Age-specific trends in all-cause and cardiorenal mortality rate differences comparing type 2 diabetes to no diabetes

Legend: CA: Canada (Ontario); ES: Spain (Catalonia); UK: United Kingdom (England). Spikes indicate 95% confidence interval.

Figure 4. Age-specific trends in cardiorenal mortality rate by diabetes, sex and country

Legend: CA: Canada (Ontario); ES: Spain (Catalonia); UK: United Kingdom (England). Areas indicate 95% confidence interval.

Table 1. Baseline characteristics of adults with and without type 2 diabetes in the 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)	-	-	1,429 (1.4)	6,904 (1.5)
1999	31,024 (3.7)	135,549 (3.9)	-	-	1,789 (1.8)	8,513 (1.8)
2000	31,377 (3.8)	135,455 (3.9)	-	-	2,807 (2.8)	13,036 (2.8)
2001	34,710 (4.2)	148,269 (4.2)	-	-	4,210 (4.1)	19,278 (4.1)
2002	37,365 (4.5)	158,226 (4.5)	-	-	5,277 (5.2)	24,028 (5.2)
2003	36,962 (4.5)	155,825 (4.5)	-	-	6,485 (6.4)	29,351 (6.3)
2004	41,362 (5.0)	173,375 (5.0)	-	-	6,587 (6.5)	29,975 (6.4)
2005	45,600 (5.5)	189,018 (5.4)	-	-	6,669 (6.5)	30,292 (6.5)
2006	48,317 (5.8)	198,821 (5.7)	34,404 (15.8)	141,368 (14.6)	7,922 (7.8)	35,714 (7.7)
2007	45,053 (5.4)	186,027 (5.3)	23,929 (11.0)	101,301 (10.5)	6,582 (6.5)	30,096 (6.5)
2008	43,271 (5.2)	179,192 (5.1)	22,545 (10.4)	97,563 (10.1)	6,692 (6.6)	30,562 (6.6)
2009	49,759 (6.0)	204,922 (5.9)	20,256 (9.3)	88,841 (9.2)	6,819 (6.7)	31,088 (6.7)
2010	45,052 (5.4)	186,753 (5.3)	18,603 (8.6)	82,309 (8.5)	6,459 (6.3)	29,482 (6.3)
2011	41,689 (5.0)	174,447 (5.0)	15,525 (7.1)	69,729 (7.2)	6,110 (6.0)	27,950 (6.0)
2012	40,361 (4.9)	170,092 (4.9)	14,410 (6.6)	65,066 (6.7)	6,283 (6.2)	28,713 (6.2)
2013	43,920 (5.3)	186,192 (5.3)	13,504 (6.2)	61,585 (6.4)	5,970 (5.9)	27,108 (5.8)
2014	43,502 (5.3)	185,442 (5.3)	11,838 (5.4)	54,417 (5.6)	4,409 (4.3)	20,168 (4.3)
2015	45,981 (5.6)	197,444 (5.6)	10,848 (5.0)	50,597 (5.2)	3,533 (3.5)	16,102 (3.5)
2016	47,210 (5.7)	203,530 (5.8)	11,050 (5.1)	52,236 (5.4)	2,698 (2.6)	12,327 (2.6)
2017	46,476 (5.6)	201,687 (5.8)	10,338 (4.8)	49,720 (5.2)	1,797 (1.8)	8,249 (1.8)
2018	-	-	10,400 (4.9)	50,619 (5.2)	1,496 (1.5)	6,838 (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)	4,151 (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)	8,285 (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)

Shown are numbers (%) and medians (interquartile range, IQR) for categorical and continuous variables, respectively.

- indicates not available.

Table 2. Total number of events and person-years in the 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)
Total person–years	7,309,544	31,488,102	1,516,692	6,375,516	940,761	4,317,366
Follow–up [median (IQR)], years	8.5 (4.2 – 12.9)	8.7 (4.3 – 13.2)	7.2 (3.7 – 10.3)	6.7 (3.2 – 9.9)	9.0 (5.6 – 12.8)	9.1 (5.5 – 12.9)
All–cause deaths, n (%)	108,932 (13.2)	343,665 (9.8)	25,569 (11.7)	103,552 (10.7)	23,698 (23.2)	89,038 (19.1)
Cardiorenal deaths, n (%)	24,361 (2.9)	73,026 (2.1)	4,676 (2.1)	18,617 (1.9)	5,853 (5.7)	20,451 (4.4)

For Ontario, total person–years and follow–up (interquartile range, IQR) for cardiorenal mortality were, respectively: 7,131,779 and 8.3 (4.0–12.7) years in subjects with type 2 diabetes and 30,708,772 and 8.5 (4.1–13.0) years in those without.