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Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016

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ABSTRACT

Introduction The objective of this study was to give an overview of prevalence, incidence and mortality of type 1 (T1D) and type 2 diabetes (T2D) in Denmark, and their temporal trends.

Research design and methods We constructed a diabetes register from existing population-based healthcare registers, including a classification of patients as T1D or T2D, with coverage from 1996 to 2016. Using complete population records for Denmark, we derived prevalence, incidence, mortality and standardized mortality ratio (SMR).

Results The overall prevalence of diabetes at 2016 was 0.5% for T1D and 4.4% for T2D, with annual increases since 1996 of 0.5% for T1D and 5.5% for T2D. Incidence rates of T1D decreased by 3.5% per year, with increase for persons under 25 years of age and a decrease for older persons. T2D incidence increased 2.5% per year until 2011, decreased until 2014 and increased after that, similar in all ages. The annual decrease in mortality was 0.3% for T1D and 2.9% for T2D. The mortality rate ratio between T1D and T2D was 1.9 for men and 1.6 for women. SMR decreased annually 2% for T1D and 0.5% for T2D.

Conclusions Incidence and prevalence of diabetes is increasing, but mortality among patients with diabetes in Denmark is decreasing faster than the mortality among persons without diabetes. T1D carries a 70% higher mortality than T2D.

Significance of this study

What is already known about this subject?

- Incidence rates of type 2 diabetes (T2D) have been increasing over the last decades, T1D in childhood too, but less so than T2D.
- There are indications that incidence rates of T2D have decreased recently or at least are showing a slower increase.

What are the new findings?

- Incidence rates of T2D showed a decrease in 2011–2014, followed by an increase.
- Incidence rates of T1D were slowly increasing in ages under 20 but decreasing in ages over 30.
- The mortality of patients with T1D is some 70% higher than that of patients with T2D, but decreasing over time.
- Mortality of both T1D and T2D relative to the population mortality showed a stable decrease.

How might these results change the focus of research or clinical practice?

- The excess mortality of patients with T1D relative to patients with T2D may require a closer focus on prevention of complications, thereby contributing to lowering mortality in patients with T1D.

INTRODUCTION

Surveillance of disease occurrence and mortality among diseased persons is a prerequisite of quality control of the healthcare system as a whole, and for planning of future resourcing of healthcare and prevention.

Recently, there have been indications in the literature that incidence rates of diabetes have been declining in recent years.[1–5] While surveillance of T1D incidence in childhood and adolescence is well established, few studies have been able to monitor T1D incidence in adulthood. Consequently, there have only been very few reports comparing the occurrence of T1D and T2D and how patients with the two diseases fare relative to each other with respect to mortality.[6 7]

In population surveillance, the most effective tools are population-wide disease registers, that is, recording of all new cases of disease as they occur. In Denmark, as in the other Nordic countries, there is a long tradition for population registration. Denmark has one of the longest standing comprehensive medicines registers going back to the beginning of 1995. This means that it is possible to construct an accurate diabetes register based on the medicines register and other healthcare registers. Moreover, recent administrative developments in Denmark have made it possible to make a good discrimination between T1D and T2D at the population level, enabling a more detailed reporting of trends in diabetes in Denmark separately for T1D and T2D.

The aim of this study was to describe the trends in prevalence, incidence and mortality of T1D and T2D over the period 1996–2016 as well as how these vary by age, and for mortality also by duration of diabetes.

RESEARCH DESIGN AND METHODS

Register data

Denmark has population-wide registers covering virtually all aspects of life, including healthcare, and all registers are linkable by a unique person ID.[8] The Danish national healthcare system is run by the state through five healthcare regions and covers all Danish citizens free of charge.

Diabetes data

We constructed a Danish diabetes register from existing Danish healthcare registers, using all available sources to obtain maximal sensitivity. In Denmark, all T1D is treated in hospital outpatient clinics. T2D care takes place in General Practice, except from approximately 20% of patients with T2D with severe complications who receive diabetes care in hospital outpatient clinics. While ICD-10 codes are not available for the large fraction of patients with T2D treated in General Practice, we captured diabetes-defining information from other sources as described below. Patients with diabetes were defined using the earliest of the following as inclusion date as proxy for date of diagnosis:

- First diagnosis of hospital-treated diabetes (ICD-8: 249, 250; ICD-10: E10, E11; these exclude gestational diabetes) in the National Patient Register (NPR), available since 1977.[9]
- First use of podiatry for patients with diabetes in the National Health Services Register available since 1990.[10]
- First date of purchase of any anti-diabetic medication (ATC A10xxx) in the Medicines Products Register available since 1995.[11]
- Earliest mentioned date of diagnosis in the Danish Adult Diabetes Database (DADD), available since 2005. DADD is a clinical quality database, with annual status of patients reported from outpatient clinics and General Practitioners and clinically validated information on diabetes in children and youth.[12]
- Earliest date of eye examination recorded in the diaBase, a clinical quality database for eye screening of patients with diabetes available since 2009.[13]

Type of diabetes

Persons were classified as T1D in the diabetes register if any of the following criteria were met, and otherwise as T2D:

- Purchase of insulin before age 30.
- DADD: classified as T1D in >50% of the person's DADD records classify the person as T1D, and similarly for T2D.
- Not classified as either T1D or T2D in DADD, but >50% of the patient's records from NPR classifies the person as T1D.

Finally, a person cannot be classified as T1D if there is no recorded date of insulin purchase. Persons not classifiable as T1D were classified as T2D.

Persons with an inclusion date in the register after 1 January 1996 were considered incident cases of diabetes, whereas those included before were only considered prevalent cases as of 1 January 1996 with uncertain date of diagnosis. Diabetes as cause of death without a diagnosis in any of the other registers was not definitional of diabetes.

Further details of the databases and the algorithm are given in the electronic supplementary material (ESM).

Population data

Complete individual-level register information on the entire Danish population, including dates of birth, emigration, immigration and death, was available.

Tabulation of data

We tabulated prevalent cases, type of diabetes and total population as of 1 January 1996–2017, sex and 1-year age class.

Follow-up time and new cases of T1D, T2D and deaths were tabulated by diabetes status (number with diabetes, T1D, T2D), sex, age and date of diagnosis and date of birth in 1-year classes as Lexis triangles.[14] For persons with diabetes diagnosed after 1996, we further tabulated by duration of disease, the first year in 3-month intervals, and beyond 1 year of duration in 1-year intervals.

A detailed account of data tabulation is given in the ESM.

Statistical methods

All statistical models were fitted separately for men and women and for no diabetes, T1D and T2D. For each tabulation unit, we devised the mean of current age, current date and duration of diabetes and date of birth, using these as quantitative explanatory variables.

Prevalence was modeled separately for each of the dates 1 January 1996–2017 in a binomial model with log-link, using restricted cubic splines for the effect of age. We also fitted models jointly for all dates in order to devise an overall annual relative change in prevalence.

Incidence and mortality rates were modeled as an age–period–cohort model using Poisson models with log person time as offset and restricted cubic spline effects of age and date of follow-up and date of birth, using 1 January 2015 as reference point for calendar time.[14]

Mortality rates of T1D and T2D were additionally modeled by duration of diabetes. Since the linear effects of current age, age at diagnosis and duration of diabetes cannot be separated because current age=age at diagnosis+duration, we reported the estimated mortality as a function of current age, using separate curves for persons diagnosed at ages 30, 45 and so on. The mortality curves are thus showing the *joint* effect of current age, age at diagnosis and duration of disease; see the detailed account of this in the ESM section on statistical methods.[15]

Since only persons included after 1 January 1996 have a reliable date of diagnosis, the mortality analyses using age at diagnosis and duration were restricted to persons included after this date. For comparability with other studies, age-specific mortality rates ignoring both age at diagnosis and duration were reported both for the restricted group of patients diagnosed after 1 January 1996 and for all patients, also including the prevalent cases as of 1 January 1996.

We computed mortality rate ratios between men and women for each type of diabetes, and T1D/T2D mortality rate ratios for men and women separately.

The standardized mortality ratio (SMR) was modeled the same way as the mortality but using the log of the expected number of deaths as offset, deriving the SMR as the mortality rate ratio between T1D, T2D and no diabetes.

A complete and detailed description of the models and procedures is given in the ESM section on Statistical methods.

Software and documentation

All registers mentioned were put at our disposal in de-identified, linkable form by the research service of Statistics Denmark. Approval for the project was granted by the Danish Data Protection board. For register processing, we used SAS V.12.4, including the %Lexis macro[16]; for statistical analyses and graphics, we used R V.3.6.0, using the Epi package, V.2.32.[17 18]

Documentation of the construction of the register and the analysis files of prevalence and follow-up can be found online (http://BendixCarstensen.com/DMreg/Reg2016.pdf), and a complete account of all statistical analyses based on these is also available (http://BendixCarstensen.com/DMreg/Ana2016.pdf).

RESULTS

In the period 1996–2016, 448 445 persons were recorded in our register as patients with diabetes in Denmark (table ESM1), about 9% as T1D and the rest as T2D, and 83 441 (19%) were prevalent cases as of 1 January 1996. The median age at diagnosis for patients with T1D was around 30 years, slightly older for men than women, whereas it was around 63 for T2D, a bit older for women than for men (table ESM1).

Prevalence

The age-specific prevalences at 1996, 2003, 2010 and 2017 are shown in figure 1 separately for T1D and T2D; the detailed numbers by sex and calendar time are shown in tables ESM2 and 3, and illustrated in figure ESM1.

The crude prevalence of T1D (0–99 years of age) was quite stable at 0.5% for men and 0.4% for women over the study period, whereas the crude prevalence of T2D tripled over the study period, from 1.2% to some 4.5%, slightly more for men than women (table ESM3): an annual increase of 5.5% per year (table 1). The fraction of T1D among all patients with diabetes has consequently dropped from about 25% in 1 January 1996 to 10% at 1 January 2017 (table ESM2).

For T1D the age-specific prevalence increased till about age 40 for men and about 30 for women (figure 1A,B). T2D showed a peak age-specific prevalence at 1 January 2017 age 80 at 19% for men and 16% for women (figure 1C,D).

Incidence

Over the study period 1996–2016, there was a total of 363 664 new cases of diabetes of which 19 712 (5.4%) were T1D (table ESM4). Persons over 100 and persons not resident at diagnosis were excluded.

For T1D, we found that incidence rates in younger ages were slightly increasing, whereas rates in older ages showed a decrease; the overall average a decrease of 3.5% per year (figure 2A,B, figure ESM2). For T2D, the patterns were almost identical in different ages, with an increase until 2011, a downturn until 2014 and an increase during the last 2 years of the study period (figure 2C,D).

The age–period–cohort models (figure ESM3) showed that men had higher incidence rates than women, and a somewhat different age pattern for T1D incidence rates. For men, there was an increase to about age 18, a plateau and a slight increase to age 40, whereas women showed an increase until about age 15 and a decrease after that.

The absolute sizes of the incidence rates of T1D and T2D are hard to compare because of the differences in ages at diagnosis, but broadly speaking T2D occur at 20–30 times the rates of T1D (figure ESM3).

Mortality and SMR

Mortality

Figure 3 shows the mortality for patients with T1D and T2D by current age and duration of diabetes for select ages at diagnosis of diabetes. Each curve shows the joint effects of increasing age and increasing diabetes duration.

Both for T1D and T2D, we saw an initial peak in mortality during the first 1–2 years after diagnosis, most pronounced for T1D (see figure 3A). For T1D, the mortality was smaller at a given age, the earlier a person was diagnosed (that is for longer diabetes durations), but this was not the case if follow-up was restricted to after 2005 (figures ESM4 and 5). For T2D men, there was a higher mortality for longer duration (earlier age at diagnosis) at any given age, whereas mortality in T2D women was independent of duration of diabetes beyond 5 years (see figure 3B); restricting follow-up to after 2005 resulted in a less pronounced effect of duration (figures ESM4 and 5).

We found that the mortality rate ratio between men and women were close to 1.5 both for T1D and T2D in all ages.

Finally, for T1D we saw an increase in mortality by calendar time until about 2005, but after this a consistent decrease (figure ESM4), the latter 4.9% per year, whereas the mortality in patients with T2D showed a consistent

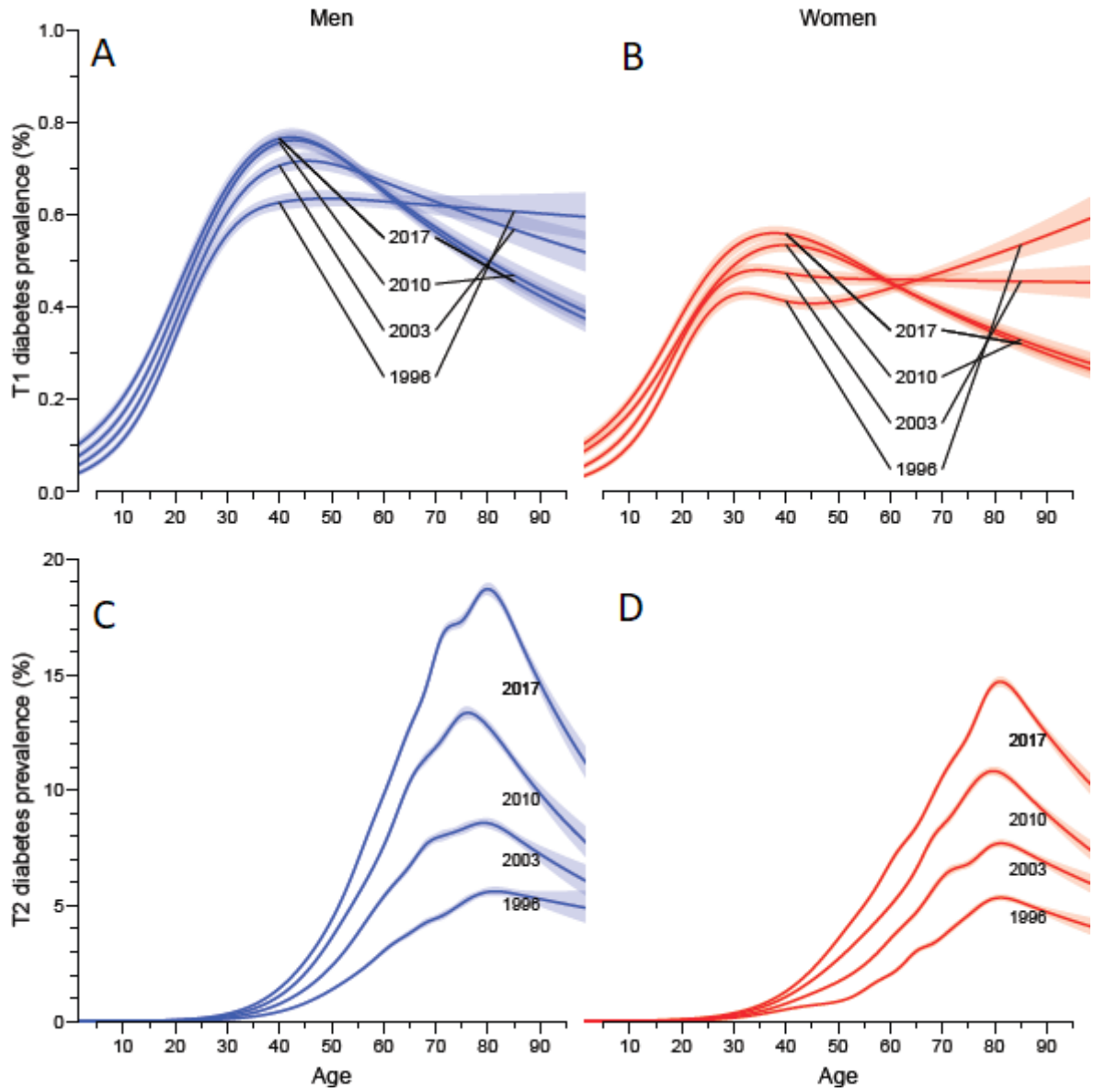

Figure 1 Age-specific prevalence of type 1 diabetes (A, B) and type 2 diabetes (C, D) in Denmark as of 1 January 1996, 2003,..., 2017. Note the different y-axes in the upper and lower panels. Blue curves are men, red curves women; shaded areas represent 95% CIs. (A) men, type 1 diabetes; (B) women, type 1 diabetes; (C) men, type 2 diabetes; (D) women, type 2 diabetes.

decrease over the entire study period of 2.9% per year (men: 3.3%/year, women: 2.5%/year, table 1).

Type 1 versus type 2 diabetes mortality ratio

We found a higher mortality among patients with T1D relative to T2D (figure ESM6); the first few years after diagnosis more than twofold, but at 10 years of duration the T1D/T2D mortality rate ratio was about 1.7, and decreasing by duration and hence by current age too. Overall, the T1D versus T2D mortality rate ratio was 1.86 (1.79;1.93) for men and 1.55 (1.48;1.63) for women.

Standardized mortality ratio

The SMR and the mortality in patients with diabetes relative to the mortality among persons without diabetes are shown in figure 3, evaluated at 1 January 2015.

For T1D, we found decreasing SMR by age/duration for a given age at diagnosis, and an overall SMR at 2015 of about 4 for men and 6 for women in younger ages, remaining at about 5 for both sexes until age 60 and declining to 2 for both sexes in age 80. We also found that the SMR on average was declining by some 2%/year (table 1) over the period after 2005.

For T2D, we found that beyond 5 years of duration, the slope in SMR by age/duration was somewhat smaller than the overall slope by age, with a smaller SMR the older the age at diagnosis. Thus, the decline in overall SMR by age for T2D is largely attributable to an effect of age at diagnosis and to a lesser extent an effect of current age. As for T1D, we also saw that the SMR for women is

Table 1 Average change (%/year) in prevalence, incidence, mortality and SMR of diabetes in Denmark over the period 1996–2016

		Men		Women	
% per year		Change	95% CI	Change	95% CI
Prevalence	T1D	0.51	(0.46 to 0.57)	0.52	(0.46 to 0.59)
	T2D	5.64	(5.61 to 5.67)	5.22	(5.19 to 5.24)
Incidence	T1D	−3.27	(−3.59 to −2.94)	3.78	(−4.19 to −3.37)
	T2D	3.43	(3.15 to 3.61)	3.16	(2.98 to 3.34)
Mortality	T1D	−0.51	(−1.34 to −0.33)	−0.17	(−1.19 to −0.86)
	T2D	−3.30	(−3.48 to −3.13)	−2.53	(−2.73 to −2.33)
SMR	T1D	2.55	(1.69 to 3.42)	2.45	(1.40 to 3.51)
	T2D	−0.46	(−0.28 to −0.64)	−0.23	(−0.44 to −0.03)
Follow-up only >2005					
Mortality	T1D	−5.10	(−3.53 to −6.63)	−4.98	(−2.88 to −7.03)
	T2D	−3.64	(−3.36 to −3.92)	−3.06	(−2.74 to −3.38)
SMR	T1D	−1.89	(−0.28 to −3.48)	−2.28	(−0.07 to −4.36)
	T2D	−0.72	(−0.43 to −1.01)	−0.60	(−0.27 to −0.92)

SMR, standardized mortality ratio; T1D, type 1 diabetes; T2D, type 2 diabetes.

larger than for men, but we saw only a moderate decline of 0.6%/year (table 1).

CONCLUSIONS

Based on nationwide registers in Denmark, we described the prevalence, incidence and mortality of T1D and T2D. Our main findings are fivefold.

First, we found that the prevalence of T1D hardly changed over the last 20 years, while T2D increased from 1% to 4.5%, so that T2D now constitute 90% of all patients with diabetes. Second, the incidence of T1D increased slightly in the younger age groups,~2%/year, and declined in the older age groups, ~5%/year, over the study period. Third, the T2D incidence increased until 2011, declined until 2014, but seems to increase again after 2015. Fourth, the mortality of patients with T1D is more than 50% higher than that of patients with T2D. Finally, we found an excess mortality for T1D and T2D compared with the general population, highest for T1D.

The overall prevalence estimates by 1 January 2017 found in this study of 0.5% for T1D and 4.5% for T2D are in the range of findings from countries like Sweden, Norway and the USA.[4 5 19]

Most studies in T1D have reported the prevalence and incidence in children and youth, and only few have included older age groups as done in our study.[20 21 22] The peak T1D incidence rates of 0.35 in men and 0.25 in women per 1000 PY up to late adolescence correspond to the rates found in countries like Sweden, Finland, Norway and UK with an incidence over 0.20 per 1000 PY.[21–24]

In our study, the incidence of T1D increased up to 20 years of age and after that declined for women, while it remained high for men until age 40 and then decreased. The excess incidence of T1D in men compared with women is consistent with findings from other studies in high-risk countries.[25 26] Similar to our findings of differential calendar time trends in T1D incidence at different ages, a nationwide Swedish study also reported differential effects with increases in ages <15 years and decreases in the older age groups (25–34 years) from 1983 to 2007, which would imply a shift to younger age at diagnosis.[24]

In the older age groups, the T1D prevalence declined over the study period. This was unexpected and may be an artifact since improvements in healthcare should have kept the prevalence more stable. This could be due to changes in diagnostic criteria with a higher tendency to diagnose insulin-dependent individuals as T1D in the past with a shift to recognizing more of these as T2D in the later part of the study period. Since the T1D classification before 2005 primarily relies on the NPR records, miscoding of insulin using patients with T2D as patients with T1D may be partly responsible for this. This also results in an implausible increase in T1D mortality up to around 2005, so interpretation of T1D mortality trends prior to 2005 should be cautious.

For T2D incidence, we saw an increase up to 2011 followed by a downturn. The total number with T2D in Denmark was 252 516 by 1 January 2017, far from the 386 700 estimated by the International Diabetes Federation (IDF).[27] IDF's assumption was based on the former Danish Diabetes Register from 2012, and the huge overestimation by IDF underlines the importance of regularly updated criteria for disease monitoring. A decline in T2D incidence or plateauing has been reported in studies from Scotland,[2 3] USA and Sweden, but in contrast to our study, the decline/plateauing happened earlier.[1 4 28]

A register-based study from Norway recently conducted by Ruiz *et al* found a decline in T2D incidence in the

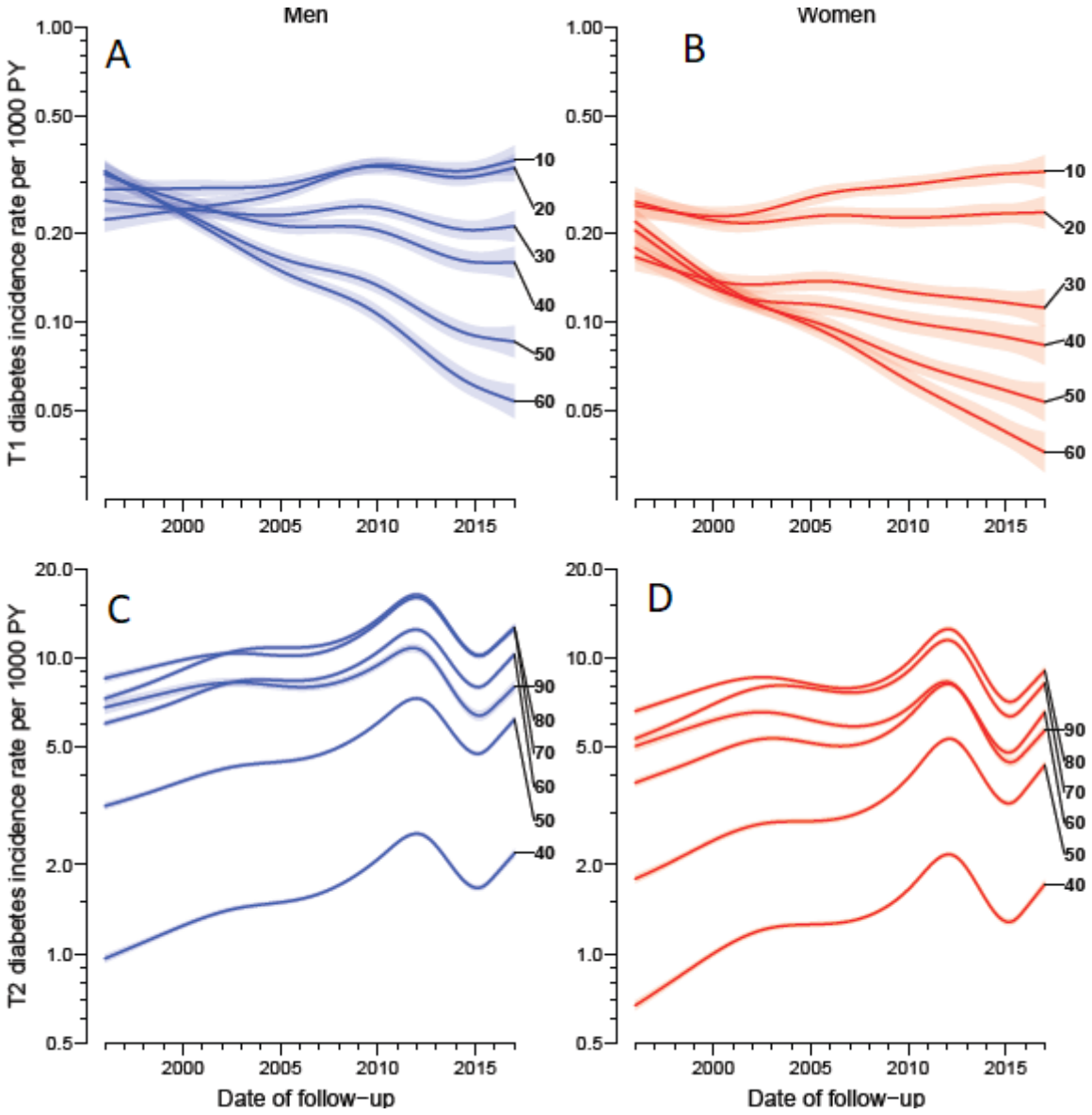

Figure 2 Age-specific incidence rates in different ages as of 1 January 2015, derived from age–period–cohort models. Note the different y-axes in the upper and lower panels but that the relative extent of the axes is the same for type 1 diabetes and type 2 diabetes. Blue curves are men, red curves women; shaded areas represent 95% CIs. (A) men, type 1 diabetes; (B) women, type 1 diabetes; (C) men, type 2 diabetes; (D) women, type 2 diabetes.

period 2009–2014 which after 2012 seemed to level off.[5] Both in Norway and Denmark, the recommendation of HbA1c as diagnostic test for diabetes was introduced in 2012 and is therefore likely to contribute to changes in incidence rates around this time; however, while the incidence in Norway seemed to level off, we saw a decline. Whether the decline in T2D incidence observed after 2011 in ours and other studies is due to changes in diagnostic criteria, a true decline in incidence or because less undiagnosed cases is found, is unknown.

A decline in mortality among patients with diabetes have been reported in several countries. We also found a decline in absolute mortality among both T1D and T2D over the period but with differential trends for T1D and T2D depending on age at diagnosis and duration.[2 3 29–31]

We found that mortality rates of T1D are higher than those of T2D for patients of similar age, but with rate ratio dissimilar between men (rate ratio 1.84) and women (rate ratio 1.55). The higher mortality in T1D corresponds to what is seen in other studies.[30 32 33]

An Australian study found the all-cause mortality to decrease from 1997 to 2010 for both patients with T1D and T2D with a larger decrease than found in the general population.[30] Similar trends have been observed in USA[29] and Scotland, which is consistent with our finding of an SMR decline for T2D of 0.6% per year.[2 3]

Early age at diagnosis and hence longer duration of diabetes was associated with a smaller mortality among patients with T1D in our study but a larger mortality among patients with T2D, although the latter effect was

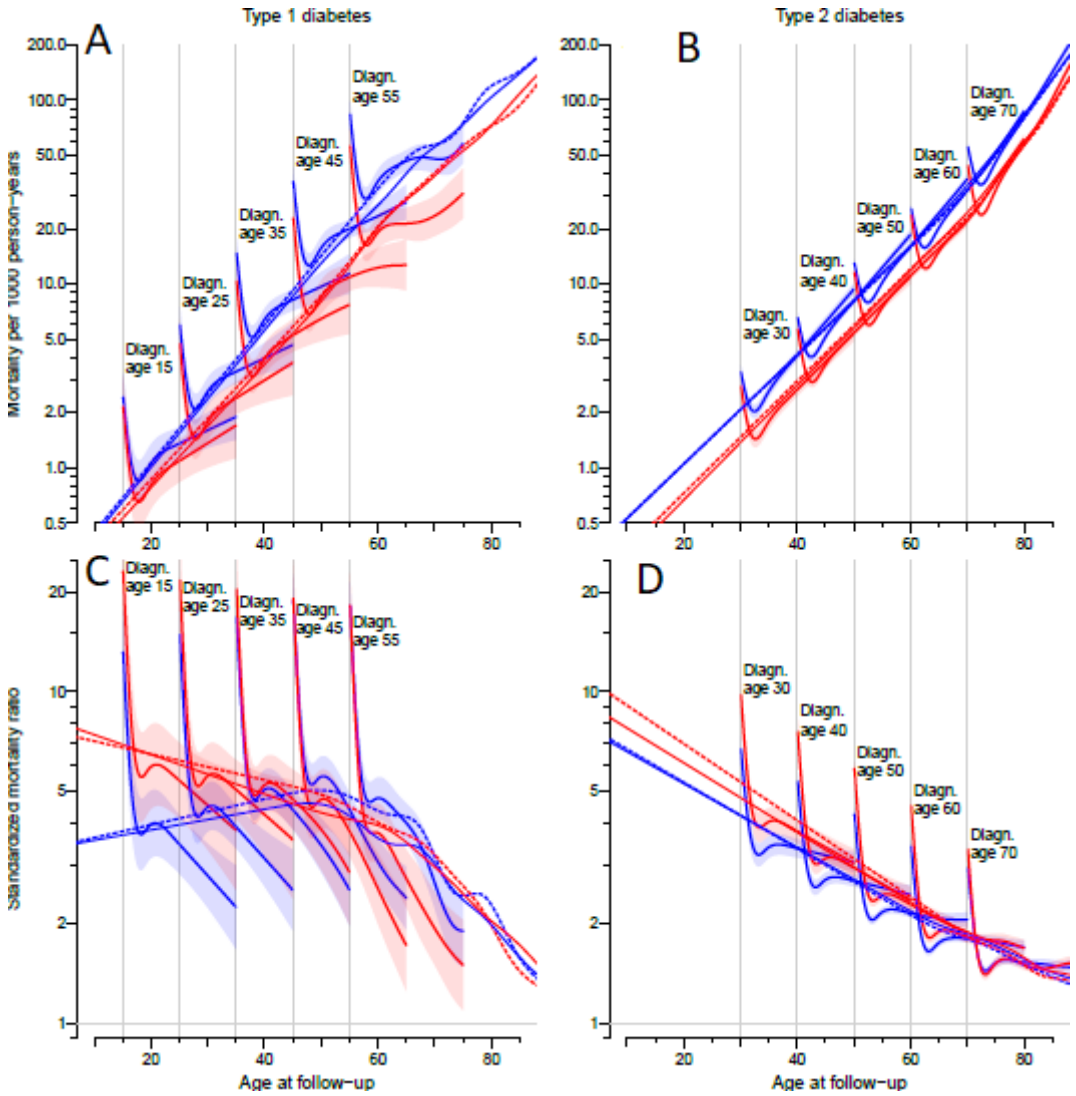

Figure 3 Age-specific mortality rates (A, B) and SMR (C, D) as of 1 January 2015 for type 1 diabetes (A, C) and type 2 diabetes (B, D). Each curve represents the mortality among patients diagnosed at ages 15, 25, 35, 45, 55 (type 1 diabetes) respectively 30, 40, 50, 60, 70 (type 2 diabetes), indicated by gray vertical lines. Each curve thus represents the joint effect of attained age and duration of diabetes for a given age at diagnosis and duration from 0 to 20 years. Thick dotted curves are from a model ignoring age at diagnosis and duration of diabetes; thin full lines additionally include prevalent cases as of 1 January 1996 in the modeling. Blue curves are men, red curves women. SMR, standardized mortality ratio.

small and mostly confined to men. This means that duration of T2D has limited effect beyond the first 2 years after diagnosis. In contrast with our results in T1D, a study by Rawshani *et al* conducted in Sweden reported a higher mortality with younger age at diagnosis of T1D, but it was not clear how this study included duration and current age, which may have affected the reported effect of age at diagnosis.[34]

The major strength of our study is that it covers the entire Danish population, the long coverage period of 21 years and our ability to distinguish T1D and T2D. Moreover, we have made full use of the register data by modeling the effects of age, calendar time and for mortality also the duration of diabetes, using the quantitative nature of the time variables age, duration and calendar time.

The weakness of our database is that inclusion date, which is used as proxy for date of diagnosis, is based solely on administrative records, and we may have defined prevalent cases among people migrating to Denmark as incident cases.

While the classification of patients as T1D or T2D based on the clinical reporting of cases to the DADD is a strength, the limited coverage of the DADD most likely underestimates the number of patients with T1D prior to 2005, and in particular among those who died before 2005, which possibly means that our mortality estimates for T1D prior to 2005 are downward biased. Analyses of mortality restricted to the period after 2005 indicated that our conclusions about duration effects may be biased downwards, and that mortality at a given age is increasing with increasing duration. Furthermore, T2D

incidence among women under 40 may be underestimated due to the classification as possible patients with polycystic ovary syndrome if metformin only is used in the age range 18–40, and some insulin-treated T2D may be misclassified as T1D below the age of 30.

Overall, we have tried to improve sensitivity by inclusion of several data sources, particularly to capture patients with T2D treated in General Practice without a diabetes diagnosis in the National Patient Register. There is, however, still a risk of underestimating the T2D population not receiving antidiabetic treatment and not seeking regular eye examination or podiatry. The risk of including people without diabetes in the register is negligible while all included information is diabetes specific.

An administratively generated diabetes register as the one at hand reflects the organization of diabetes care in Denmark, primarily distinguishing between T1D and T2D, and other ICD-10 codes than DE10.x and DE11.x were excluded. This approach somehow ignores the growing clinical acknowledgment of several subtypes of diabetes, such as slowly evolving immune-mediated diabetes and ketosis-prone T2DM, but no data are available for further qualification of the categorization.

During a 21-year period, we observed increasing prevalence and incidence rates but with a decreasing incidence of T2D from 2012. From a public health and prevention perspective, it is imperative to confirm or deny the apparent increase in T2D incidence observed again after 2014. The incidence for T1D remained more stable over the period; however, reflecting differential patterns according to age at diagnosis, and the mechanisms underlying the increase in T1D incidence among children and adolescents remains unsolved. The decline in mortality was found both among T1D and T2D, but mostly for T1D in the most recent period, which may be due to improved treatment. Despite a reduction in mortality, patients with diabetes still experience an excess mortality relative to persons without diabetes, highest for patients with T1D. This can only partially be attributed to differences in disease duration, and quality measures of diabetes care in Denmark indicate a less aggressive approach to manage cardiovascular risk factors in T1D.[35] The excess mortality underlines the need for continuous improvements in prevention and treatment of complications especially among patients with T1D.

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Contributors BC and MEJ conceived the structure of the underlying register and designed the study. PFR provided support for obtaining data access and contributed to data definition. BC detailed the statistical methods needed, performed all data analysis and wrote a first draft of the manuscript. MEJ and PFR contributed substantially to the writing of the manuscript. All authors contributed to critical revision and take responsibility for the content. BC 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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Disclaimer Sanofi Aventis had no influence on study design or analyses.

Competing interests BC and MEJ own shares in NovoNordisk. BC has received lecture and consultancy fees from NovoNordisk and LeoPharma. MEJ is PI on a trial sponsored by AstraZeneca, and received research grants from AMGEN AB, AstraZeneca, Sanofi Aventis and Boehringer Ingelheim. PFR has nothing to disclose.

Patient consent for publication Not required.

Ethics approval This study was approved by the Danish Data Protection Agency (registration no. 2015-41-4148). Ethical approval is not required for register-based studies in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data for this study are population-wide registers, placed at our disposal on the servers of Statistics Denmark. They are barred from release to the public on grounds of confidentiality. A full documentation of the register is given in the Electronic Supplementary Material.

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Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016

Electronic Supplementary Material

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1 Material and methods

This section provides further details on the underlying register and the statistical methods used in the analysis.

A complete documentation of the construction of the register and the analysis files of prevalence and follow-up can be found in
http://BendixCarstensen.com/DMreg/Reg2016.pdf , and a complete account of all statistical analyses based on these is available in
http://BendixCarstensen.com/DMreg/Ana2016.pdf. Both documents are approximately 300 pages, as they contain a complete code documentation and extensive tabulations of results.

1.1 Register data

The Danish national health care system (NHS) is run by the state (through 5 health care regions) and covers all Danish citizens free of charge. Thus all citizens are in the *same* system.

Furthermore, in Denmark (as in all Nordic Countries) there are population-wide registers covering virtually all aspects of life, including heath care. All registers are linkable by a unique person id [1], so residents of Denmark can be followed with respect to disease occurrence, medicine purchase, health care use, migration etc.

The registers are available for research purposes at a secure server at Statistics Denmark in anonymized, linkable form; Statistics Denmark generates an id which can be used for linkage across the registers at our disposal, but not to identify a person. Thus, linkage is exact, not probabilistic.

1.1.1 Diabetes data

We constructed a Danish diabetes register from existing Danish health care registers. The five registers are considered to be those where diabetes patients will appear, so our approach has been to maximize sensitivity. We included persons as diabetes patients using the *earliest* of the following dates from the registers as inclusion date (all registers may have multiple records per person):

- first diagnosis of diabetes (ICD-8: 249, 250; ICD-10: E10, E11) in the National Patient Register [2] (NPR; 1977–). The NPR is a register of all contacts with the hospital system, from 1990 also including visits to out-patient clinics.

- first use of "podiatry for diabetes patients" as recorded in the National Health Services Register [3] (NHSR, 1990–). The NHSR includes all billings for health services paid to health care providers, and "podiatry for diabetes patients" are only available for persons with a referral from physician. Hence everyone in this database is a verified diabetes patient.

- first date of purchase of any anti-diabetic medication (ATC A10xxx) in the Medicines Products Register [4] ("Prescription register") (MPR, 1995–). The MPR includes all filled prescriptions since 1995-01-01 with detailed information on product and amount, linked to the person-id.

- first date of diagnosis mentioned in the Danish Adult Diabetes Database [5] (DADD, 2005–). The DADD is a database for quality monitoring where clinical information on diabetes patients is reported annually by GPs and outpatient clinics. The reports include information on type of diabetes (as T1D, T2D or other type). Hence everyone in this database is a verified diabetes patient. The information from outpatient clinics is complete, but that from general practice is currently incomplete. But since all T1D patients are seen in outpatient clinics, this data base will identify all T1D patients, in the period of coverage.

  The dates of diagnosis are inaccurate (83% are either 1 Jan or 15 Jul), so the date from DADD is only used if DADD is the only source for a given person. Thus DADD is mainly used for classification of patients as T1D/T2D.

- first date of eye examination recorded in the diaBase [6] (diaB, 2009–). The diaBase is a data base for quality monitoring of retinopathy screening, where eye-screenings of diabetes patients are reported. Hence everyone in this database is a verified diabetes patient.

In order to increase specificity of the recording we included only persons from the second date of either NPR or MPR recording; we extracted the two first dates of NPR recordings and the dates of two first MPR recording, and used the second of these four dates as the inclusion date.

Dates within 30 days prior and 365 days after a recorded diagnosis of gestational diabetes in the NPR were disregarded. Dates of metformin purchase between a date of polycystic ovary syndrome (PCOS) and the woman's 40^{th} birthday were disregarded. Purchase of metformin in women between 18 and 40 were disregarded because purchase of metformin alone was considered most likely to be part of treatment of infertility in a PCOS patient.

Type of diabetes: A person was classified as T1D from DADD if the majority of the person's records classified the person as T1D, and similarly for T2D. Persons not meeting any of these criteria were left unclassified by the DADD — this would be persons classified as other type of DM or with an equal number of classifications as T1D and T2D.

A person was classified as T1D from NPR if the majority of the person's records classified the person as T1D, and similarly for T2D. Persons not meeting any of these criteria were left unclassified by the NPR — this would be persons with an equal number of records with classification as T1D and T2D.

Persons were classified as T1D in the diabetes register if any of the following criteria were met (and otherwise as T2D):

- Purchase of oral anti-diabetic drugs (OAD) before age 15
- Purchase of insulin before age 30
- DADD classification as T1D.
- Unclassified from DADD, but classified as T1D from NPR.

Finally, persons without a recorded insulin purchase in the MPR, will always be classified a T2D regardless of the above. Persons not classified as T1D are classified as T2D.

The main source of T1D status was the DADD, which however only comprises persons alive at 2005 or later, so the sensitivity of the T1D classification is declining backwards in time prior to 2005, particularly for persons who died before 2005.

Strictly speaking, the classification of persons by type (as of the date of inclusion) depends on recordings *later* than the date of inclusion, and so we are formally conditioning on the future in the definition of diabetes type.

Time-range of the constructed register: The MPR is complete from 1995-01-01, so if the first recorded anti-diabetic drug purchase was after 1996-01-01, *i.e.* after at least one year with no recorded purchase, we assumed that it was actually a first drug purchase for that person. Since the other major sources of information predates 1996, we assume the constructed register to be reliable as incidence register from 1996-01-01, with the persons in the register alive as of that date to be a reliable recording of prevalent cases. This implies that dates of entry to the register before 1996-01-01 are unreliable as dates of diagnosis of diabetes, and these persons are only included as prevalent cases of diabetes as of 1996-01-01. The latter limits analyses involving duration of diabetes to persons included in the register after 1996-01-01.

1.1.2 Population data

In addition to the registers mentioned above, we had access to complete individual level register information on the entire Danish population, including sex and dates of birth, emigration, immigration and death as well as cause of death.

1.2 Tabulation of data

With the described register information we were able to classify all follow-up time (person-years and events of diabetes and death) in the entire Danish resident population as being either without diabetes or with T1D or T2D. We have observations from the registers for the 21 calendar years 1996 through 2016, so the last date of observation is 2016-12-31, which we for convenience in connection with dates of prevalence will label as 2017-01-01 (or just 2017).

1.2.1 Prevalence

The number of prevalent cases of T1D and T2D separately, alive at 1 January 1996–2017 were tabulated by sex and 1-year age group. The corresponding total population counts at each date were derived from our total register of the Danish population.

1.2.2 Follow-up

Periods after emigration and before immigration were excluded from the tabulation of follow-up. The follow-up (time at risk, events of diabetes by type and death by cause) in the Danish population 1996–2016 incl. was tabulated by current diabetes status (no DM, T1D, T2D), sex, age and date of follow-up and date of birth in 1-year classes (Lexis triangles, [7]). As an example, persons who contribute follow-up in the age class 66 during the year 2006 are classified by date of birth in one of two groups: those born in 1939 (who are 66 years of age as of 2006-01-01), and those born in 1940 (who turn 66 during 2006).

Among those born in 1939 the mean age at follow-up is $66\frac{2}{3}$, and the mean date of follow-up is $2006\frac{1}{3}$, and consequently the mean date of birth $1939\frac{2}{3}$. Among those born in 1940 the mean age at follow-up is $66\frac{1}{3}$, and the mean date of follow-up is $2006\frac{2}{3}$, and consequently the mean date of birth is $1940\frac{1}{3}$.

Further, the follow-up among diabetes patients diagnosed after 1996-01-01 (for whom date of diagnosis was known) were further classified by duration of diabetes in intervals divided at 0, 0.2, 0.5, 1, 2,... years, *i.e.* with means 0.1, 0.35, 0.75, 1.5, 2.5,... years.

These mean values are used as *quantitative* variables in the modeling of age, calender time, birth cohort and duration effects on incidence and mortality rates, as well as duration effects on mortality.

1.3 Statistical methods

All statistical models were fitted separately for men and women and for no DM (where relevant), T1D and T2D. For each tabulation unit (Lexis triangle) we used the mean of current age (occasionally termed attained age or age at follow-up), date and duration of diabetes and date of birth, as *quantitative* explanatory variables. The effect of these were modeled by natural splines (restricted cubic splines).

1.3.1 Prevalence

We modeled prevalence separately for each of the dates 1 January 1996–2017 by restricted cubic splines for age, using a binomial model with log-link. The resulting age-curves were shown for each of the 22 dates. We also fitted models jointly for all dates with a linear effect of date in order to devise an overall annual relative change in prevalence.

1.3.2 Incidence rates

Incidence rates were modeled using Poisson models with log person time as offset and natural cubic spline effects of current age and date of follow-up and date of birth (age-period-cohort (APC) model [7]). We used 2015-01-01 as reference point for calendar time, thus rendering the age-specific rates estimates of the rates as of this date, the period effects as estimates of RR relative to 2015-01-01 and the cohort effects as residual effects relative to this. We extracted the overall linear trend (drift) from the APC models. Finally, we also show the non-linear time-trends evaluated at different ages derived from these models.

1.3.3 Mortality rates

Mortality rates were modeled using Poisson models with log person time as offset and natural cubic spine effects of calendar time, current age, duration of diabetes, age at diagnosis (calculated as current age minus duration).

We used 2015-01-01 as reference point for the calendar time, thus rendering the age-specific mortality rates estimates of the rates as of this date. As model check we also show the residuals by date of birth as RRs from this model.

1.3.4 Age, duration and age at diagnosis

Since the variables current age, duration and age at diagnosis are linearly connected (current age = age at diagnosis + duration of diabetes) we cannot separate the effects of them without further assumptions (see e.g. [7]). For example, we may claim that mortality increases more by current age, if we are willing to assume that it increases correspondingly less by diabetes duration and age at diabetes diagnosis. Hence if we include all three variables in a model we cannot make a claim as to an isolated effect of any particular of the three.

Specifically, suppose we aim to describe the mortality rates (μ) as a function of current age, a; duration of diabetes, d and age at diagnosis, $e = a - d$ ("e" for age at diagnosis; *e*ntry into diabetes), then we have that $a - d - e = 0$. If we formally set up a model with only the effect of current age and age at diagnosis of diabetes:

$$\log\big(\mu(a,d)\big) = f(a) + h(e)$$

it is only superficially that this does not include duration: since $a-d-e=0$, we may write:

$$\begin{aligned}\log\big(\mu(a,d)\big) &= f(a) + h(e)\\ &= f(a) + h(e) + \gamma(a-e-d)\\ &= \big(f(a)+\gamma a\big) + \big(h(e)-\gamma e\big) - \gamma d\end{aligned}$$

Thus, even if duration is not formally included in the model we may claim that is has any *linear* effect we like, by simply asserting that the age and age at diagnosis effects are different by a similar linear amount. Thus there is no way to allocate a "correct" duration effect, let alone effects of current age and age at diagnosis. One might of course on purely external grounds (*i.e.* unrelated to the data at hand) assert that there is no duration effect, but this can never be founded in data.

Therefore, it makes more sense to set up a model with non-linear effects of all three variables. But we still have the problem from the linear dependence:

$$\begin{aligned}\log\big(\mu(a,d)\big) &= f(a) + g(d) + h(e)\\ &= f(a) + g(d) + h(e) + \gamma(a-d-e)\\ &= \big(f(a)+\gamma a\big) + \big(g(d)-\gamma d\big) + \big(h(e)-\gamma e\big)\\ &= \tilde{f}(a) + \tilde{g}(d) + \tilde{h}(e)\end{aligned}$$

Here it is seen that we can have two *different* sets of three effects that together produce the same mortality rates; moreover this would be the case for *any* value of γ we care to stick into the formula.

Even if we cannot separate the three effects in the model, we can still make perfectly valid predictions from the model, and certain contrasts will also be identifiable from the model. Notably it is possible to estimate the mortality rate-ratio at a given age (a) between persons diagnosed at different ages, e_1 and e_0, and hence with durations $a - e_1$ and $a - e_0$:

$$\begin{aligned}\log(\mathrm{RR}_{e_1 \text{vs } e_0}) =& f(a) + g(a-e_1) + h(e_1) -\\ & f(a) - g(a-e_0) - h(e_0)\\ =& g(a-e_1) - g(a-e_0) + h(e_1) - h(e_0)\end{aligned}$$

Using another set of effects $\tilde{f}$, $\tilde{g}$ and $\tilde{h}$ the sum of which is distinguished from these by a term $\gamma(a-d-e)$:

$$\begin{aligned}
\log(\mathrm{RR}_{e_1 \text{ vs } e_0}) =& \tilde{g}(a-e_1) - \tilde{g}(a-e_0) + \tilde{h}(e_1) - \tilde{h}(e_0) \\
=& \big(g(a-e_1) - \gamma(a-e_1)\big) - \\
& \big(g(a-e_0) - \gamma(a-e_0)\big) + \\
& \big(h(e_1) - \gamma e_1\big) - \\
& \big(h(e_0) - \gamma e_0\big) \\
=& g(a-e_1) - g(a-e_0) + h(e_1) - h(e_0) + \gamma(-a+e_1+a-e_0-e_1+e_0) \\
=& g(a-e_1) - g(a-e_0) + h(e_1) - h(e_0)
\end{aligned}$$

This shows that these contrasts are invariant under *any* reparametrization, and hence *are* identifiable from any parametrization of the model.

Since the intercept and the linear effects of current age, age at diagnosis and duration of diabetes cannot be separated, we reported the estimated mortality as a function of current age, using separate curves for persons diagnosed at ages 30, 45 etc. (different between T1D and T2D); each curve stretching from the age at diagnosis and 20 years on (20 years being the range of duration for which we have reasonably reliable information). The mortality curves are thus showing the *joint* effect of current age, age at diagnosis and duration of disease (see *e.g.* [8].)

1.3.5 Mortality data range

Since only persons included after 1996-01-01 have a reliable date of diagnosis, mortality analyses using age at diagnosis and duration were restricted to persons included after this date. For comparability with other studies, age-specific mortality rates ignoring both age at diagnosis and duration were reported both for the restricted group of patients diagnosed after 1996-01-01 and for all patients (that is, also including the prevalent cases as of 1996-01-01).

Analyses were made separately for men and women and for T1D and T2D separately. We computed M/W mortality rate-ratios for each type of diabetes, and T1D/T2D mortality rate-ratios for men and women separately.

1.3.6 Standardized Mortality Ratio (SMR)

We used the data from persons without DM to calculate empirical mortality rates among persons without diabetes, classified by sex, age, date of follow-up and date of birth. Multiplying these with the corresponding person years among diabetes patients yielded the expected number of deaths during T1D and T2D follow-up.

The SMR was modeled exactly as the mortality by current age, duration of diabetes and age at diagnosis, but using the log of the expected number of deaths as offset deriving the SMR as the mortality rate-ratio between T1D, resp. T2D and no DM.

1.4 Sensitivity analyses

Due to the larger uncertainty of T1D/T2D classification prior to 2005 we made separate mortality analyses using only follow-up after 2005, shown in ESM figure 5 — compared

with ESM figure 4.

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Table ESM 1: *Number of prevalent diabetes patients in Denmark at 1 January each year 1996–2017 by diabetes type and sex. Includes also persons over 100 years of age.*

	T1D		T2D		%T1		All DM		
Date	M	W	M	W	M	W	M	W	M+W
1996	12,328	9,549	30,269	31,313	28.9	23.4	42,597	40,862	83,459
1997	12,677	9,776	33,790	34,110	27.3	22.3	46,467	43,886	90,353
1998	12,958	9,986	36,952	36,433	26.0	21.5	49,910	46,419	96,329
1999	13,222	10,113	40,711	39,166	24.5	20.5	53,933	49,279	103,212
2000	13,386	10,235	44,398	42,132	23.2	19.5	57,784	52,367	110,151
2001	13,560	10,295	47,960	44,905	22.0	18.7	61,520	55,200	116,720
2002	13,729	10,371	51,627	47,480	21.0	17.9	65,356	57,851	123,207
2003	13,845	10,452	56,329	51,822	19.7	16.8	70,174	62,274	132,448
2004	13,948	10,479	61,908	56,419	18.4	15.7	75,856	66,898	142,754
2005	14,012	10,567	67,642	61,118	17.2	14.7	81,654	71,685	153,339
2006	14,072	10,644	72,161	64,348	16.3	14.2	86,233	74,992	161,225
2007	14,209	10,715	76,556	66,962	15.7	13.8	90,765	77,677	168,442
2008	14,339	10,801	81,389	70,320	15.0	13.3	95,728	81,121	176,849
2009	14,485	10,901	87,374	74,596	14.2	12.8	101,859	85,497	187,356
2010	14,648	10,979	93,778	78,796	13.5	12.2	108,426	89,775	198,201
2011	14,745	11,078	101,220	83,763	12.7	11.7	115,965	94,841	210,806
2012	14,860	11,177	112,085	93,133	11.7	10.7	126,945	104,310	231,255
2013	14,988	11,289	119,930	99,369	11.1	10.2	134,918	110,658	245,576
2014	15,116	11,458	125,077	103,338	10.8	10.0	140,193	114,796	254,989
2015	15,304	11,614	129,587	106,584	10.6	9.8	144,891	118,198	263,089
2016	15,512	11,826	134,172	109,844	10.4	9.7	149,684	121,670	271,354
2017	15,684	11,930	139,209	113,307	10.1	9.5	154,893	125,237	280,130

Table ESM 2: *Crude prevalence (%) of diabetes in Denmark at 1 January 1996–2017 by diabetes type and sex. Includes also persons over 100 years of age.*

	T1D		T2D		All DM		
Date	M	W	M	W	M	W	M+W
1996	0.47	0.36	1.16	1.17	1.64	1.53	1.58
1997	0.48	0.37	1.29	1.27	1.78	1.64	1.71
1998	0.49	0.37	1.41	1.36	1.90	1.73	1.81
1999	0.50	0.38	1.54	1.45	2.05	1.83	1.94
2000	0.51	0.38	1.68	1.56	2.19	1.94	2.06
2001	0.51	0.38	1.81	1.66	2.32	2.04	2.17
2002	0.52	0.38	1.94	1.74	2.45	2.13	2.29
2003	0.52	0.38	2.11	1.90	2.62	2.28	2.45
2004	0.52	0.38	2.31	2.06	2.83	2.45	2.64
2005	0.52	0.39	2.52	2.23	3.04	2.61	2.82
2006	0.52	0.39	2.68	2.34	3.20	2.73	2.96
2007	0.52	0.39	2.83	2.43	3.35	2.82	3.08
2008	0.53	0.39	2.99	2.54	3.52	2.93	3.22
2009	0.53	0.39	3.19	2.68	3.72	3.07	3.39
2010	0.53	0.39	3.41	2.82	3.94	3.21	3.57
2011	0.53	0.39	3.66	2.98	4.19	3.38	3.78
2012	0.54	0.40	4.04	3.30	4.57	3.70	4.13
2013	0.54	0.40	4.30	3.51	4.84	3.91	4.37
2014	0.54	0.40	4.46	3.64	5.00	4.04	4.52
2015	0.54	0.41	4.59	3.73	5.13	4.13	4.63
2016	0.54	0.41	4.70	3.81	5.24	4.22	4.73
2017	0.54	0.41	4.83	3.90	5.38	4.31	4.84

Table ESM 3: *Number of incident diabetes cases during each year 1996–2016 by diabetes type and sex. Excludes persons over 100 years of age and persons not resident at date of diagnosis.*

	T1D		T2D		All DM		
Period	M	W	M	W	M	W	M+W
1996	678	516	6,115	5,290	6,793	5,806	12,599
1997	684	489	5,839	4,918	6,523	5,407	11,930
1998	657	454	6,529	5,295	7,186	5,749	12,935
1999	592	413	6,739	5,707	7,331	6,120	13,451
2000	596	392	6,593	5,604	7,189	5,996	13,185
2001	586	415	6,795	5,449	7,381	5,864	13,245
2002	602	386	8,022	7,334	8,624	7,720	16,344
2003	545	386	9,146	7,673	9,691	8,059	17,750
2004	509	388	9,259	7,751	9,768	8,139	17,907
2005	517	379	8,174	6,510	8,691	6,889	15,580
2006	554	382	8,172	5,940	8,726	6,322	15,048
2007	564	384	8,738	6,792	9,302	7,176	16,478
2008	546	367	9,846	7,554	10,392	7,921	18,313
2009	568	357	10,762	7,720	11,330	8,077	19,407
2010	529	367	11,867	8,704	12,396	9,071	21,467
2011	496	358	15,593	13,150	16,089	13,508	29,597
2012	486	315	12,782	10,017	13,268	10,332	23,600
2013	471	351	10,215	7,971	10,686	8,322	19,008
2014	465	341	9,883	7,358	10,348	7,699	18,047
2015	476	375	9,987	7,638	10,463	8,013	18,476
2016	460	316	10,666	7,855	11,126	8,171	19,297
Sum	11,581	8,131	191,722	152,230	203,303	160,361	363,664

Table ESM 4: *Number of deaths among diabetes patients during each year 1996–2016 by diabetes type and sex. Only diabetes patients diagnosed since 1996-01-01.*

	T1D		T2D		All DM			non-DM
Period	M	W	M	W	M	W	M+W	M+W
1996	14	12	255	222	269	234	503	53,839
1997	28	16	577	455	605	471	1,076	53,020
1998	50	30	860	715	910	745	1,655	51,549
1999	85	34	1,217	908	1,302	942	2,244	51,971
2000	101	58	1,435	1,180	1,536	1,238	2,774	50,206
2001	97	83	1,737	1,356	1,834	1,439	3,273	50,734
2002	142	70	1,929	1,616	2,071	1,686	3,757	50,474
2003	141	100	2,279	1,828	2,420	1,928	4,348	49,280
2004	157	102	2,349	1,968	2,506	2,070	4,576	47,276
2005	196	111	2,600	2,194	2,796	2,305	5,101	46,366
2006	189	129	2,736	2,335	2,925	2,464	5,389	46,122
2007	186	108	2,990	2,529	3,176	2,637	5,813	46,507
2008	206	128	3,083	2,536	3,289	2,664	5,953	45,115
2009	194	129	3,507	2,797	3,701	2,926	6,627	45,008
2010	199	125	3,664	2,970	3,863	3,095	6,958	44,088
2011	166	107	3,831	2,999	3,997	3,106	7,103	42,294
2012	151	105	4,159	3,138	4,310	3,243	7,553	41,579
2013	147	84	4,336	3,341	4,483	3,425	7,908	41,183
2014	114	95	4,613	3,544	4,727	3,639	8,366	39,944
2015	123	81	4,796	3,779	4,919	3,860	8,779	40,947
2016	133	76	4,988	3,874	5,121	3,950	9,071	40,643

Table ESM 5: *Number of deaths among diabetes patients during each year 1996–2016 by diabetes type and sex. Includes both diabetes patients diagnosed from 1996-01-01 as well as prevalent cases of diabetes at this date.*

	T1D		T2D		All DM			non-DM
Period	M	W	M	W	M	W	M+W	M+W
1996	363	334	2,798	2,621	3,161	2,955	6,116	53,839
1997	442	311	2,819	2,734	3,261	3,045	6,306	53,020
1998	420	340	2,928	2,709	3,348	3,049	6,397	51,549
1999	453	331	3,193	2,864	3,646	3,195	6,841	51,971
2000	453	361	3,168	2,965	3,621	3,326	6,947	50,206
2001	433	357	3,276	2,988	3,709	3,345	7,054	50,734
2002	513	323	3,453	3,117	3,966	3,440	7,406	50,474
2003	473	381	3,667	3,226	4,140	3,607	7,747	49,280
2004	466	319	3,655	3,169	4,121	3,488	7,609	47,276
2005	487	329	3,724	3,362	4,211	3,691	7,902	46,366
2006	450	337	3,832	3,381	4,282	3,718	8,000	46,122
2007	425	278	3,911	3,544	4,336	3,822	8,158	46,507
2008	382	261	3,984	3,407	4,366	3,668	8,034	45,115
2009	357	256	4,464	3,639	4,821	3,895	8,716	45,008
2010	348	235	4,452	3,773	4,800	4,008	8,808	44,088
2011	311	200	4,614	3,714	4,925	3,914	8,839	42,294
2012	258	170	4,926	3,804	5,184	3,974	9,158	41,579
2013	240	143	5,054	3,994	5,294	4,137	9,431	41,183
2014	180	135	5,327	4,104	5,507	4,239	9,746	39,944
2015	185	118	5,431	4,345	5,616	4,463	10,079	40,947
2016	174	124	5,598	4,363	5,772	4,487	10,259	40,643

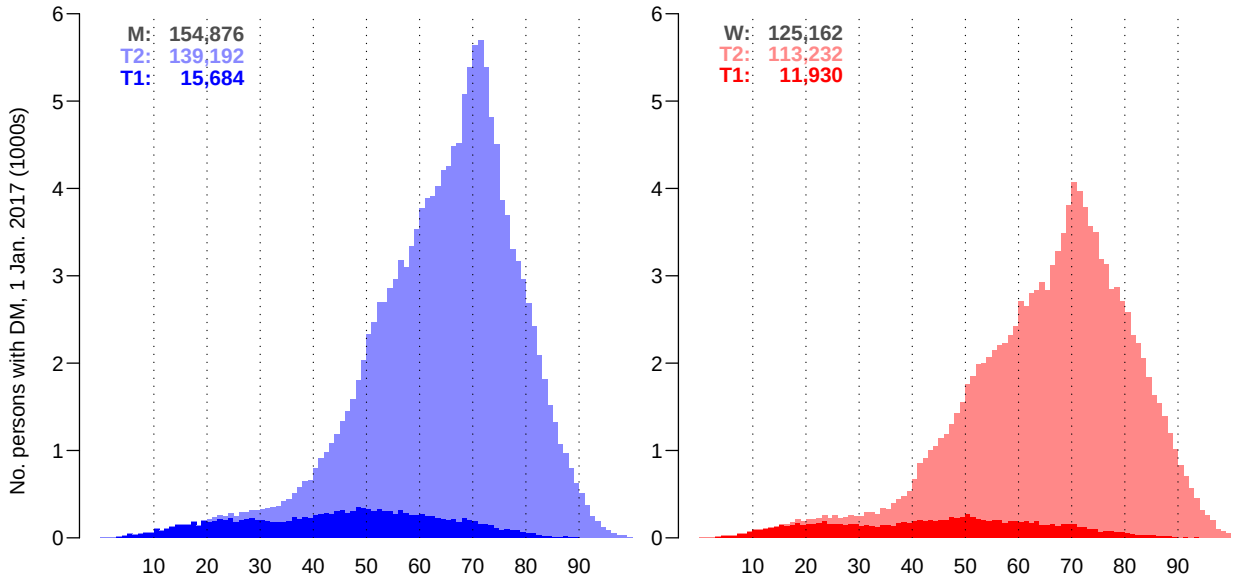

Figure ESM 1: *Number of T1D (dark color) and T2D (bright color) patients in Denmark as of 1 January 2017, the blue bars are men, red bars are women. The numbers in the corner of the plots indicate the number of prevalent cases, the black numbers are the total number of prevalent cases.*

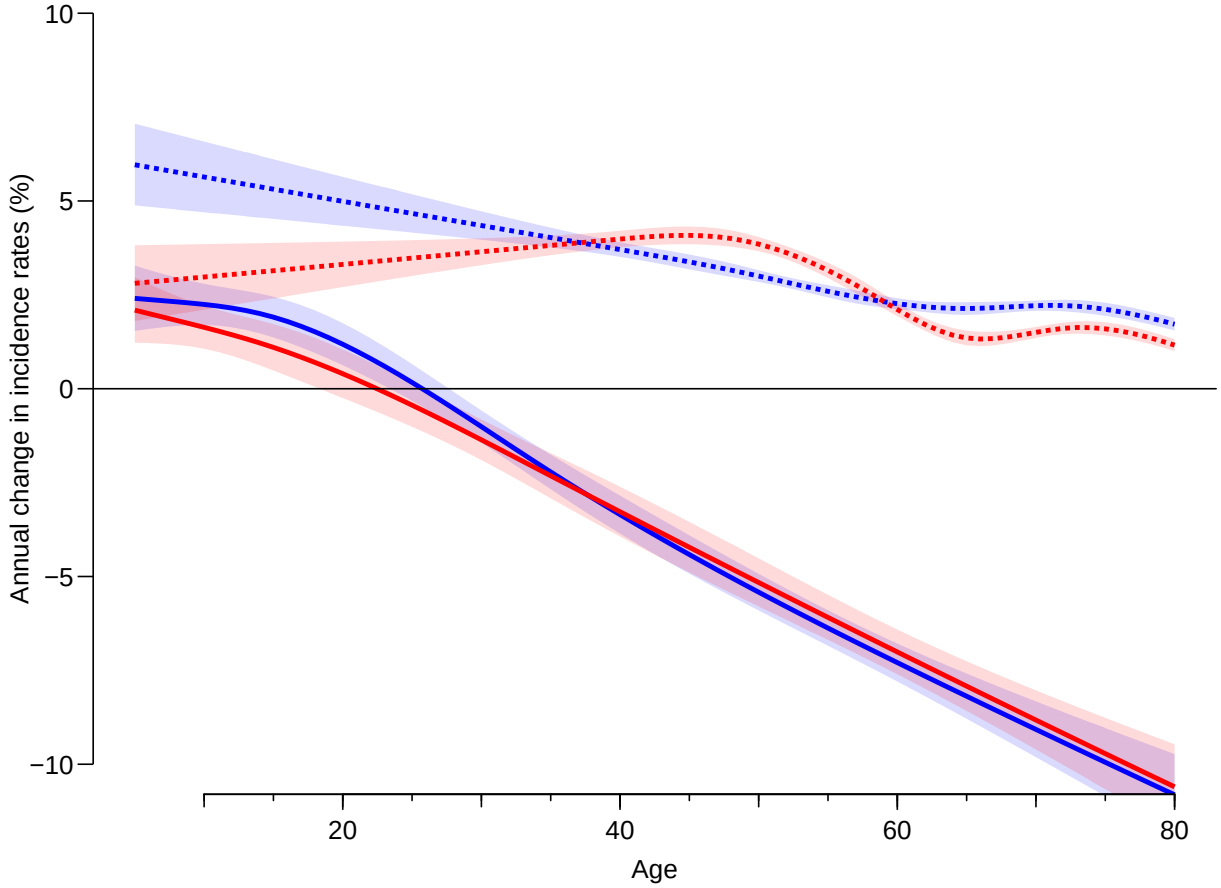

Figure ESM 2: *Age-specific average annual change in incidence rates of T1D and T2D in Denmark 1996–2016; a.k.a. "local drifts". Estimates are from models with a smooth effect of age and an interaction between a smooth age term and a linear calendar time term (varying coefficients model). Full lines are T1D, broken lines T2D, blue curves are men, red curves women. The shaded areas indicate 95% confidence intervals.*
It is seen that a summary of overall annual increase in T2D of 3.5% is quite reasonable, but that the change in incidence rates of T1D is positive under age 20 and negative over age 30.

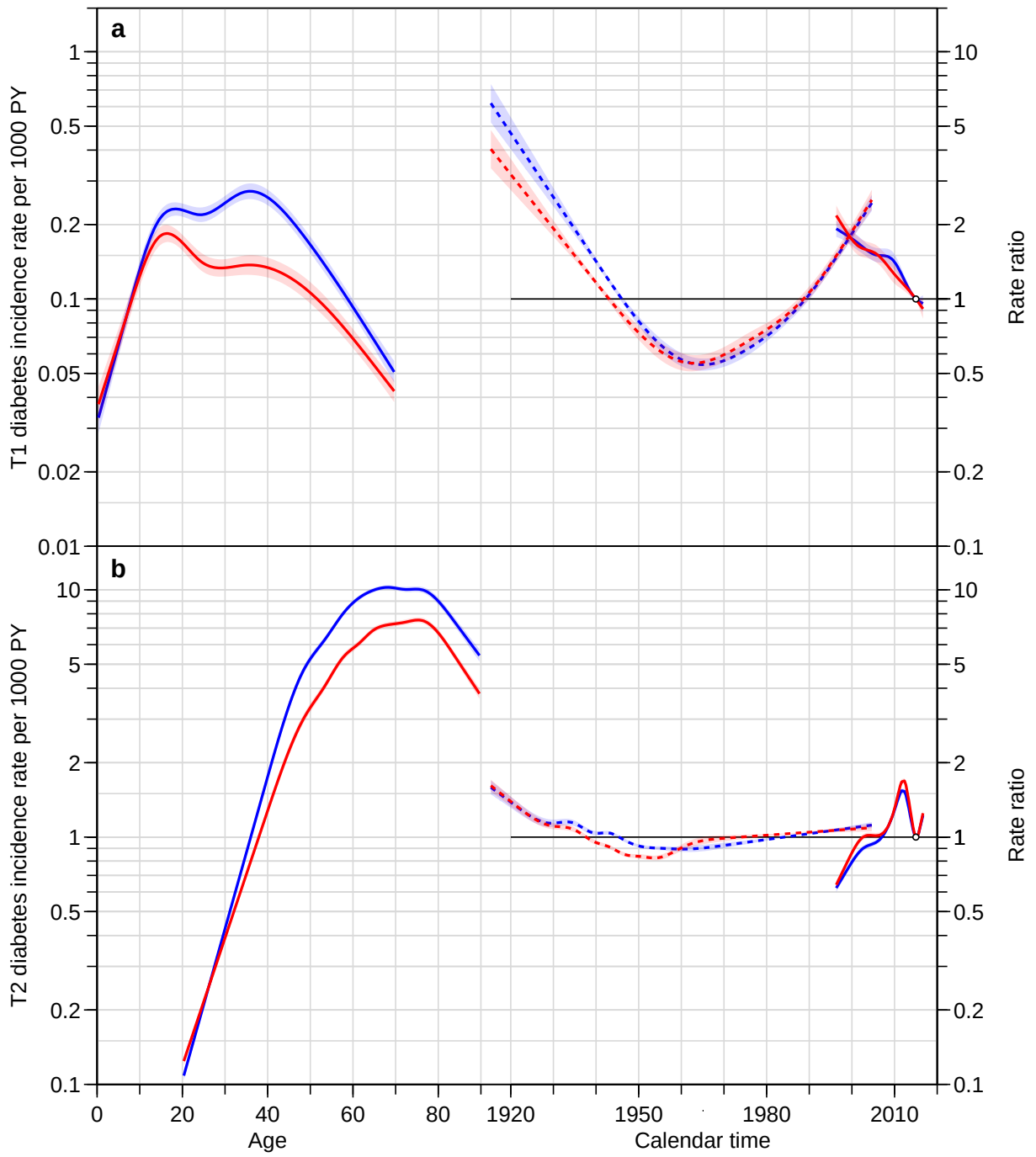

Figure ESM 3: *Estimates of effects from Age-Period-Cohort models for diabetes incidence rates in Denmark, using smooth effects of age, period and cohort (restricted cubic splines): Age-specific incidence rates (leftmost curves) as of 1 January 2015, period effects relative to this (rightmost curves, full lines) and cohort residual curves (middle set of curves — broken lines). Upper panel: T1D, lower panel: T2D. Blue curves are men, red curves women; shaded areas represent 95% confidence intervals.*
Note that all vertical axes have the same relative *extent, namely a factor 150 from bottom to top. Likewise, one year of age, date of birth and date of FU has the same physical extent on the horizontal axes.*

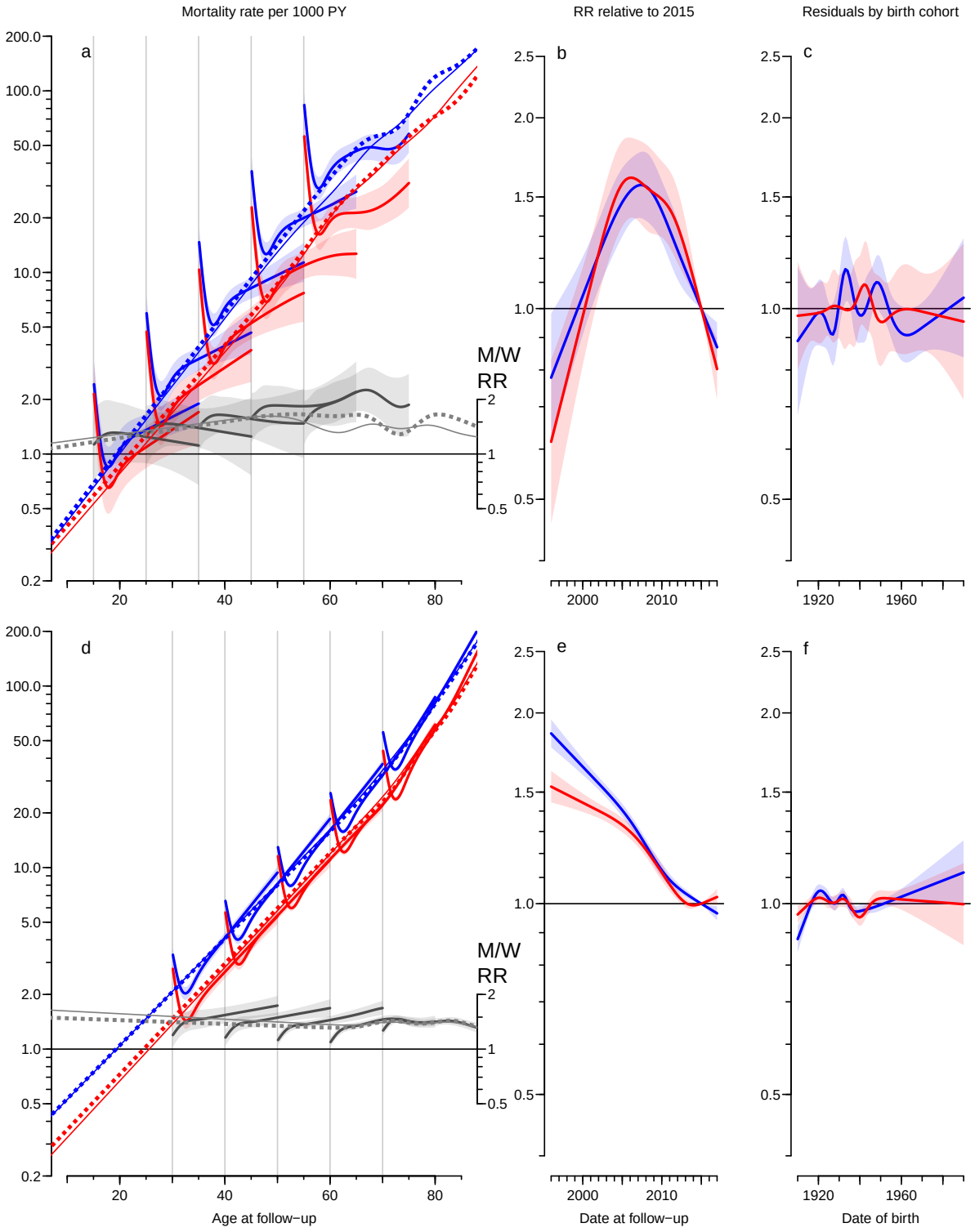

Figure ESM4: *Mortality (a,c), and RR relative to 2015-01-01 (b,d) and birth cohort residuals (c,f). Upper panels (a,b,c) are T1D and lower panels (d,e,f) are T2D. Leftmost plot shows the mortality rates at 2015-01-01 for persons diagnosed in ages 15, 25, . . . , followed for 0–20 years of diabetes duration. These curves are the same as those in figure 3 of the main paper. Broken lines in leftmost plot are mortality rates modeled ignoring age at diagnosis and duration of diabetes. Thin full lines are overall mortality also including prevalent cases as of 1996-01-01.*

Red curves are for women, blue for men, black are M/W RR; shaded areas indicate 95% confidence intervals.

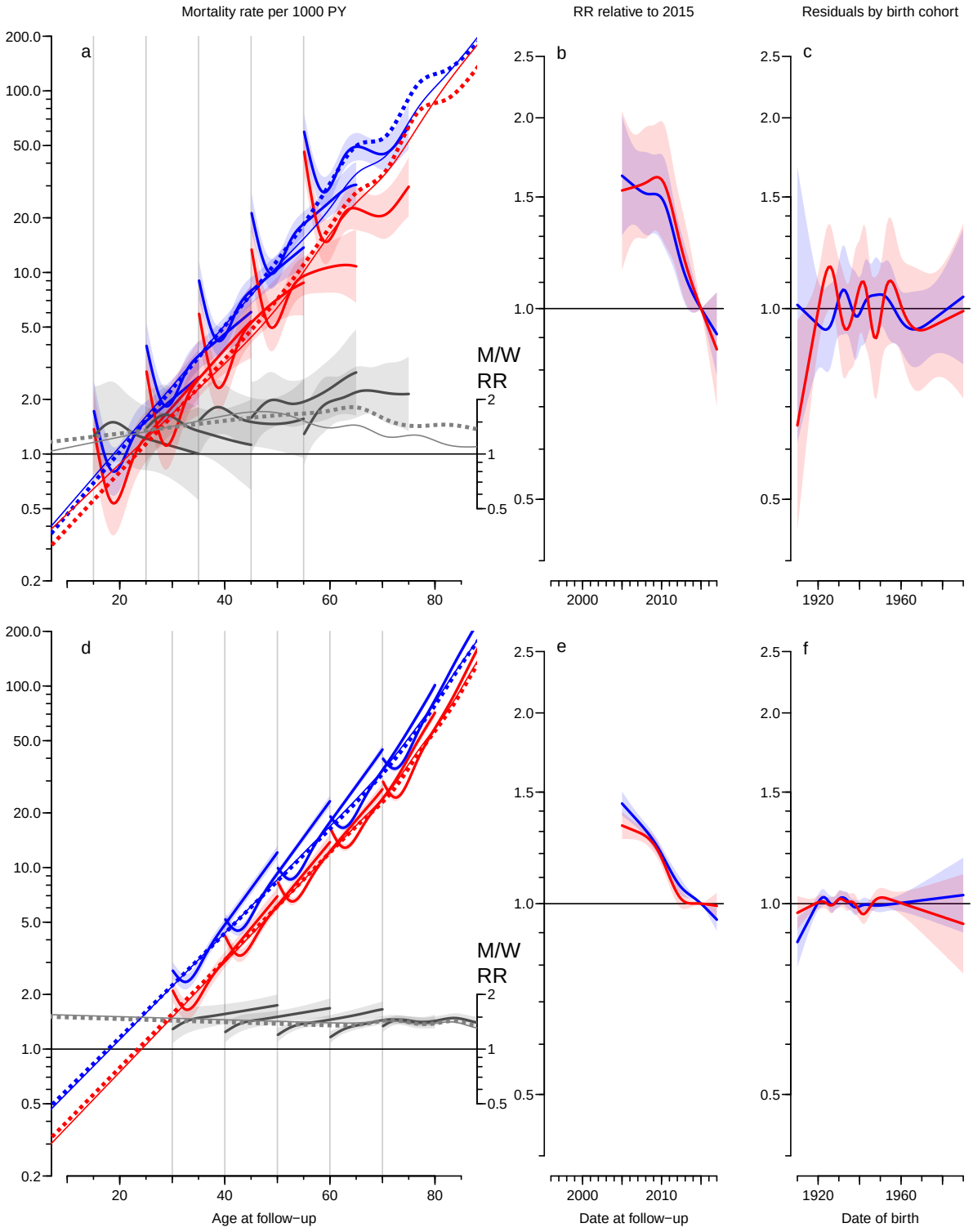

Figure ESM5: *Mortality (a,c), and RR relative to 2015-01-01 (b,d) and birth cohort residuals (c,f), based on follow up after 2005 only. Upper panels (a,b,c) are T1D and lower panels (d,e,f) are T2D. Leftmost plot shows the mortality rates at 2015-01-01 for persons diagnosed in ages 15, 25, . . . , followed for 0–20 years of diabetes duration. These curves are the same as those in figure 3 of the main paper. Broken lines in leftmost plot are mortality rates modeled ignoring age at diagnosis and duration of diabetes. Thin full lines are overall mortality also including prevalent cases as of 1996-01-01.*
Red curves are for women, blue for men, black are M/W RR; shaded areas indicate 95% confidence intervals.

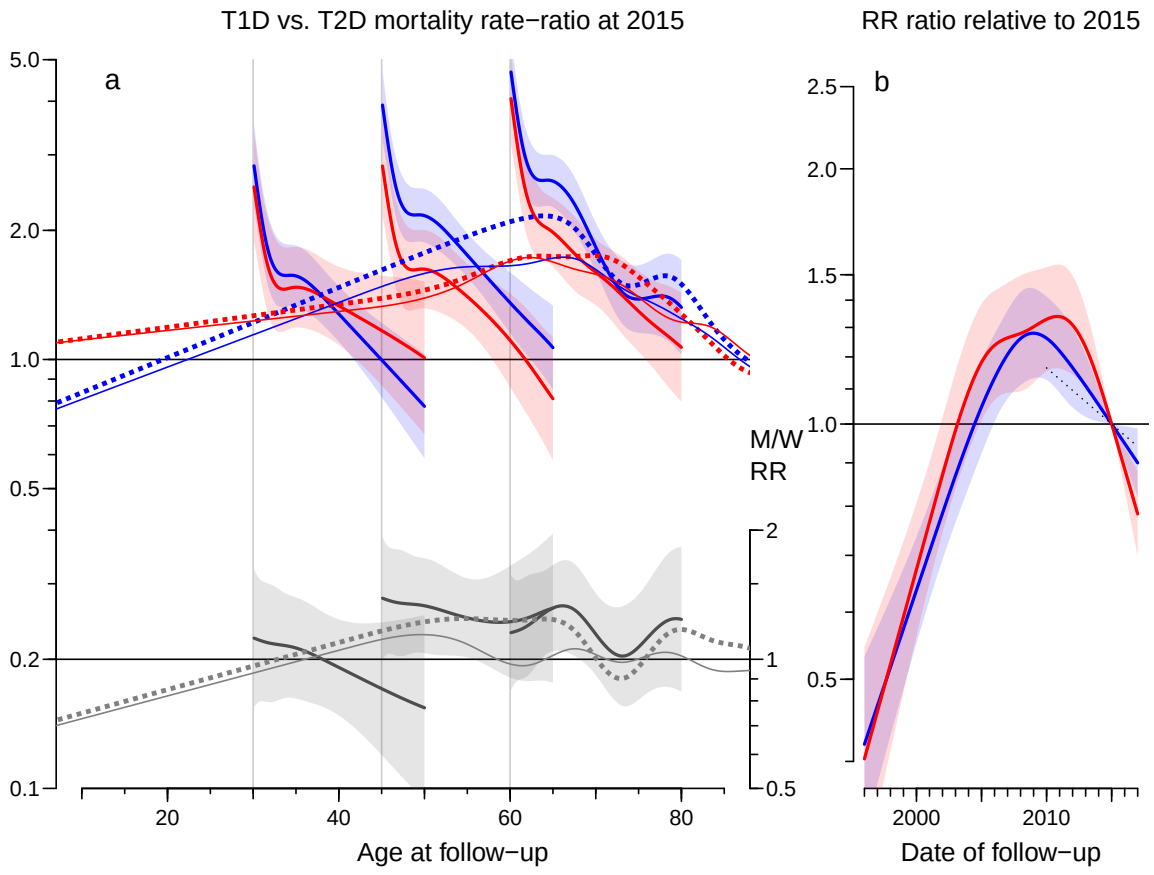

Figure ESM 6: *T1D versus T2D mortality RR at 2015-01-01. Leftmost plot shows the mortality RR at 2015-01-01 for persons diagnosed in ages 30, 45 and 60 years. Broken lines in leftmost plot are mortality RRs modeled ignoring age at diagnosis and duration of diabetes. Thin full lines are overall mortality RR also including prevalent cases as of 1996-01-01.*
Red curves are for women, blue for men, black are M/W RR ratio; shaded areas indicate 95% confidence intervals.

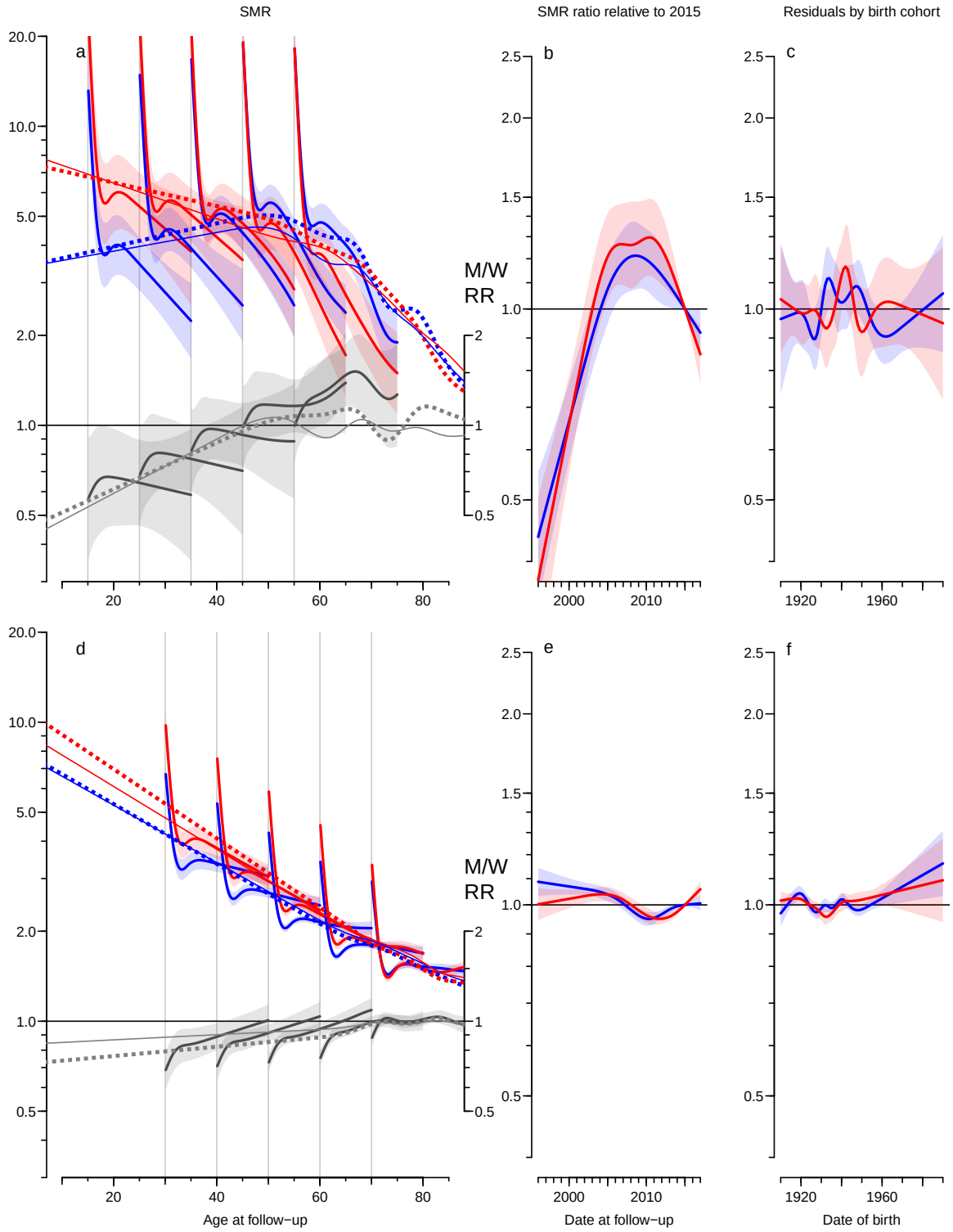

Figure ESM 7: *SMR (a,c) SMR-ratios relative to 2015-01-01 (b,d) and birth cohort residuals (c,f). The leftmost plots (a,c) shows the mortality rates at 2015-01-01 for persons diagnosed in ages 15, 30, 45, 60 and 75 followed for 0–20 years of diabetes duration. Broken lines in leftmost plot are SMR modeled ignoring age at diagnosis and duration of diabetes. Thin full lines represent SMR also including prevalent cases as of 1996-01-01.*
Red curves are for women, blue for men, black are SMR ratios between M and W; shaded areas indicate 95% confidence intervals.

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Components of diabetes prevalence in Denmark 1996–2016 and future trends until 2030

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ABSTRACT

Introduction Incidence rates of diabetes have been increasing and mortality rates have been decreasing. Our aim is the quantification of the effects of these on the prevalence and prediction of the future burden of diabetes.

Research design and methods From population-based registers of Denmark, we derived diabetes incidence and mortality rates and mortality rates for persons without diabetes for the period 1996–2016. Rates were modeled by smooth parametric terms using Poisson regression. Estimated rates were used to assess the relative contribution of incidence and mortality to changes in prevalence over the study period as well as for prediction of future rates and prevalence 2017–2040.

Results The major contributors to prevalence was increasing incidence (22%) and epidemiological imbalance between incidence and mortality (27%). The decrease in mortality rates over the period 1996–2016 contributes only 9% of the prevalent cases at 2016. We estimated that 467 000 persons in Denmark would be living with diabetes in 2030. The age distribution of patients in the period 2017–2030 is predicted to change toward older ages. The total number of persons needing diabetes care will increase by 67% over the next 13 years, an average annual increase of 4.0%.

Conclusions Lowering mortality among patients with diabetes even further is not likely to influence the prevalence substantially. Since the size and the increase in incidence of diabetes are major drivers of the increasing prevalence, the prevention of new cases of diabetes is required.

Significance of this study

What is already known about this subject?

- Incidence rates of diabetes have been increasing.
- Mortality rates have been decreasing both in the diabetic and non-diabetic population.
- The equation prevalence=incidence/mortality does not take age structure of the population into account.

What are the new findings?

- Increasing diabetes incidence over the period 1996–2016 contributed 22% of the prevalent cases in 2016 and an epidemiological imbalance between incidence and mortality contributed 27%.
- The decrease in mortality contributed only 9%.
- An estimated 467 000 (7.7%) persons in Denmark will be living with diabetes in 2030.
- The proportion of patients with diabetes over 70 years is predicted to increase from 43% to 46% for women and from 38% to 45% for men.

How might these results change the focus of research or clinical practice?

- Given the major contribution of incidence to increasing prevalence, prevention of new diabetes cases remains a key effort.
- The total number of people needing diabetes care will increase in the future.

INTRODUCTION

Diabetes is among the leading causes of death in Europe with diabetic macrovascular and microvascular complications resulting in increased disability and enormous healthcare costs.[1] It is unlikely that these costs will decrease any time soon; the number of patients will increase over the next decades. However, it is of importance for planning purposes (in all sectors of the healthcare system) that the likely number of patients with diabetes in the future is known as precisely as possible, but for preventive purposes also to know which factors drive the increasing prevalence.

Many countries have faced a rapid increase in diabetes prevalence.[2] Data from the US Center for Disease Control and Prevention show a near quadrupling of diagnosed diabetes from 5.5 million persons in 1980 to 21.1 million in 2010.[3] The most recent Scottish Diabetes Survey (2016) estimates that 5.4% of the population had a diagnosis of diabetes in Scotland at the start of 2016, compared with 4.1% in 2007.[4]

The increase in prevalence is most likely caused by an increase in incidence due to changes in underlying risk factors, primarily obesity and aging of the population. Significant declines in mortality rates have been reported, both in type 1 and type 2 diabetes.[5–10] Also, in the non-diabetic background populations, there has been a decrease in mortality,

but not to the same extent as among persons with diabetes.

The relationship between prevalence, incidence and duration (=survival with diabetes, the inverse of mortality) is usually stated as prevalence=incidence×duration=incidence/mortality, so both increasing incidence and decreasing mortality contribute to increasing prevalence. The formula is only a rough approximation to reality as it concerns a steady-state situation and does not take the age structure of the population into account. As such, it should therefore be regarded as a qualitative statement about the relationship.

A number of papers have pointed this qualitative relationship out, but so far, the only study that has attempted a quantification is Evans *et al*, however not quantifying effects by age and using a very crude age adjustment with 20-year age classes.[11–13]

There have been numerous reports predicting the future burden of diabetes, some even as far as 2050 or further, all ending with substantial predicted increases in numbers, mostly in the range 40%–60% for the period 2015–2030.[14–21]

In this work, we used a newly established Danish Diabetes Register to provide the prevalent cases each year 1996–2017, as well as the incident cases and deaths for the period 1996–2016 to model incidence and mortality rates for the period in order to quantify the relative contribution of the incidence and mortality to prevalence at 2017 as well as the future incidence and mortality rates for the period 2017–2040, and ultimately the future number of patients with diabetes.[22]

RESEARCH DESIGN AND METHODS

Data

We used data from the Danish diabetes register to compute prevalence and incidence of diabetes and mortality among persons with and without diabetes for the period 1996–2016.[22] As we are concerned with the total number of persons with diabetes in Denmark, we did not distinguish between type 1 diabetes and type 2 diabetes.

Using prevalence, incidence and mortality for prediction

We estimated prevalence at 1996 as a smooth function of age using natural splines. Incidence and mortality rates were estimated as smooth functions of age and calendar time for the period 1996–2016 using age–period–cohort (APC) models with natural splines for the three effects.[23]

Starting with the estimated prevalences at 1 January 1996 in 1-month age intervals, we used the estimated incidence and mortality rates to compute the prevalence in steps of 1 month for successive dates in the period of interest. The technicalities of this is given in online supplementary material.

Components of prevalence

The main idea is to begin with the prevalence of diabetes at 1 January 1996 and then use estimated incidence and mortality rates to predict future prevalence of diabetes—independent of the absolute numbers. Thus, we are using the term 'prevalence' to refer to the *proportion* of persons in the population affected by diabetes.

We derived the predicted incidence and mortality rates from the APC models; we evaluated rates at 1-month intervals over the age range 0–100 and period 1 January 1996 through 1 January 2017.

If we begin with the estimated prevalence as of 1 January 1996 in 1-month age intervals, then a set of age-specific incidence and mortality rates can be used to predict from the prevalence at a given age. The fraction of persons with and without diabetes that will die during the next month, and the fraction of persons without diabetes that will get diabetes during the next month is a function of the rates. So we know the fraction of the persons that after the month will be alive with and without diabetes, and hence also the prevalence of diabetes 1 month later in a 1-month-older age. The crucial point here is that we update the prevalences, not the number of persons; the mathematical formulae are given in online supplementary material.

The interval of 1 month was chosen to minimize the probability of getting diabetes and subsequently die within one interval, a probability that we formally consider as 0 in the calculations.

This machinery was run separately for men and women, under four different scenarios for the age range 0–100 and the period 1 January 1996 through 1 January 2017:

1. incidence and mortality rates as estimated—this scenario should yield the actually observed prevalence at 1 January 2017 (it did, see online supplementary material figure 3).
2. Incidence rates as estimated, but mortality rates assumed constant at the level of 1 January 1996.
3. Mortality rates as estimated, but incidence rates assumed constant at the level of 1 January 1996.
4. Incidence and mortality rates both assumed constant at the level of 1 January 1996.

The difference between scenario 4 at 1 January 2017 and the age-specific rates at 1 January 1996 is the increase in prevalence solely attributable to the imbalance between incidence and mortality as they were at 1 January 1996; what we call the epidemiological imbalance as of 1 January 1996. This is solely a function of the prevalences and incidence and mortality rates as of 1 January 1996 (and the length of the period, in this case 21 years—the longer the period the more prominent this will usually be).

The difference between the prevalences based on scenarios 1 and 2 as well as the differences between scenarios 3 and 4 can both be seen as the contribution from changing mortality rates; the difference between the scenarios are whether mortality rates are used as changing or constant. We used the average of these two differences as the contribution from the changing mortality to the (age-specific) prevalence at 1 January 2017.

Similarly, the difference between scenarios 1 and 3 and between scenarios 2 and 4 can be seen as the contribution from changing incidences. We used the average of these two as the contribution from the changing incidence rates to the (age-specific) prevalence at 1 January 2017.

The sum of these three defined contributions is precisely the difference between the predicted prevalences at 1 January 2017 and the prevalences at 1 January 1996, thus providing a partition of the change in age-specific prevalences as of 1 January 2017 into three components attributable to changing mortality, changing incidence rates, and imbalance between mortality and incidence rates as of 1 January 1996.

Future prevalence

The APC models were used to extrapolate incidence and mortality rates for the period 2017–2040 by extending the linear part of the natural spline for period and cohort.[24] As a second scenario, the trends in extrapolated incidence rates were attenuated by halving the slope every 5 years. For sensitivity, we also made predictions based on annual incidence rate increases from the 2017 level of 0, 2, 4 and 6%.

For each of these scenarios, we predicted the future prevalences by starting with the estimated prevalences as of 1 January 2017 and predicting in 1-month steps until 2040 as described earlier. Multiplying the projected age-specific prevalences by the predicted population size 2017–2040 from Statistics Denmark, we obtained the predicted number of patients with diabetes for the period 2017–2040. A detailed account of this procedure can be found in online supplementary material.

RESULTS

In the study period, during some 115 million person-years, there were 363 664 new cases of diabetes and about 1.15 million deaths, of which 161 762 were among patients with diabetes (online supplementary table ESM1). There was a marked decrease in the number of new diabetes cases after 2012 and an increase again in 2015 and 2016.[22]

Trends in incidence and mortality rates

From the fitted APC models, we extracted the average annual trend in rates; as seen from table 1, there was an average increase in incidence rates of diabetes of 2.8% per year. Mortality rates were decreasing; 2.7% per year for persons without diabetes, but 3.7% per year for persons with diabetes, and the relative mortality comparing with the general population was decreasing by 1.1% per year (table 1).

Components of prevalence

The predicted prevalences as of 2017 from combining age-specific prevalences in 1996 and the fitted incidence and mortality rates from the APC models for the period 1996–2016 showed a very good agreement with the observed prevalences in 2017 (online supplementary figure ESM3). Thus, the prediction modeling of the incidence and mortality rates method is sufficiently accurate to yield credible results for the scenarios considered.

Table 1 Average annual change (%) in diabetes incidence, mortality, and standardized mortality rates (SMR) in Denmark in the period 1996–2017.

	Annual % change (95% CI)
No diabetes:	
DM incidence	
Men	2.95 (2.82 to 3.09)
Women	2.79 (2.64 to 2.93)
Mortality	
Men	−2.89 (−2.94 to −2.84)
Women	−2.46 (−2.51 to −2.41)
Diabetes:	
Mortality	
Men	−3.93 (−4.04 to −3.82)
Women	−3.48 (−3.61 to −3.36)
SMR (DM vs no DM)	
Men	−1.11 (−1.22 to −0.99)
Women	−1.16 (−1.28 to −1.03)

DM, diabetes mellitus.

The components of the prevalences as derived from the models are shown in online supplementary figure ESM4, where it is seen that the fraction of the diabetes prevalence attributable to decreasing mortality is quite substantial in older ages. However, it is equally clear that the dominant components in the changing diabetes prevalence are the increasing incidence and the fact that the prevailing incidence and mortality rates in 1995 were not in equilibrium with the prevalences, meaning that more people were diagnosed with diabetes than patients with diabetes were dying; the so-called epidemiological imbalance.

Figure 1 shows the number of patients with diabetes in the Danish population attributable to each of the contributing components. The mortality decrease has a comparatively small impact on the number of cases because its effect is confined to older ages where the number of prevalent diabetes cases is limited. The fraction of diabetes cases attributable to declining mortality over the period 1996–2016 was 10%, whereas the fraction attributable to increasing incidence of diabetes was 20%, and 33% were attributable to the imbalance between incidence and mortality already present in 1996. The remaining 37% of prevalent cases in 2017 is the number corresponding to the age-specific and sex-specific prevalences as of 1996. There were only small differences between men and women (figure 1).

The development of the components as a fraction of all prevalent diabetes cases in different ages is shown in figure 2, and not surprisingly, the mortality decrease has

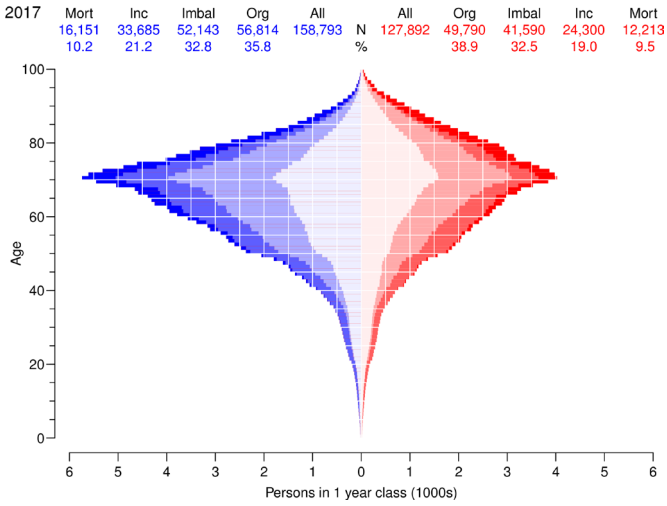

Figure 1 Age distribution of persons with diabetes in Denmark as of 1 January 2017 according to components of the changes in diabetes prevalence 1996–2016. Figures at the top is the number, respectively percentages attributable to the four factors. The colored areas are number of cases attributable to Mort: declining mortality (full color), Inc: increasing incidence (pale color) and Imbal: incidence/mortality imbalance 1996 (weak color). The weakest color in the middle (Org) corresponds to the number of cases that would have been present if age-specific prevalences were as of 1 January 1996. Men in blue, women in red.

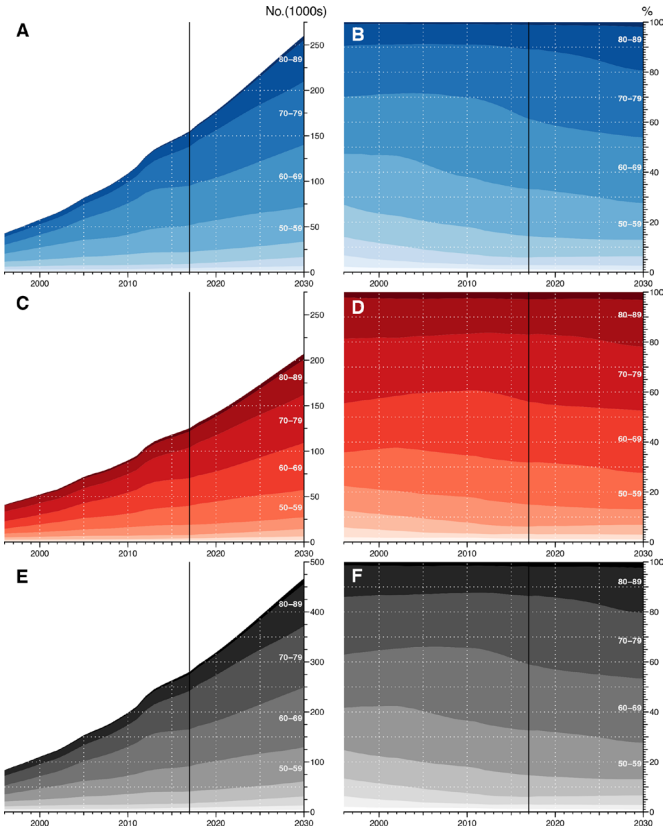

Figure 2 Observed and predicted number of patients with diabetes 1996–2030. Left panels are number of men (A), women (C) and total number of diabetic persons (E); right panels show age distributions in 10-year classes for men (B), women (C) and all (F). Blue is men, red is women and gray both sexes combined; different shades correspond to 10-year age classes. The black vertical line delineates the observed (data) from the prediction.

the largest impact on the prevalences in older ages. We found that the fraction attributable to mortality decline was around 5% in age 60, 10% in age 70 and almost 20% at age 80 for men, and slightly less in women (figure 2).

Future prevalence

At 1 January 2017, there were 280 130 prevalent cases of diabetes in the Danish population, corresponding to 4.8% of the population.[22]

The incidence rates showed an increase until around 2011, then a decrease from 2012 to 2014 and an increase again from 2015 (online supplementary figures ESM6–8). It was therefore difficult to make any single soundly founded projections for the time beyond 1 January 2017, so we used six different scenarios as described in the methods section. The resulting predicted numbers are shown in table 2 for all six incidence rate prediction scenarios using a 5-year halving time for attenuation of the trend in mortality rates. From table 2, it is seen that using the attenuation of incidence rates gives a prediction between the scenarios with annual increase of 2% and 4%, for 2030 a total number of some 467 000 persons (260 000 men and 207 000 women) with diabetes, corresponding to a 67% increase in the number of patients with diabetes from 2017 to 2030.

The other prediction scenarios have deliberately been chosen to be on the low side (fixed rates, ie, 0% annual increase) or high side (6% annual increase), and they produce estimates quite far from the attenuation estimate of prevalent number of patients with diabetes by 2030 (392 000, respectively 526 000). The scenarios with 2% and 4% annual increase in incidence rates were chosen to be on either side of the average increase in rates over the entire period 1996–2016 (2.8%/year), and they produce estimates of 445 000 and 482 000, respectively; quite close to the results from the attenuation scenario.

A graphical representation of predicted numbers is given in figure 2.

We found minimal differences between the scenarios for the mortality rates; this can be seen from the graphical representation of the predictions in online supplementary figures ESM10–12.

DISCUSSION

We have shown that over the last decades in Denmark, the decline in mortality has had some impact on the increasing prevalence of diabetes, whereas the major drivers of the prevalence increase have been the increase in diabetes incidence as well as the imbalance between incidence and mortality already present in 1995.

The absolute number of cases attributable to the different components is of course heavily dependent on the particular age distribution in the Danish population.

Table 2 Predicted number of prevalent patients with diabetes and prevalence 2017–2040, using six different prediction scenarios for incidence rates: naive prediction from a splines-based APC model, attenuation with halving of rate change per 5 years, fixing rates at the level of 1 January 2017 and an increase of incidence of 2%, 4% and 6% per year (mortality rate changes are also attenuated by a halving of rate change per 5 years in all scenarios)

							Fixed annual incidence increase					
Date	**APC-naive**		**Attenuation**		**0%/year**		**2%/year**		**4%/year**		**6%/year**	
1 Jan	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
M												
2018	163 046	5.7	163 031	**5.7**	162 695	5.6	162 996	5.7	163 014	5.7	163 031	5.7
2019	169 921	5.9	169 787	**5.9**	168 426	5.8	169 557	5.9	169 713	5.9	169 871	5.9
2020	177 504	6.1	177 038	**6.1**	174 029	6.0	176 421	6.1	176 956	6.1	177 504	6.1
2025	227 155	7.6	217 909	**7.3**	199 718	6.7	212 735	7.1	219 519	7.4	226 953	7.6
2030	299 745	9.9	260 187	**8.6**	220 633	7.3	249 815	8.2	270 791	8.9	295 261	9.7
2035	400 956	13.0	298 297	9.7	236 477	7.7	286 589	9.3	330 343	10.7	384 353	12.5
2040	537 954	17.2	330 611	10.6	248 358	8.0	323 695	10.4	399 279	12.8	497 106	15.9
W												
2018	131 442	4.5	131 429	**4.5**	131 138	4.5	131 397	4.5	131 410	4.5	131 423	4.5
2019	136 492	4.7	136 375	**4.7**	135 187	4.6	136 156	4.7	136 275	4.7	136 396	4.7
2020	142 177	4.8	141 763	**4.8**	139 126	4.7	141 160	4.8	141 571	4.8	141 992	4.8
2025	181 787	6.1	173 236	**5.8**	156 961	5.2	167 788	5.6	173 054	5.8	178 833	6.0
2030	245 124	8.0	207 174	**6.8**	171 229	5.6	195 238	6.4	211 675	6.9	230 955	7.6
2035	340 134	11.0	238 481	7.7	181 736	5.9	222 661	7.2	257 289	8.3	300 584	9.7
2040	475 714	15.2	265 069	8.5	189 225	6.0	250 399	8.0	310 896	9.9	391 134	12.5
M+W												
2018	294 489	5.1	294 460	**5.1**	293 833	5.1	294 393	5.1	294 424	5.1	294 455	5.1
2019	306 414	5.3	306 162	**5.3**	303 613	5.2	305 713	5.3	305 989	5.3	306 267	5.3
2020	319 680	5.5	318 801	**5.5**	313 156	5.4	317 581	5.4	318 527	5.5	319 496	5.5
2025	408 942	6.8	391 145	**6.5**	356 679	6.0	380 523	6.4	392 573	6.6	405 786	6.8
2030	544 869	8.9	467 362	**7.7**	391 862	6.4	445 053	7.3	482 466	7.9	526 217	8.6
2035	741 090	12.0	536 778	8.7	418 213	6.8	509 250	8.2	587 633	9.5	684 936	11.1
2040	1 013 668	16.2	595 680	9.5	437 582	7.0	574 094	9.2	710 175	11.4	888 240	14.2

The boldface numbers are the predictions we report as the most reliable and used in figure 2. It should be noted that figures beyond 2030 are very uncertain.
APC, age–period–cohort; M, men; W, women.

The finding of a decline in diabetes-related mortality is encouraging, although the resulting increase in diabetes prevalence obviously challenges the healthcare system. A larger number of older people will survive with diabetes complications with increased costs of diabetes treatment, as well as costs related to screening for and treatment of complications. On the other hand, the observed increase in diabetes incidence as a major driver calls for intensified preventive strategies in persons without diabetes. Thus, the increasing diabetes prevalence has different public health consequences according to the contributing prevalence components, a finding that underscores the value of a detailed examination as ours.

Comparison with other studies

Few studies have addressed the relative contributions of mortality vs incidence to diabetes prevalence. A recent study from Israel observed a deceleration in the upward trend in diabetes prevalence despite declining mortality.[25]

Støvring *et al* merely analyzed relative annual changes in incidence, prevalence and mortality, and no formal quantification of the relative impact of mortality and incidence changes were made, so it is not possible to make a precise comparison.[26] But the authors concluded that "Although our data do not allow a firm conclusion as to why prevalence is rising, we believe that the decrease in mortality should be taken into account. Otherwise, incorrect conclusions could be drawn about the relation between the western lifestyle and the rising number of diabetics." This is indeed confirmed by this study as we estimate that as much as 10% of the current diabetes cases can be ascribed to the last 21 years' decreasing mortality, less for ages under 70, somewhat more for older ages.

Evans *et al* used Tayside (Scotland) data to attempt a quantification of the relative contributions of incidence and mortality.[13] They showed that 60% of the increase in diabetes prevalence over the period 1993–2004 was attributable to the initial imbalance between incidence and mortality; 25% to the increasing incidence and only 11% to decreasing mortality, which only in very broad terms is similar to our results; their study period was only half as long as ours.

In our most realistic scenario, we predicted the total number of patients with diabetes to be 467 000 in 2030, an increase of 67% over the level at the beginning of 2017, which is more than other studies have found elsewhere.[17 19] This corresponds to a crude prevalence of 7.7%, up from 5.0% in 2017. Our sensitivity analysis suggests that this number would hardly be less than 450 000 nor above 500 000. Our predictions for 2040 are so variable between scenarios that we do not consider it relevant to use any of them; results for these years are merely included in table 2 to demonstrate their limited usefulness.

Sortsø *et al* used a similarly looking multistate model arriving at a prediction for 2040 of well over 1 million patents with diabetes in Denmark, possibly due to a very crude age classification (25-year intervals).[27]

Andersson *et al* used simple annual changes in incidence and mortality rates for prediction of the number of patients with diabetes in Sweden and arrived at some 50% increase in the number over the period 2013–2030 (from some 500 000 to 750 000, derived from the figure in the paper), and also with quite large differences between scenarios even though the authors only used 1% increase in incidence rates (in Denmark, the average increase in diabetes incidence rates were 3.1%/year).[17] Holman *et al* used predictions of the prevalence of obesity to inform the prediction of diabetes; they found that for England, the prevalence of diabetes would increase from 8.5% to 9.5% over the period 2015–2030, but did not model change in diabetes incidence rates beyond the dependence on obesity.[14]

Because of the very large fluctuations in birth rates over calendar time and the uneven age distribution in the population, predictions of future numbers must rely on a prediction model for the rates of diabetes and death, which in turn is used to predict the fraction of persons in the population with diabetes/the prevalence. This is then converted to number of persons with diabetes using official age-specific forecasts of population size in the future. In our approach, we have relied on Statistics Denmark's population forecast which is based on assumptions of mortality and fertility trends in the entire population as well as assumptions about future emigration and immigration patterns.

This way, we believe that we have produced fairly robust predictions, and in particular it is transparent what our assumptions are and the weaknesses of these. The central assumption we are making is that the most recent pace of change in incidence and mortality rates is not going to continue in the future; the rates will become more stable. This is implemented in our attenuation assumption. This was done in order not to overemphasize the effect of the changes in incidence rates only observed during the last few years of the study period.

The attenuation assumption is presumably most doubtful for mortality rates; they have been declining pretty constantly over the last 20 years with absolutely no sign of change, but on the other hand, the influence of different mortality scenarios on the predictions is minimal (online supplementary figures ESM5–7).

Strengths and limitations

We developed a model for partitioning prevalence changes in three parts, which was based on application of well-known demographic concepts and classical epidemiological modeling of occurrence rates. While this machinery in principle is straightforward to use to assess the contributions to current prevalence as well for predicting the total future prevalence, it does rely on the availability of detailed register data of diabetes incidence and mortality.

The register-based approach in our study has some limitations since it is not possible to determine whether the observed increase in diabetes incidence reflects a true change in incidence or whether it is caused by intensified diagnostic activity, resulting in more low-risk people with diabetes being included in the Danish diabetes register. Similarly, an apparent change in incidence may also result from an increasing number of persons receiving diabetes-defining services, for example, diabetes-specific podiatry or diabetic eye examination.[22] Accordingly, such inaccuracies might influence the predicted future diabetes estimates; however, this is something we have tried to consider by applying six different prediction scenarios.

CONCLUSION

We showed that the increasing prevalence of diabetes is influenced by the decline in mortality affecting primarily the oldest part of the population. However, the major drivers of the prevalence increase were the increase in diabetes incidence and in particular imbalance between incidence and mortality already present in 1996.

With a realistic scenario for future rates of diabetes incidence and mortality among persons with and without diabetes, we predicted the number of patients with diabetes in Denmark at 2030 to be 467 000, a 67% increase over 2017, corresponding to an overall prevalence of 7.7%. In 2017, the percentage of men among patients with diabetes were 54.6%; in 2030, it was predicted to be 56.1%, a very modest increase. The proportion of patients with diabetes over 70 years of age were predicted to increase from 43% to 46% for women and from 38% to 45% for men.

The development of incidence rates of diabetes in Denmark since 2010 has been very unstable, so any

prediction endeavor will naturally entail a substantial component of arbitrary assumptions, and ours is no exception.

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Contributors BC and MEJ conceived the structure of the underlying register and designed the study. PFR provided support for obtaining data access and contributed to data definition. BC detailed and developed the statistical methods needed, performed all data analysis and wrote a first draft of the manuscript. MEJ and PFR contributed substantially to the writing of the manuscript. All authors contributed to critical revision and take responsibility for the content. BC 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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Competing interests BC and MEJ own shares in NovoNordisk. BC has received lecture and consultancy fees from NovoNordisk and LeoPharma. MEJ is PI on a trial sponsored by AstraZeneca, and received research grants from AMGEN AB, AstraZeneca, Sanofi Aventis and Boehringer Ingelheim. PFR has nothing to disclose.

Patient consent for publication Not required.

Ethics approval This study was approved by the Danish Data Protection Agency (registration no. 2015-41-4148). Ethical approval is not required for register-based studies in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data for this study are population-wide registers, placed at our disposal on the servers of Statistics Denmark. They are barred from release to the public on grounds of confidentiality. A full documentation of the register is given in the electronic supplementary material.

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Components of diabetes prevalence in Denmark 1996–2016 and future trends till 2030

Electronic Supplementary Material

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1 Material and methods

1.1 Probability model

The following is to some extent a repetition of standard theory from demography / probability theory, and the extension to several age-classes and time-varying incidence and mortality rates is if not straight-forward, then a part of many curricula in demography and probability theory.

Diabetes incidence and mortality in the population can be described by a 3-state model, with three transition rates (Figure 1). If each of these rates is assumed to depend on sex, and continuously on age, calendar time and date of birth, it is possible to use the age-distribution of prevalent diabetes patients at the start of the observation period (1 January 1996) in conjunction with the incidence and mortality rates over the period to predict the age-specific prevalence at the end of the period, 1 January 2017.

Likewise we can take the observed age-specific prevalences at 1 January 2017 and apply *projected* future rates for the period (say) 2017–2040 to predict age-specific prevalences at any date in that period.

In practice this is done by using a sex-, age- and period-specific transition probabilities between the three states "noDM", "DM" and "Dead" (Figure 1). In each step, the population at a given time in a given (say 1-month) age-class with and without diabetes is updated for one month, so that we know how many there are in the three states the next month — being one month older.

Specifically, we considered transitions over a small interval of length ℓ and with the notation $\mathrm{P}_{\mathrm{noDM,DM}}(\ell)$ for $\mathrm{P}\{\text{DM at } (a+\ell, p+\ell) \mid \text{noDM at } (a,p)\}$, the following transition

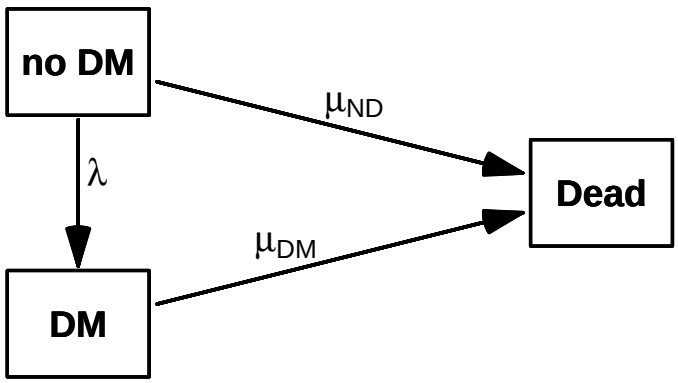

Figure ESM 1: *States and transition rates used: λ: Incidence rate, μ_{nD}: mortality rate in persons without diabetes, μ_{DM}: mortality rate in persons with diabetes. Prevalence of diabetes is the fraction in state "DM" relative to all in states "noDM" and "DM".*
Each rate is modeled separately for men and women, using an age-period-cohort model with continuous smooth effects.

probabilities were used:

$$\begin{aligned}
\mathrm{P}_{\mathrm{noDM,noDM}}(\ell) &= \exp\bigl(-(\lambda+\mu_{\mathrm{nD}})\ell\bigr) && \approx 1-(\lambda+\mu_{\mathrm{nD}})\ell \\
\mathrm{P}_{\mathrm{DM,DM}}(\ell) &= \exp\bigl(-\mu_{\mathrm{DM}}\ell\bigr) && \approx 1-\mu_{\mathrm{DM}}\ell \\
\mathrm{P}_{\mathrm{noDM,DM}}(\ell) &= \frac{\lambda}{\lambda+\mu_{\mathrm{nD}}}\Bigl(1-\exp\bigl(-(\lambda+\mu_{\mathrm{nD}})\ell\bigr)\Bigr) && \approx \lambda\ell \\
\mathrm{P}_{\mathrm{noDM,Dead}}(\ell) &= \frac{\mu_{\mathrm{nD}}}{\lambda+\mu_{\mathrm{nD}}}\Bigl(1-\exp\bigl(-(\lambda+\mu_{\mathrm{nD}})\ell\bigr)\Bigr) && \approx \mu_{\mathrm{nD}}\ell \\
\mathrm{P}_{\mathrm{DM,Dead}}(\ell) &= 1-\exp\bigl(-\mu_{\mathrm{DM}}\ell\bigr) && \approx \mu_{\mathrm{DM}}\ell
\end{aligned}$$

The rates are assumed to depend on a and p, but this has been left out of the formulae for clarity of exposition. We chose ℓ to be as small as one month, since the formulae above are only valid if the probability of two transitions "no DM"→"DM"→ "Dead" occurring in one interval is negligible. If we had used an interval length of 1 year, our predictions would have been inaccurate because of this. Using 1 month intervals will render the updating machinery sufficiently accurate to predict the prevalences at the end of the study period.

1.1.1 Projecting prevalences

To the extent we are only interested in the prevalences, the above formulae can be used to predict the *fraction* of persons alive with and without diabetes at (a,p) who at $(a+\ell,p+\ell)$ are dead, alive with resp. without diabetes. The immediate result will be in terms of the fraction of persons alive at (a,p) who are in each category at $(a+\ell,p+\ell)$. But from that we can compute the prevalence by dividing by the proportion alive (with or without diabetes). This is what we have done, "prevalence" in this context refers to a proportion.

1.2 Prevalence and rates 1996–2017

For the no. of prevalent cases at each of the dates 1 January 1996 through 1 January 2017, we fitted separate log-link binomial models for men and women using natural splines (restricted cubic splines) to describe the age-dependence. These models provided estimates of diabetes prevalence as a continuous function of age for each of the dates 1 January 1996–2017.

We fitted age-period-cohort models [1] for the period 1996-2016 for diabetes incidence rates and mortality among persons with and without diabetes, separately for each sex. Effects of age, date of follow-up (period) and date of birth (cohort) were modeled by natural splines (restricted cubic splines). The models thus provide predicted incidence and mortality rates as continuous functions of age and date of follow-up, so that we can predict rates at any age and date during the study period 1996–2016.

Since we only use the age-period-cohort (APC) models for prediction of rates, the usual identification problem of the parametrization of effects in APC models is not relevant here.

We estimated the average time trend from the APC models using the observed number of events as weights as described in Carstensen [1].

1.3 Demographic components

We used the models fitted to predict the incidence and mortality rates at the midpoint of all 252 months from 1 January 1996 through 1 January 2017 at the start of each of 1200 1

month age-classes between 0 and 100 years, *i.e.* we used $\ell = 1$ month (formally 365.25/12 days). For updating the prevalence in age class $(a, a+\ell)$ at time p to the prevalence in age-class $(a+\ell, a+2\ell)$ at time $p+\ell$, we used rates predicted at age $a+\ell$ at time $p+\frac{\ell}{2}$. As a check on the appropriateness of the calculations, the predicted prevalences from this projection at the end of the study period is compared with the actual observed prevalences as smoothed by the binomial regression of the 2016 data.

The same exercise was then repeated in scenarios where we fixed the (age-specific) incidence and/or mortality rates to be as in 1996. The difference between predicted prevalences under these scenarios and the actually observed will then represent the contributions to the prevalence in 2016 from increasing incidence and decreasing mortality respectively.

The contribution from changing incidence rates were computed in two different ways:

1. Difference between results with 1996-fixed resp. observed incidence rates using the mortality rates as observed over the period.

2. Difference between results with 1996-fixed resp. observed incidence rates using the mortality rates fixed at the 1996 level.

— and vice versa for the contribution from the changing mortality rates.

The contributions from changing incidence resp. mortality were taken as the average of the two approaches for each.

Finally, we took the difference between the observed prevalences in 1996 and those predicted for 2017-01-01 by fixing *both* incidence and mortality rates to the 1996 level throughout, as the component of prevalence attributable to the demographic imbalance in 1996 — the change in prevalence occurring because incidence and mortality rates in 1996 were *not* in a steady-state equilibrium with equal number of incident cases of DM and deaths among DM patients.

1.4 Projection of rates 2017–2040

We fitted log-link binomial models for the no. of prevalent cases at 2017-01-01 using natural splines (restricted cubic splines), providing estimates of diabetes prevalence as a continuous function of age at 2017-01-01, separately for men and women.

The age-period-cohort (APC) models [1] for incidence and mortality rates for the period 1996–2016 were used as basis for prediction of future rates. A naive prediction based on extrapolation of linear effects from natural spline components [2] is highly unrealistic with the shape of the incidence rates we see in Denmark [3]. We therefore set up 5 further scenarios for projection of incidence rates and 3 different scenarios for mortality rates (rates for persons with and without diabetes are treated similarly); a total of 18 scenarios combined; all based on APC models for the rates:

- Incidence rates:
  - Naive projection from spline models
  - Attenuate the projection from spline models, halving the *increase* in rates every 5 years
  - Fix rates at the levels of 2017-01-01

  - Increase rates from the level at 2017-01-01 by 2%/year
  - Increase rates from the level at 2017-01-01 by 4%/year
  - Increase rates from the level at 2017-01-01 by 6%/year

- Mortality rates
  - Naive projection from spline models
  - Fix rates at the levels of 2017-01-01
  - Attenuate the projection from spline models, halving the *decrease* in mortality rates every 5 years

1.5 Models for rate projection

1.5.1 Attenuation of predictions

The following is an empirical approach to adjust rates predicted into the future. We use a damping mechanism, taking an approach that does not rely on any particular mathematical form of the predictions, but merely on the predictions being available in suitably small intervals.

Suppose we have prediction of future rates (or log-rates) $\lambda(a, p)$ from an APC-model (well, this goes for any model) — estimated occurrence rates in the period-direction.

A slope-attenuation can be numerically implemented by using the empirical gradients of the predictions, so suppose that for a *fixed* value of age (a) the rates are in the vector `f` and the corresponding dates (p) in the vector `t`. In practise `t` will be the "prediction time", that is the time sice the starting date of prediction (in this scenario 2017-01-01)

The empirical slopes between successive time points is simply `diff(f)/diff(t)`. We can attenuate these slopes by multiplying them by d^τ where d is the chosen damping factor and τ is the midpoint of the interval. Mathematically, the machinery is briefly to differentiate f w.r.t. to t, apply the damping factor to f' and integrate the result to get a function on the original scale.

```
# difference on t-scale
dt <- diff(t)
# interval mdpoints
mt <- t[-1] - dt/2
# f derivative
df <- diff(f) / dt
# attenuated f derivative
ddf <- df * dd^mt
# this should give the original function back
iof <- c( f[1], f[1] + cumsum( df)*dt )
# this is the attenuated function
idf <- c( f[1], f[1] + cumsum(ddf)*dt )
```

Now this is easily implemented in a function which takes the function values `f`, times `t` and damping factor as arguments.

1.5.2 Adding a drift to a prediction

For the diabetes incidence we have observed that the incidence rates show a dramatically increasing tendency over the last year of observation ($\approx 15 - -20\%$/year), hence we may

want not only to investigate a scenario where rates are kept or attenuated to constant, but also one where we simply let the rates increase by some (arbitrarily chosen) fixed amount, say 4% per year. This is only going to be used for the incidence rates as a sensitivity analysis.

To this end we update the damping function just outlined by allowing adding a trend (drift) in time on top of the attenuated prediction; we phase it in quadratically over a period of ℓ, by the function q — a parabola with slope 0 at 0 and slope δ at ℓ, and a linear function with slope δ beyond ℓ, defined as:

$$q(t) = \begin{cases} 0 < t < \ell & : \quad \big(\delta/(2\ell)\big)t^2 \\ \ell < t < \infty & : \quad -\delta\ell/2 + \delta t \end{cases}$$

We see that $q(0) = 0$, and using the first line of the definition, the value at $t = \ell$ is: $q(\ell) = \big(\delta/(2\ell)\big)\ell^2 = \delta\ell/2$, which is also obtained using the second line of the definition. Moreover, the slopes are identical at ℓ too: $q'(t) = t\delta/\ell|_{t=\ell} = \delta$.

In R-code this function becomes:

```
qs <-
function( t, ell, delta ) ifelse( t < ell, delta / ell / 2 * t^2,
                                           delta * t - delta * ell / 2 )
```

. . . which is incorporated in a general function for adjusting projected rates defined below.

1.5.3 Implementation of damping and adding

We implement this attenuation and slope addition in a function `damp` which takes 6 arguments:

`f` — a vector of predicted function values (rates or log-rates) to be modified by damping and/or addition of a trend

`t` — an ordered vector of time points where `f` is given. Need not be equidistant. Note that `t-t[1]` is used as exponent to the damping factor, so results will be invariant under translation of `t`. Basically we are considering time since the *first* `t`.

`h` — a scalar, the halving time for the slope. In the function it is converted to a damping factor which will be elevated to the power of `t`, thus dependent on the scaling of `t`: For halving time h we have $d^h = 0.5 \Leftrightarrow d = 0.5^{1/h}$.

`delta` — scalar; the extra slope added to the predictions, beyond `ell` (`t`≥`ell`), before `ell` the addition is a quadratic starting at 0 and a slope fitting with the linear at `ell`. This is an additive factor, so a 10% increase per unit of `t` is obtained by `delta=0.1`, correponding to a multiplier of 1.1.

`ell` — scalar; the run-in interval (on the `t`-scale) for the extra slope.

`logf` — logical indicating whether the supplied `f` represent log-rates or rates. In any case the attenuation is made on the log-rate scale.

With this, a value of 0 for `h` produces an immediately flat (constant) modified curve, corresponding to a fixing of rates at `t` = 0. Likewise a choice of 0 for the interval length `ell` corresponds to an immediate start of an added slope of `delta`. Thus the function will accommodate at scenarios considered.

```
damp <-
function( f, t, h, delta = 0,      # added slope (% per t unit),
                    ell = 0,      # phase-in interval for added slope
                   logf = FALSE ) # is f a vector of log-rates
{
# all operations are on log-rates so if we have rates make them log
if( !logf ) f <- log( f )
# compute the damping factor from half-time
d <- 0.5^(1/h)
# make sure t start at 0
t <- t - t[1]
# difference between timepoints of prediction
dt <- diff(t)
# midpoints of intervals
mt <- t[-1] - dt/2
# slopes in each interval
dfdt <- diff(f) / dt
# attenuated slopes
atdf <- dfdt * d^mt
# function values after attenuating the slope
idf <- f[1] + cumsum(c(0,atdf*dt))
# remember delta is taken as being in % per t
delta <- delta/100
# add the extra slope to this
idf <- idf + ifelse( t < ell, delta/(2*ell)*t^2,
                              delta*(t-ell/2) )
if( !logf ) idf <- exp( idf )
idf
}
```

We can illustrate the damping effect in a number of different ways. First, the time it takes to reduce the slope to say, 50, 10 and 1% (ζ, say) of the original one, is illustrated by simply solving:

$$d^t = \zeta \quad \Leftrightarrow \quad t\log(d) = \log(\zeta) \quad \Leftrightarrow \quad t = \log(\zeta)/\log(d)$$

This is the left panel in figure 2; the other one illustrates the resulting damped / amended curves relative to an arbitrary constant slope:

```
par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
clr <- rainbow(3)
d <- seq(0,1,,200)
zeta <- c(0.5,0.1,0.01)
matplot( d, outer( d, zeta, function(d,zeta) log(zeta)/log(d) ),
         type="l", lwd=4, lty=1, col=clr,
         ylim=c(0,25), xlab="Damping factor",
         ylab=paste( "Time to reduction to ",
                     paste( round(zeta*100,1), collapse=", "),
                     "%, respectively", sep="" ) )
abline( v=c(0.92, 0.88, 0.7) )
abline( h=0:10, lty=2, col=gray(0.8) )
 axis( at=c(0.92, 0.88, 0.7), las=2, side=1 )
text( 0.1, 23+0:2, paste(round(zeta*100),"%"), col=clr, adj=1, font=2 )
# right plot
clr <- c("black",rainbow(7))
tt <- seq( 0,25,0.1)
ff <- 2 + 0.4 * tt
t0 <- 8
t  <- (tt-t0)[tt>=t0]
f  <-      ff[tt>=t0]
plot( tt, ff, lty=1, lwd=5, type="l", ylim=c(2,12),
              xlab="Time", ylab="Damped effect")
matlines( t+t0, cbind( f, damp(f,t,h=5),
                          damp(f,t,h=Inf),
```

```
                          damp(f,t,h=10,delta=5,ell=5),
                          damp(f,t,h=2  ,delta=5,ell=5),
                          damp(f,t,h=2),
                          damp(f,t,h=2  ,delta=-5,ell=5) ),
          lty=1, lwd=c(5,rep(3,6)), type="l", col=clr,
          xlab="Time", ylab="Damped effect")
text( 5, 12-0:6/2, c( "Half-time",
                      formatC( c(5,Inf,10,2,2,2), format="f", digits=2 ) ),
                   font=2, col=clr, adj=1 )
text( 7, 12-0:6/2, c( "Added slope / yr",
                      formatC( c(0,0,1/20,abs(1:-1)/20), format="f", digits=2 ) ),
                   font=2, col=clr, adj=0 )
text( 6.9, 12-6/2, "-", font=2, col=clr[7], adj=1 )
segments( c(t0,t0+5), 1,
          c(t0,t0+5), 8:9 )
```

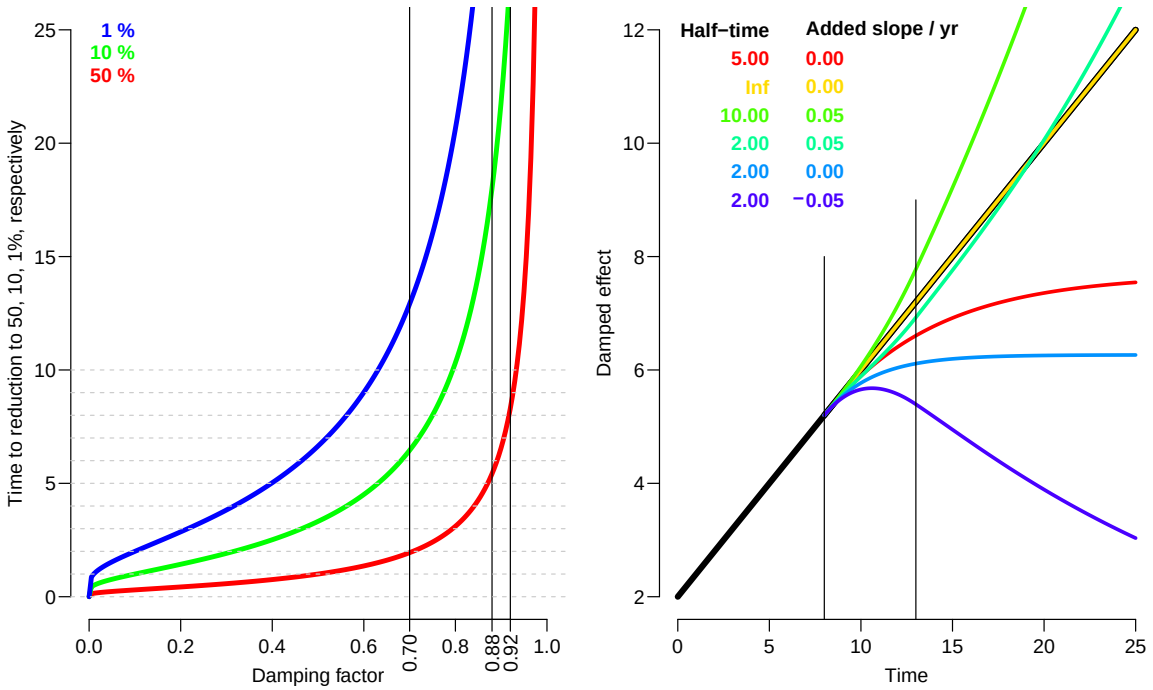

Figure ESM 2: *The left panel shows the time to reduction of the slope of a curve to 50, 10 and 1% of the original for different values of the damping factor. The right hand panel illustrates the* `damp` *function for attenuation of effects and addition of linear terms for various combinations of the two. The two vertical black lines indicate the starting point of the attenuation and the end of the phase-in of the added slope.*

1.6 Detailed documentation

A full account of all calculations is available in the chapters "Components of prevalence", "Analysis and prediction of rates" and "Predicting prevalence of diabetes" in:
http://bendixcarstensen.com/DMreg/NewAna.pdf

References

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[2] M. J. Rutherford, J. R. Thompson, and P. C. Lambert. Projecting cancer incidence using age-period-cohort models incorporating restricted cubic splines. *Int J Biostat*, 8(1):33, Nov 2012.

[3] B. Carstensen, M.E. Jørgensen, and P.F. Rønn. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016. *SomeJournal*, va(na):pa–qa, 2019.

Table ESM 1: *Events and person-years (in 1000s) in the Danish population in the 21 year study period 1996–2016 (3-year intervals). Only follow up till 100 years of age.*

		No diabetes			Diabetes	
		DM diag	Deaths	P-years	Deaths	P-years
Men	1996–1998	20,502	78,885	7,715,200	9,076	145,141
	1999–2001	21,901	74,519	7,766,999	10,279	179,389
	2002–2004	28,083	71,680	7,810,245	11,505	219,973
	2005–2007	26,719	67,787	7,842,954	12,144	266,133
	2008–2010	34,118	65,825	7,916,764	13,420	314,841
	2011–2013	40,043	61,410	7,956,646	15,031	386,881
	2014–2016	31,937	60,230	8,066,473	16,613	435,714
	1996–2016	203,303	480,336	55,075,282	88,068	1,948,073
Women	1996–1998	16,962	80,783	7,908,376	8,489	135,558
	1999–2001	17,980	79,691	7,959,048	9,270	161,353
	2002–2004	23,918	76,751	7,997,847	9,866	194,132
	2005–2007	20,387	72,678	8,029,151	10,582	229,208
	2008–2010	25,069	70,084	8,102,806	11,035	261,108
	2011–2013	32,162	65,296	8,149,037	11,571	315,245
	2014–2016	23,883	62,950	8,234,517	12,881	352,422
	1996–2016	160,361	508,233	56,380,782	73,694	1,649,027
M+W	1996–1998	37,464	159,668	15,623,576	17,565	280,700
	1999–2001	39,881	154,210	15,726,047	19,549	340,742
	2002–2004	52,001	148,431	15,808,092	21,371	414,105
	2005–2007	47,106	140,465	15,872,105	22,726	495,342
	2008–2010	59,187	135,909	16,019,570	24,455	575,949
	2011–2013	72,205	126,706	16,105,683	26,602	702,126
	2014–2016	55,820	123,180	16,300,990	29,494	788,137
	1996–2016	363,664	988,569	111,456,064	161,762	3,597,100

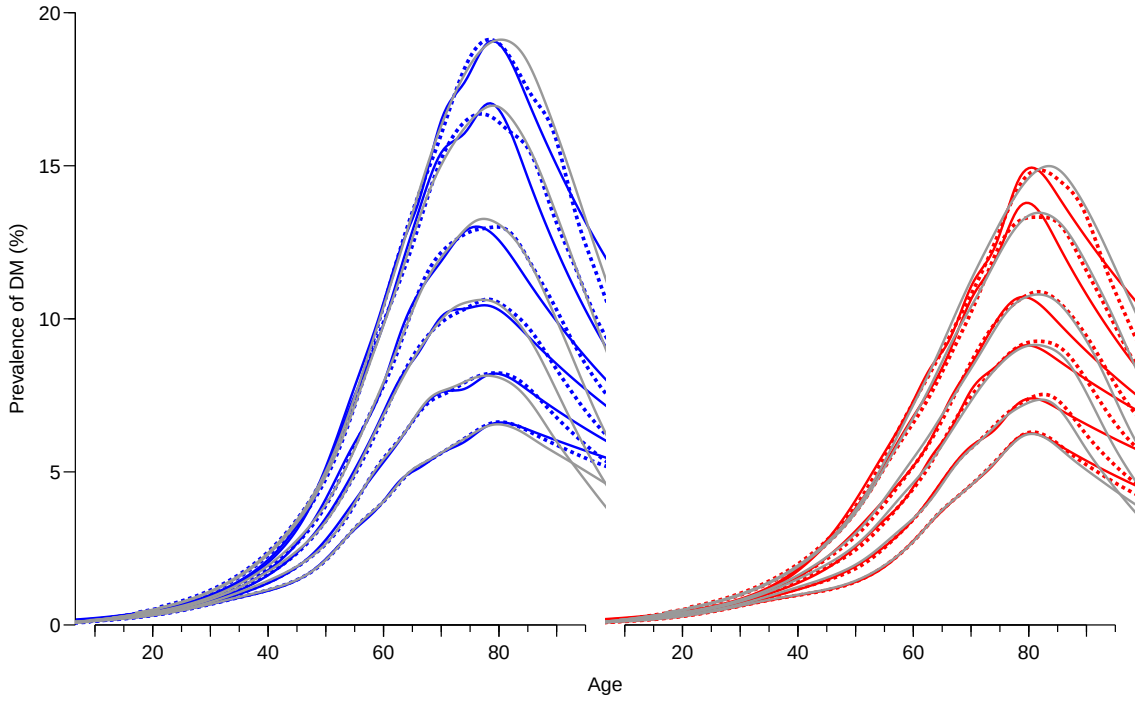

Figure ESM 3: *Observed (full lines) and predicted (broken lines) prevalence of DM in Denmark (from low to high) 1997, 2001,ldots,2017. The observed prevalences are smoothed using natural splines. The predicted prevalences are based on the prevalences as of 1995 and estimated rates from age-period-cohort models for the incidence and mortality rates for the transitions in figure 1. Men in blue, women in red; thin gray lines represent fit from age-period models.*

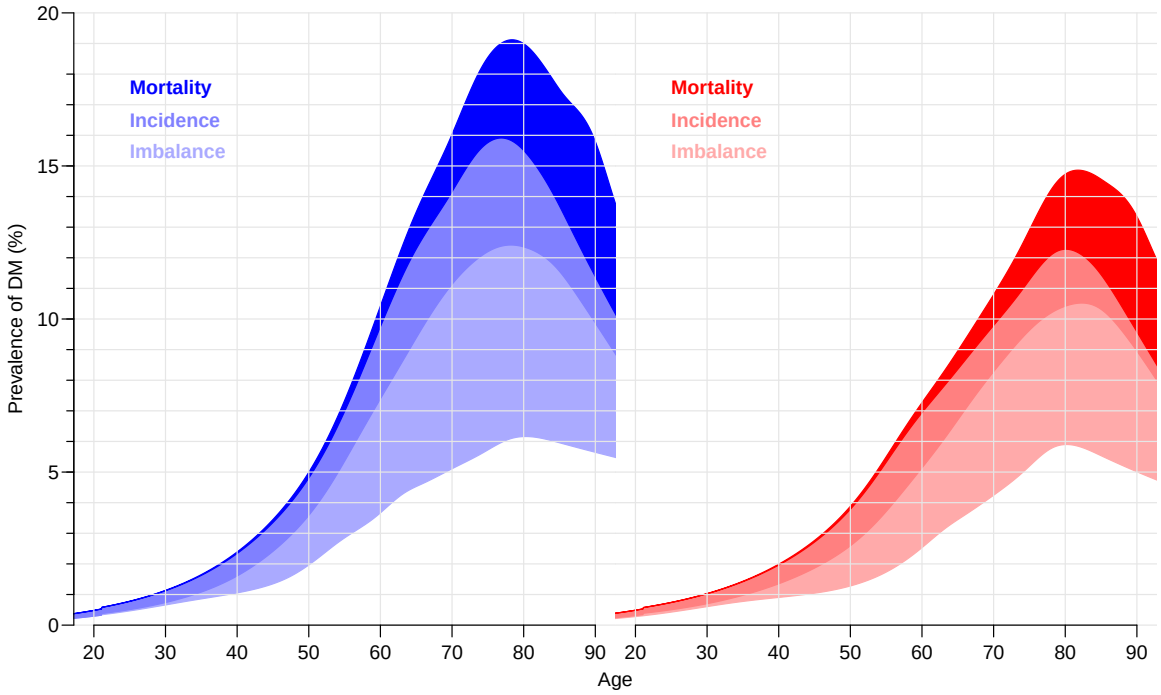

Figure ESM 4: *Age-specific prevalence as of 1 January 2017 subdivided by the components of the changes in diabetes prevalence in the period 1996–2016, based on prevalence in 1996 and models for incidence and mortality in the period. Men in blue, women in red. The white area at the bottom represents the age-specific prevalences at 1 January 1996, and the upper edge of the coloured areas represent the age-specific prevalences at 1 January 2017.*

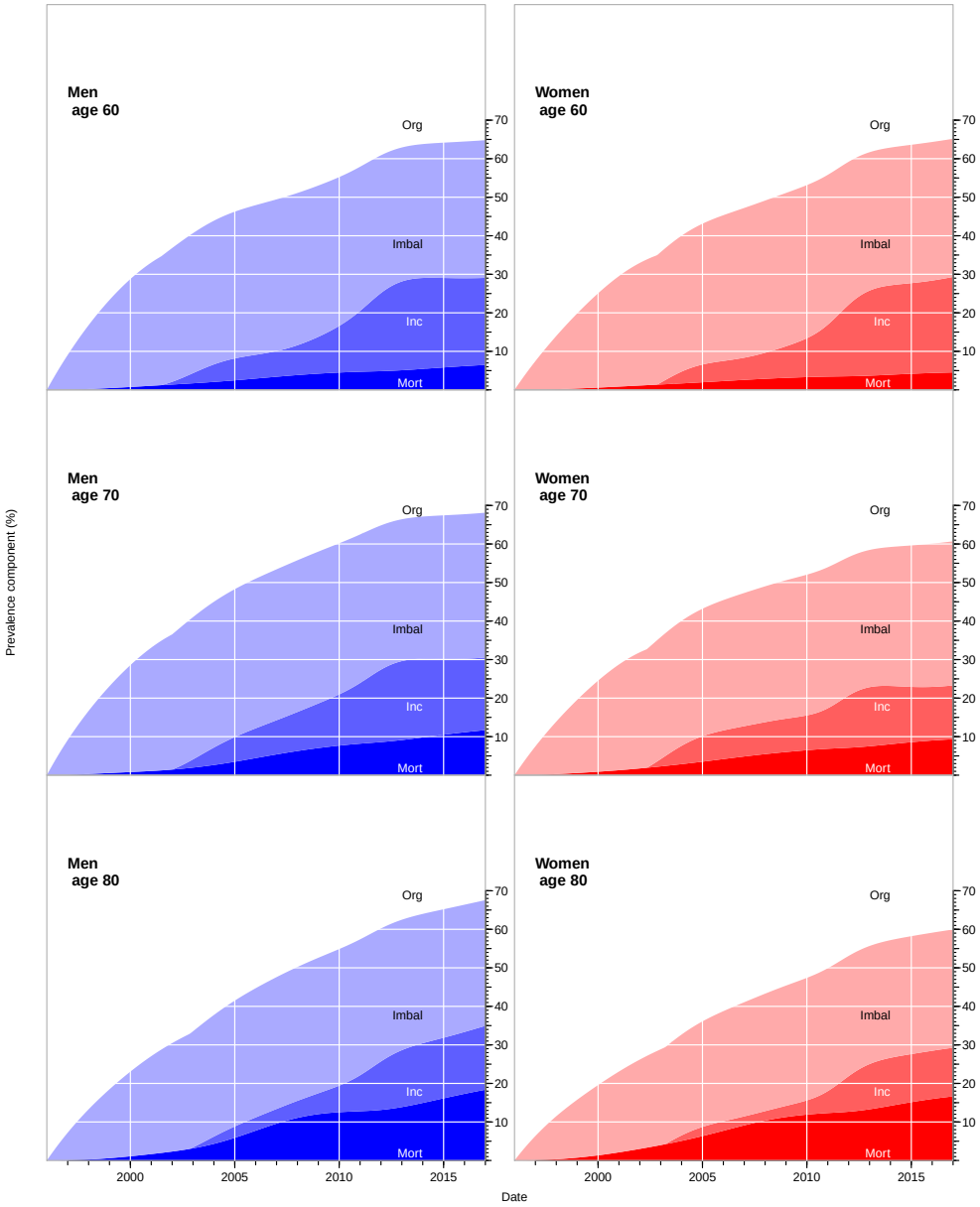

Figure ESM 5: *Fraction of the prevalent cases at different times attributable to a) declining mortality (bottom, full color), b) increasing incidence (middle, pale color) and c) incidence/mortality imbalance 1996 (top, weak color). The white areas above the curves correspond to the fraction of the cases that would have been present if age-specific prevalences were as of 1 January 1996. Men in blue, women in red.*

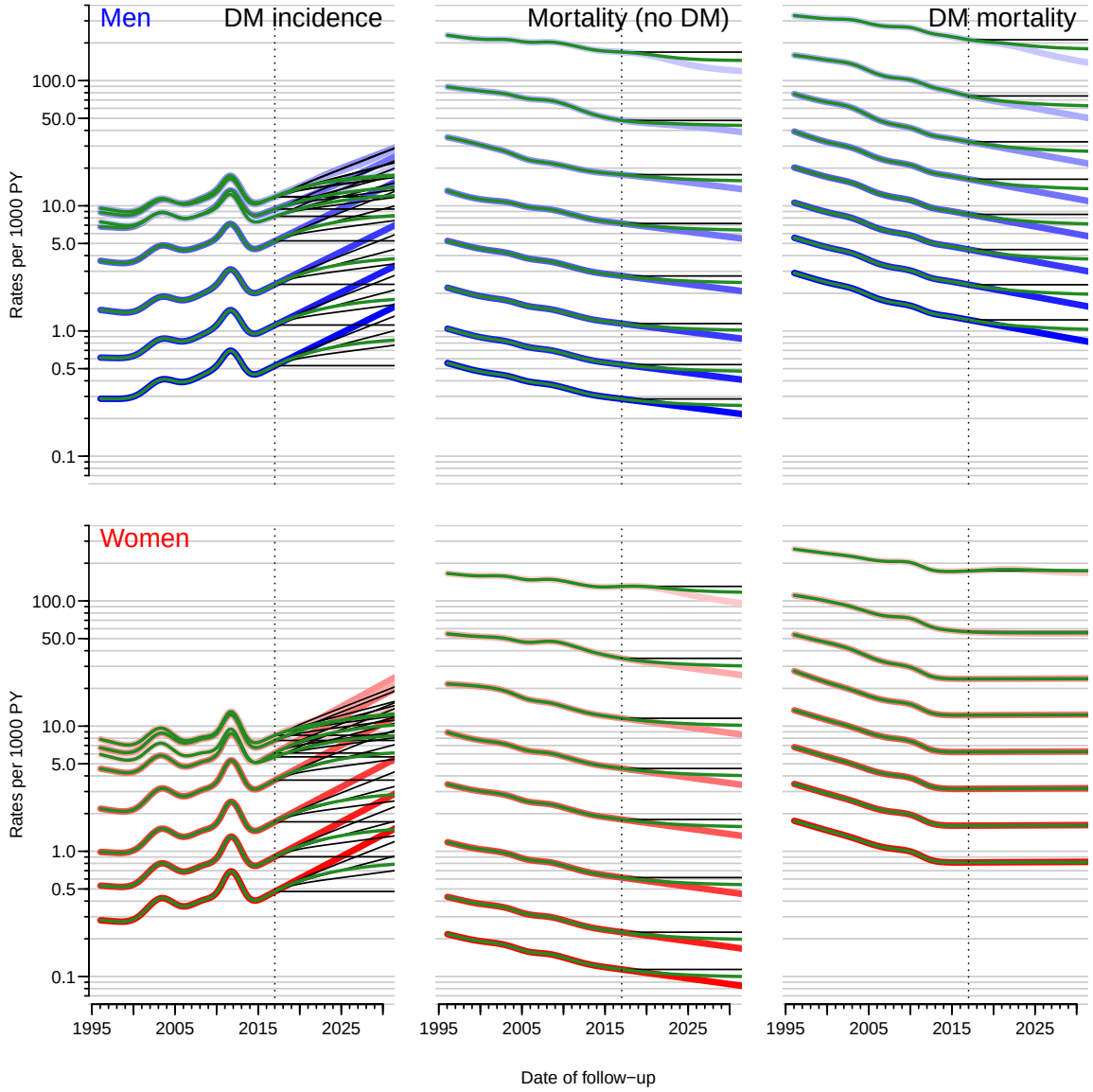

Figure ESM 6: *Observed and predicted incidence and mortality rates 1996–2030 for ages 20, 30,...,90. The naïve prediction based on natural spline models are shown in blue for men and red for women. The black predictions are rates fixed at the level of 2017-01-01. Green predictions are attenuated rates (halving of slope every 5 years), and for incidence rates also the increase of 2, 4 and 6% per year from 2017-01-01. The vertical dotted lines indicate the end of data and start of prediction.*

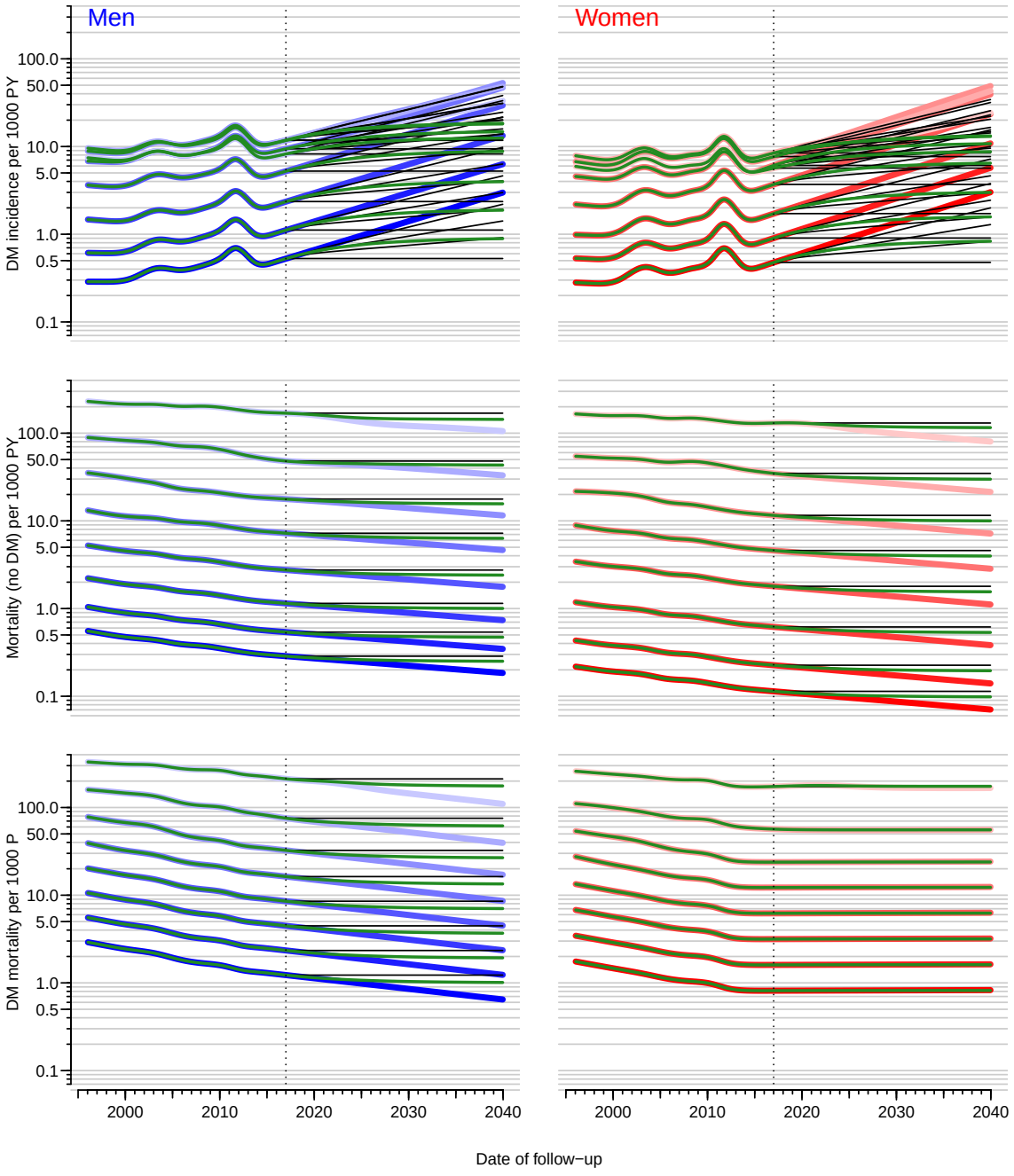

Figure ESM7: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2040 for ages 20, 30,. . . ,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

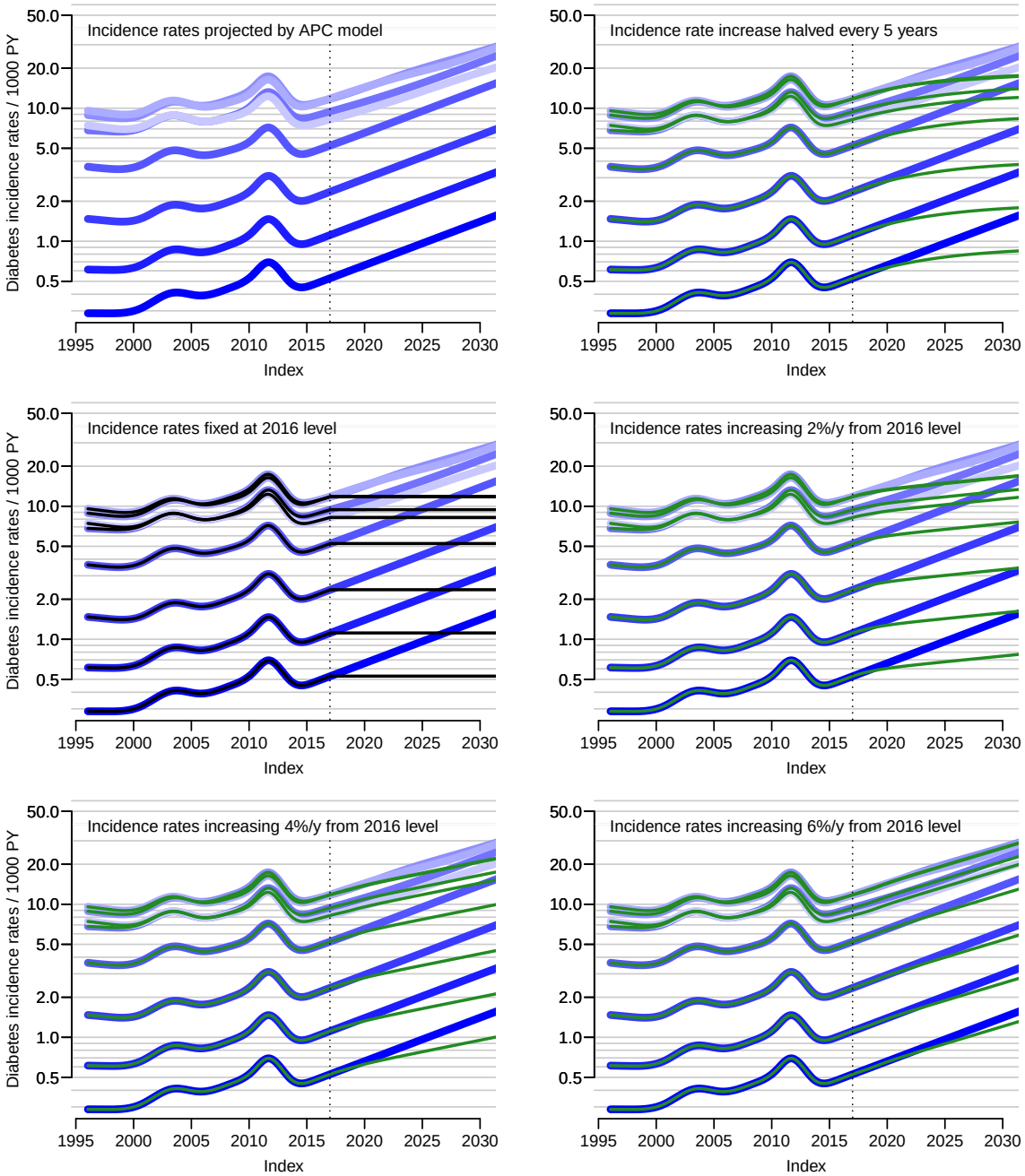

Figure ESM 8: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2030 for man at ages 20, 30,. . . ,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

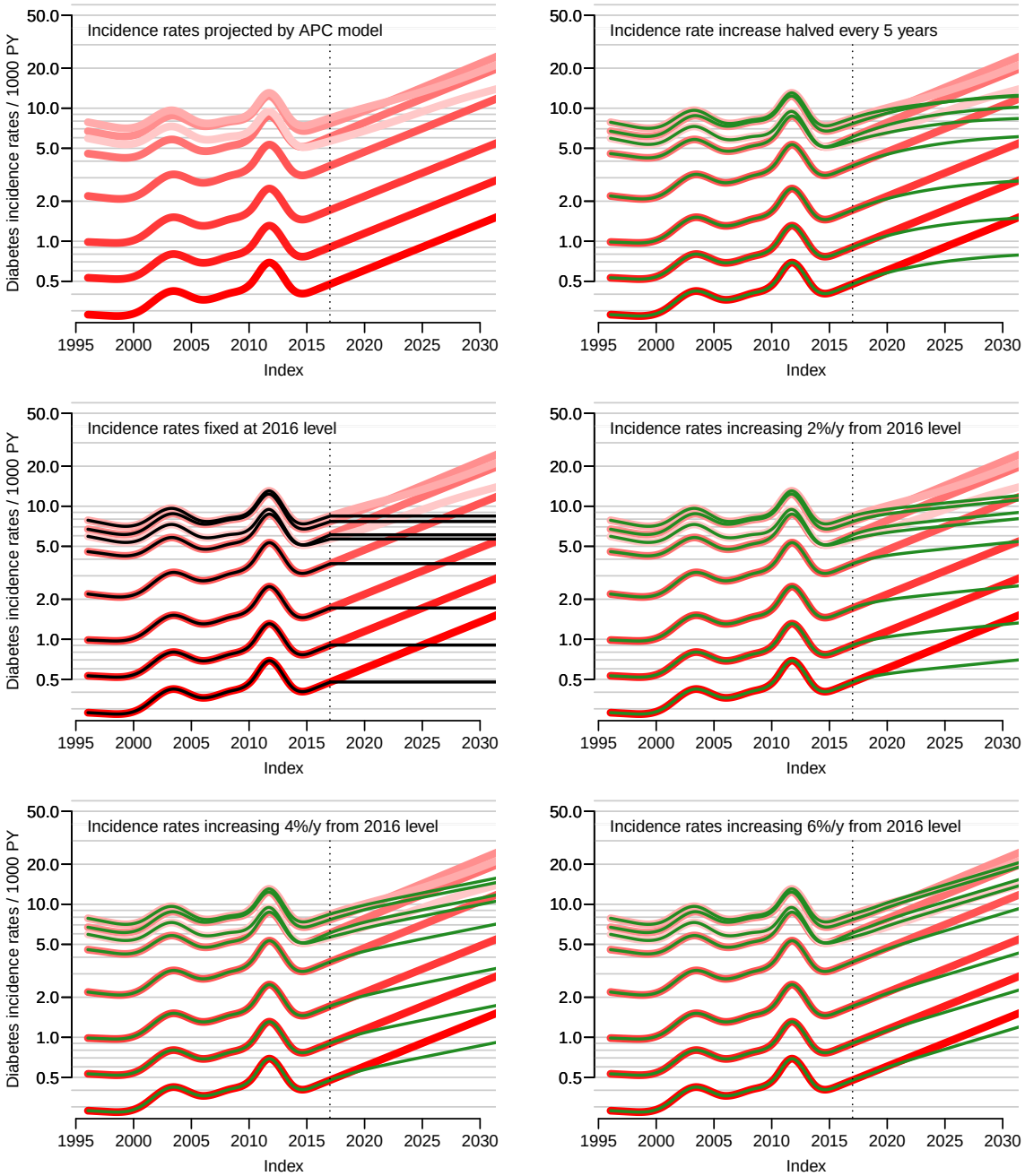

Figure ESM9: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2030 for women at ages 20, 30,...,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

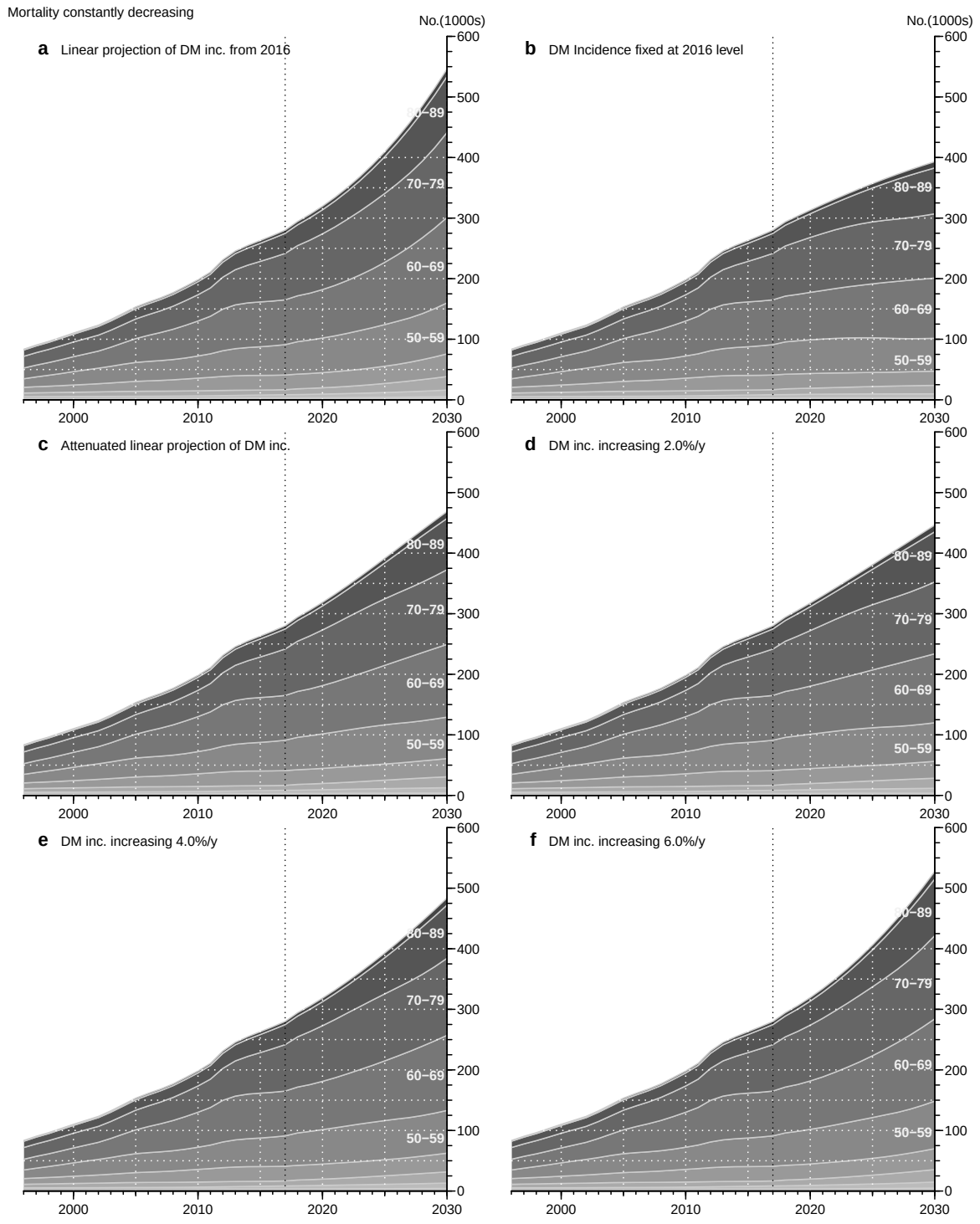

Figure ESM 10: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 with mortality rates predicted form the APC model. Numbers are combined for men and women, and subdivided by 10-year age-groups in different gray tones. The top right panel is the prediction on which we base our conclusions. The vertical dotted line indicates the end of data and start of prediction.*

BMJ Open Diabetes Research & Care

Lifetime risk and years lost to type 1 and type 2 diabetes in Denmark, 1996–2016

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ABSTRACT

Introduction Lifetime risk and lifetime lost to diabetes are measures of current diabetes burden in a population. We aimed at quantifying these measures in the Danish population.

Research design and methods We modeled incidence and mortality of type 1 diabetes (T1D) and type 2 diabetes (T2D) and non-diabetes mortality based on complete follow-up of the entire population of Denmark in 1996–2016. A multistate model with these transition rates was used to assess the lifetime risk of diabetes, as well as the difference in expected lifetime between persons with type 1 and T2D and persons without.

Results In 2016, the lifetime risk of T1D was 1.1% and that for T2D 24%, the latter a 50% increase from 1996. For 50-year-old persons, the lifetime lost was 6.6 years for T1D and 4.8 years for T2D. These figures have been declining over the study period.

At 2016, the total foreseeable lives lost in Denmark among patients with T1D were 182 000 years, and those among patients with T2D were 766 000 years, corresponding to 6.6 and 3.0 years per person, respectively.

Conclusion At the individual level, improvements in the disease burden for both T1D and T2D have occurred. At the population level, the increasing number of patients with T2D has contributed to a large increase in the total loss of lifetime.

Significance of this study

What is already known about this subject?

- Studies from the Western world have shown that the years of life lost to diabetes in mid-life (around 50 years) is between 5 and 10 years, with large difference between countries.
- Studies have focused on either type 1 diabetes (T1D) or type 2 diabetes (T2D) or have not distinguished between types of diabetes.

What are the new findings?

- In similar ages, the years of life lost to T1D are about twice as high as for T1D; for 50-year-old persons the lifetime lost was 6.6 years for T1D and 4.8 years for T2D. This has been decreasing over the last decades.
- The lifetime risk of T1D is currently 1.1%, and that for for T2D is 24%. At 2016, the total foreseeable life lost in Denmark among patients with T1D was 182 000 years, and that among patients with T2D was 766 000 years.

How might these results change the focus of research or clinical practice?

- There is a clear indication that the *individual* outlook for a person with diabetes is improving, whereas the *population* burden is increasing, indicating the prevention is an important focus area.

INTRODUCTION

Relatively few studies have looked at lifetime lost to diabetes,[1–5] and even fewer have provided figures of the lifetime risk of diabetes.[1 2 6 7] The lifetime lost or years of life lost to a disease have been given many interpretations in the literature (for an overview, see Andersen[8]). In this study, we used the standard definition from demography, namely, as the difference in expected lifetime between persons with and without diabetes at a given age. We base our calculations of lifetime risk and of lifetime lost to diabetes on a proper multistate model, taking both type 1 diabetes (T1D) and type 2 diabetes (T2D) into account.

RESEARCH DESIGN AND MATERIAL

Data

We used a newly established Danish Diabetes Register[9 10] linked to the total population of Denmark, including the causes of death register. Detailed information on diabetes incidence, prevalence, mortality, and current and predicted future numbers with diabetes is given in previous publications.[9 10] We constructed tables of person-years, incident cases of T1D, T2D and deaths by cause for the entire Danish population subdivided by current diabetes status (no diabetes, T1D and T2D). The causes of death used were cardiovascular disease (International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10): I00–I999), cancer (ICD-10: C00–D099, so carcinoma in situ are included, benign and unspecified tumors *ex*cluded), respiratory (ICD-10: J00–J999) and other causes. These tables were classified by sex, age and date of follow-up and

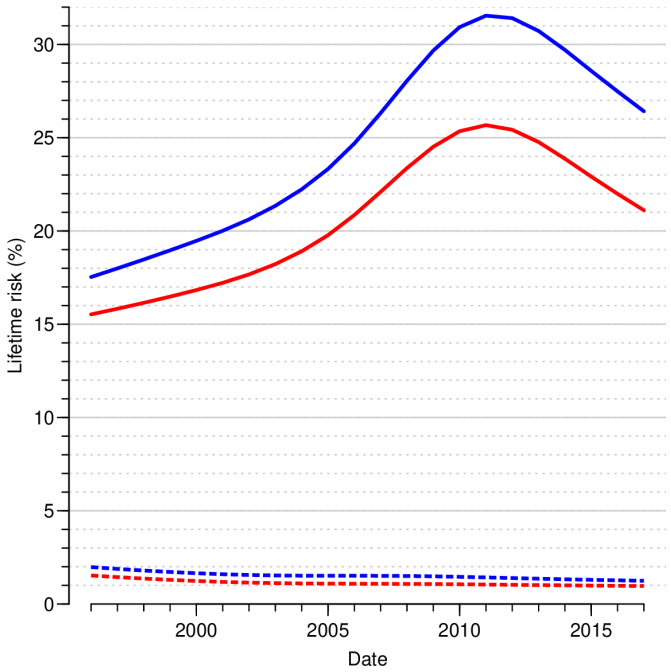

Figure 1 Lifetime risk of T1D and T2D by sex and date of reference. The calculations are based on annual estimated cross-sectional incidence and mortality rates from age–period–cohort models for incidence and mortality. Blue curves are men, red curves women; dotted lines T1D, full lines T2D. T1D, type 1 diabetes; T2D, type 2 diabetes.

date of birth in 1-year intervals, so called Lexis triangles[11]; further details are given in the electronic online supplemental material 1 (ESM), including a detailed overview of causes of death (online supplemental table 2)

Statistical methods

We fitted models for incidence rates of T1D and T2D, and cause-specific mortality rates for persons without diabetes and with T1D and T2D separately. All models were age–period–cohort (APC) models with smooth effects of current age, date of follow-up (period) and date of birth (cohort), providing estimated age-specific rates at each January 1, 1996–2017. Analyses were done separately for men and women—for further details, see the ESM.

Estimated rates were used in a multistate model with states 'no diabetes', 'T1D', 'T2D' and the four causes of death.

Measures

The lifetime risk of diabetes is the probability of getting diabetes before death. The expected lifetime (at birth) is the area under the survival curve, so the lifetime lost to diabetes is the difference in the area *between* the survival curves for a person with and a person without diabetes. If we condition on being alive at a given age, we used the *conditional* survival curves for that age. We subdivided the years of life lost by cause of death.[8]

We used the age-specific rates at each January 1 to compute the lifetime risk of T1D and T2D and the years of life lost to different causes of death. We also computed the *population* burden as the future years of life lost, both among prevalent cases of diabetes at a given date and among persons diagnosed with diabetes during a given year. A detailed account of methods used for computation of these measures is in the ESM.

RESULTS

In the study period 1996–2016 inclusive, there were 19 712 T1D diagnoses and 343 952 T2D diagnoses, while there was 12 762 deaths among patients with T1D, 149 000 among patients with T2D and 988 569 among persons without diabetes (online supplemental table 1). The dominant single cause of death was CVD except for T1D, where the dominant cause of death was other causes.

Lifetime risk of diabetes

The lifetime risk of T1D declined from 2.0% to 1.2% for men and from 1.5% to 1.0% for women over the study period, while lifetime risk for T2D showed a peak around 2011 of more than 30% for men and 25% for women (driven by the very high recorded incidences that year[9]). The lifetime risk of T2D was 26% for men and 21% for women on January 1, 2017, corresponding to increases of 51% and 36% since 1996 (figure 1 and table 1).

EXPECTED LIFETIME

In the study period, the expected lifetime (at birth) without diabetes increased from 70.2 to 74.4 for men and from 75.5 to 78.8 years for women. At the population level, the expected lifetime spent (sojourn time) with T1D was 0.6 years for men and 0.5 years for women, unchanged over the study period, while the expected lifetime with T2D increased from 2.0 to 4.6 years, similar for men and women (table 1). Thus, of the increase in expected lifetime in the period, more than half was expected to be years with T2D (table 1).

Years of life lost to diabetes

At the beginning of 2017, the lifetime lost to T1D was 8.3 years at age 20 years and about 5.6 years at age 60 years (online supplemental table 5). Lifetime lost to T2D at age 60 years was 3.8 years (online supplemental table 6), so T1D carries about 30% higher lifetime loss compared with T2D (figure 2 and online supplemental tables 5 and 6), reflecting the earlier diagnosis and hence longer duration of diabetes at a given age for T1D as compared with T2D. We also found that the years lost to diabetes have been diminishing over the study period, at age 50 years from about 9 to 7 years for T1D and from 8 to 5 years for T2D.

Future years of life lost

The future years of life lost among *patients with prevalent diabetes*—the currently accumulated future population burden in Denmark—was 947 600 years on January 1, 2017 (online supplemental table 3), 19% of which were among persons with T1D, despite only 10% of Danish

Table 1 Lifetime risk, expected lifetime spent with diabetes and lifetime lost by type of diabetes, sex and date (January 1 each year)

	Lifetime risk (%)		Expected lifetime (years) spent with			Lifetime lost (years) to							
						T1D, at ages				T2D, at ages			
Date	T1D	T2D	No DM	T1D	T2D	25	40	50	60	40	50	60	75
Men													
1996	2.0	17.5	70.2	0.6	2.1	9.6	8.3	6.6	4.7	9.5	7.7	5.7	2.9
1999	1.7	19.0	70.9	0.5	2.4	11.4	10.0	8.2	6.1	8.7	7.1	5.2	2.7
2002	1.6	20.6	71.5	0.5	2.8	12.7	11.1	9.3	6.9	8.1	6.5	4.9	2.4
2005	1.5	23.3	71.8	0.5	3.4	13.2	11.6	9.7	7.3	7.3	5.9	4.4	2.2
2008	1.5	28.1	71.4	0.5	4.4	13.6	12.0	10.1	7.8	6.4	5.1	3.9	2.0
2011	1.4	31.5	71.4	0.6	5.2	12.4	11.0	9.4	7.5	5.7	4.6	3.5	1.9
2014	1.3	29.7	72.7	0.6	5.1	10.2	9.1	7.9	6.4	5.6	4.6	3.6	2.0
2017	1.2	26.4	74.4	0.6	4.6	8.1	7.3	6.3	5.2	5.7	4.7	3.7	2.1
Women													
1996	1.5	15.5	75.5	0.5	2.0	10.9	9.7	8.3	6.4	9.5	8.1	6.3	3.5
1999	1.3	16.5	75.9	0.4	2.3	11.5	10.3	9.1	7.1	8.6	7.3	5.7	3.2
2002	1.1	17.7	76.3	0.4	2.6	11.9	10.8	9.5	7.7	7.8	6.6	5.1	2.9
2005	1.1	19.8	76.5	0.4	3.2	12.4	11.2	9.9	8.1	7.0	5.9	4.6	2.5
2008	1.1	23.4	76.2	0.4	4.0	12.6	11.4	10.2	8.4	6.2	5.2	4.0	2.1
2011	1.0	25.7	76.3	0.5	4.7	11.4	10.4	9.4	7.9	5.7	4.8	3.7	2.0
2014	1.0	23.9	77.4	0.5	4.5	9.8	9.0	8.1	6.9	5.6	4.8	3.7	2.0
2017	1.0	21.1	78.8	0.5	4.1	8.2	7.6	6.9	6.0	5.7	4.9	3.8	2.1

Note the different ages at calculation of life lost for T1D and T2D, accommodating the different age distributions of T1D and T2D.
DM, diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes.

patients with diabetes are T1D.[9] The average future lifetime lost was 6.6 years for T1D and 3.0 years for T2D, partly attributable to different age distributions.

The *extra* future lifetime lost among *newly diagnosed patients with diabetes* in a single year was around 70 000 years during 2016, some 10% of these from T1D, even if only 5% of newly diagnosed cases are T1D (online supplemental table 3). The average lifetime lost for persons diagnosed in 2016 were 8.2 years for T1D and 3.6 years for T2D (online supplemental figure 2).

For both of these measures, we found an increase at the population level over time, but at the *individual* level, we found that the *average* lifetime lost among patients was decreasing over the study period, over the last 10 years, some 35% for T1D, but less than 10% for T2D (online supplemental tables 3 and 4).

Years of life lost by cause of death

We found that the major contributor to years of life lost in T1D (online supplemental table 5 and online supplemental figures 4–7) was other causes of death (4.1 years at age 50) and only second was CVD (2 years at age 50), whereas respiratory causes contribute slightly less than 1 year throughout the age range. Cancer contributes almost nothing in women with T1D and a negative 1 year among men with T1D. In T2D (online supplemental table 6 and online supplemental figures 4–7), other causes and CVD contribute similar amounts of life lost—about 1.5 years each at age 50, and respiratory causes less than 0.5 years.

DISCUSSION

Our study is the first to simultaneously evaluate the lifetime risk as well as the lifetime lost to T1D and T2D in an entire population using a proper multistate methodology. We evaluated both the individual and the population levels of years of life lost to diabetes.

We found the lifetime risk of T1D to be just over 1% and that of T2D to be about 25%—both of these figures properly account for the competing type of diabetes as well as death, and the lifetime risk of any type of diabetes is therefore 26%.

Whichever way the lifetime lost to diabetes is illustrated, there has been a very clear improvement over the last two decades at the individual patient level, but the overall population burden, particularly for T2D, has been massively increasing.

Life years lost to T1D are some 30% higher than those lost to T2D at any given age. That may be due to longer exposure to risk factors for acute and chronic microvascular and macrovascular complications to diabetes with earlier onset. Furthermore, the aggressive approach to manage cardiometabolic risk factors in T2D is less well

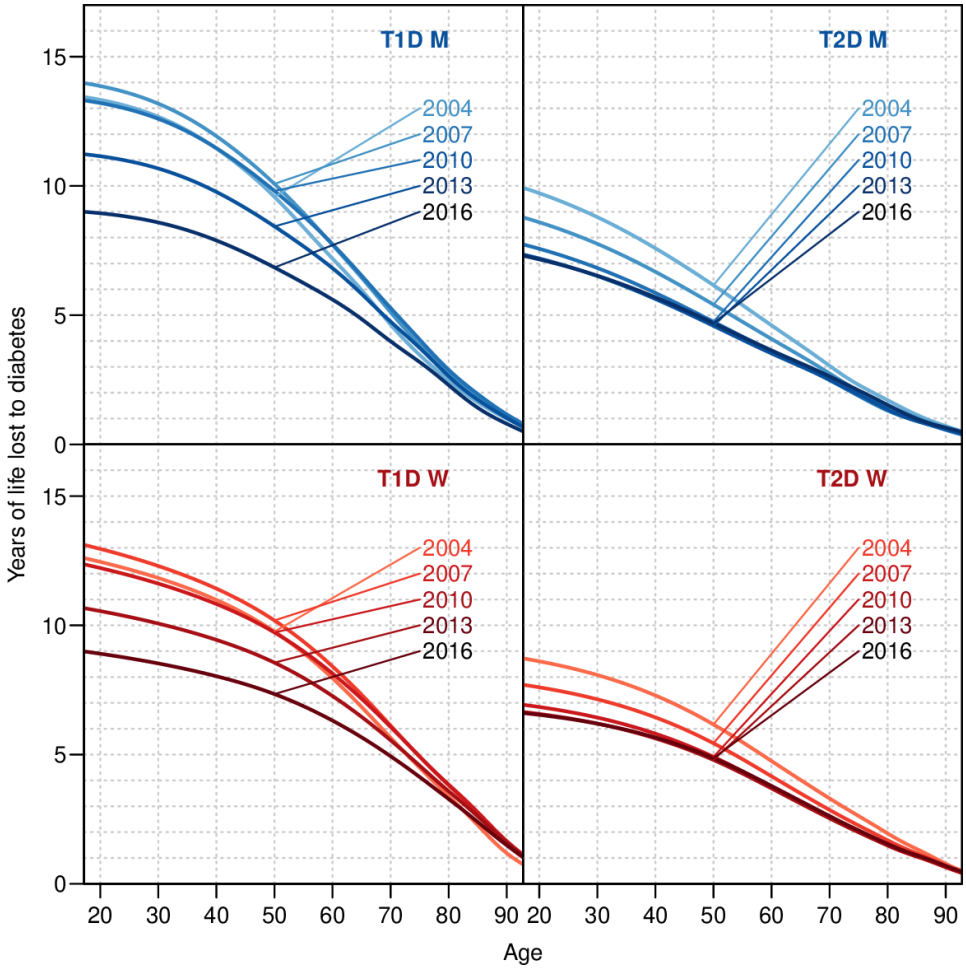

Figure 2 Years of life lost to T1D and T2D in January 1, 2004, 2007, …, 2016, by sex. The calculations are based on annual estimated cross-sectional incidence and mortality rates from age–period–cohort models for incidence and mortality. M, men; T1D, type 1 diabetes; T2D, type 2 diabetes; W, women.

documented in T1D, and quality registers have proven less favorable blood pressure and lipid levels in T1D compared with T2D, as well as some renal-protective and cardioprotective undertreatment.[12]

A number of studies modeling life years lost to diabetes[4 5 13–16] are old or have used suboptimal methods for calculations or very crude model assumptions, and are therefore not directly comparable to ours. The studies by Narayan *et al*[1] and Gregg *et al*[2] use similar methodology as we do, comparing the mortality among persons with and without diabetes at a given survey date (ignoring subsequent diabetes development—not explicitly mentioned in any of the papers), which gives a more valid picture of the lifetime lost to diabetes. The most recent study by Gregg *et al* arrived at years of life lost to diabetes at age 40 years for white men of 5.8 and 6.8 years for white women in the period 2000–2011, where we found 7.3 and 7.0 years in 2005. The validity of this study, however, is limited by the fact that the diagnosis of diabetes is derived from a telephone survey.

Livingstone *et al*[3] provided estimates of lifetime lost to T1D in Scotland for the period 2008–2010 of 9.2 years for men and 10.8 years for women aged 40 years. Huo *et al*[17] estimated the lifetime lost to T1D in Australia for the period 1997–2010 to 10.0 years for men and 11.2 years for women aged 40 years. For 2008, we found 6.4 years for men and 6.2 years for women at age 40 years somewhat smaller than the Scottish and Australian studies.

Strengths and weaknesses

A major strength of our study is the total population coverage, which eliminates sampling biases, and the use of a multistate model to compute realistic survival curves for persons without diabetes, taking the future possibility of both T1D and T2D into account. Moreover, we used 1-month updating intervals in model updating, minimizing the approximation bias, and we took calendar time and cohort trends in rates into account, enabling us to derive these measures for successive years, and thus realistically account for trends.

One study weakness is potential misclassification of insulin treated T2D as T1D in the early years of the diabetes register (before 2005). Thus, years of life lost to T1D may be underestimated before 2005 due to contamination with patients with T2D.

SUMMARY

Our study shows that there has been a decrease in lifetime risk of T1D to slightly over 1% and an increase in T2D risk to 25%.

Further, we demonstrated a decline in the individual burden of T2D over the last two decades, but also clearly demonstrated that the population burden is increasing, indicating that preventive measures have not had the desired effect yet, and in particular, that the burden of T1D still is quite high, despite decreasing lifetime risk.

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Contributors BC and MEJ conceived the structure of the underlying register. PFR provided support for obtaining data access and contributed to data definition. BC detailed and developed the study and the statistical methods needed, performed all data analysis, and wrote the first draft of the manuscript. MEJ and PFR contributed substantially to the writing of the manuscript. All authors contributed to critical revision and take responsibility for the content. BC 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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Competing interests BC and MEJ own shares in NovoNordisk. BC has received lecture and consultancy fees from NovoNordisk and LeoPharma. MEJ is principal investigator on a trial sponsored by AstraZeneca and received research grants from AMGEN AB, AstraZeneca, Sanofi Aventis and Boehringer Ingelheim. PFR has nothing to disclose.

Patient consent for publication Not required.

Ethics approval This study was approved by the Danish Data Protection Agency (registration number 2015-41-4148). Ethical approval is not required for register-based studies in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are not publicly available. The data for this study are population-wide registers, placed at our disposal on the servers of Statistics Denmark. They are barred from release to the public on grounds of confidentiality. A full documentation of the register is given in the electronic supplemental material.

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Lifetime risk and years lost to type 1 and type 2 diabetes in Denmark 1996–2016

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1 Calculation of life expectancy and lifetime lost

This is a detailed, albeit quite short description of theory and methods underlying the calculation of the life expectancy and life lost. A complete account of the statistical analysis and all code used is available in
http://bendixcarstensen.com/DMreg/Ana2016.pdf, pp. 235 ff.

1.1 Life expectancy: definition and tradition

The life expectancy as reported by most statistics bureaus is the area under the survival curve constructed from cross-sectional age-specific mortality rates[1]. It represents the expected lifetime of a person at birth under the assumption that the age-specific mortality rates are as the cross-sectional population mortality rates during the person's life. This measure may also be reported for persons that have attained a certain age, a; the expected *residual* life time at age a. This will typically appear as a column in life tables, see *e.g.* https://dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=29442&sid=befudv2017, table 4.7, p. 45. The expected residual life time at age a is derived as the area under the *conditional* survival curve given survival till age a.

1.2 Lifetime lost

Lifetime lost to a disease comes in many guises, see for example [2], but here we shall use the standard definition as the difference between the expected residual lifetimes of a diseased person and a person of the same age without the disease. This is the area between the survival curves for persons with and without the disease ('years of life lost', YLL), formally:

$$\mathrm{YLL}(a) = \int_a^\infty S_{\mathrm{pop}}(u|a) - S_{\mathrm{dis}}(u|a)\,\mathrm{d}u$$

where $S(u|a)$ is the probability of surviving till age u, given attained age a. In simple cases with only one time scale and only transition from alive to dead, $S(u|a) = S(u)/S(a)$, but in more realistic situations this is not the case.

Andersen [1] also introduced the "τ-restricted" life expectancy and the corresponding lifetime lost by considering only a time span of τ after the age we refer to; formally we compare the area between the *conditional* survival curves in the interval $[a, a+\tau]$:

$$\mathrm{YLL}_\tau(a) = \int_a^{a+\tau} S_{\mathrm{pop}}(u|a) - S_{\mathrm{dis}}(u|)\,\mathrm{d}u$$

Thus, the prerequisite for calculation of life lost to a disease is the availability of survival curves for diseased and non-diseased persons. Or more specifically, *conditional* survival curves given survival to a given (set of) age(s), $S_{\mathrm{pop}}(u|a)$. Such survival curves can be derived from the age-specific mortality rates; in some cases disease incidence rates are needed too — see below.

We may compare population survival with either patients alive at a given age (prevalent cases) or patients diagnosed at a given age (incident cases). If we assume that mortality

[1] A short mathematical derivation of this can be found in https://bendixcarstensen.com/AdvCoh/relations.pdf.

rates depend on disease duration these two will be different. In our data we only have observed diabetes duration up to 20 years, and the calculations would need duration effects till at least 50 years, so we do not have the data basis for calculating life lost at a given age at diagnosis.

1.3 Constructing survival curves

The survival curve for persons with diabetes (or newly diagnosed with diabetes) at a given age is a simple transformation of the age-specific mortalities, μ_{DM} (with or without duration included):

$$S_{\text{DM}}(t|a) = \exp\left(-\int_a^t \mu_{\text{DM}}(u)\,\mathrm{d}u\right)$$

On the other hand, a comparison survival curve for persons without disease can be computed in three different ways:

1. use mortality rates among non-diseased persons (μ_{noDM}), transform these to a survival curve by $S_a(t|a) = \exp(-\int_a^t \mu_{\text{noDM}}(u)\,\mathrm{d}u)$, and compute the integral under this curve. This will *over*-estimate the survival among persons without diabetes and hence the expected lifetime among persons without disease, because it ignores the possibility that a non-diseased person later falls ill from diabetes and thus moves to a state with higher mortality.

2. use a multistate model with *both* incidence rates of disease and mortality rates of persons with and without disease to compute a survival function for a person that is non-diseased at a given age. The survival function is computed as the probability of being alive (diseased or non-diseased) at any given age. This is the correct way of computing the expected residual life time among persons without disease at a given time, because it refers to a real-world scenario of persons alive at a given age, with no assumptions about their future life-course.

3. use mortality rates for the *entire* population. This will (slightly) *under*-estimate the survival, because the mortality rates also include persons who already has the disease at age a. If the the disease is not too prevalent or does not carry too high excess mortality this approach may be a reasonable alternative to the correct.

In our calculations we used a more elaborate version of option 2 above, using a multistate model with separate incidence rates of type 1 diabetes and type 2 diabetes, as indicated in figure 1 using different rates for causes of death.

1.4 Models for rates

We tabulated transitions (D, occurrences of type 1 diabetes, type 2 diabetes and death) and person years (Y) by current age, date of follow up (period) and date of birth (cohort) in 1-year classes (Lexis triangles). These were further classified by the current status of persons (noDM, T1D and T2D), as illustrated in figure ESM 1 and table ESM 1.

Thus for each of the left hand boxes in figure ESM 1 we have person-time Y classified by sex, age, period and cohort. Similarly, each instance of the 14 transitions (D) illustrated by the arrows in figure ESM 1 were classified by sex, age, period and cohort and the type of transition (from, to).

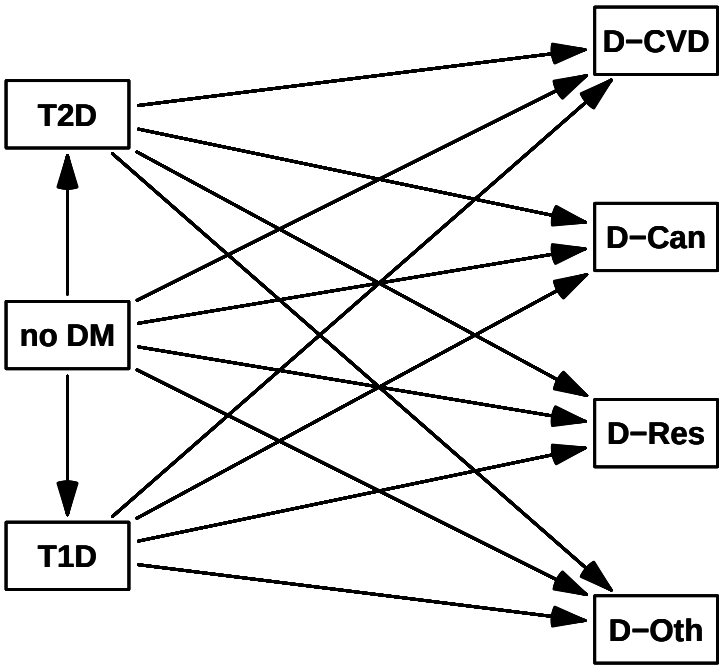

Figure ESM 1: *Multistate model used to compute the survival probabilities of persons in each of the states "no DM", "T1D" and "T2D". The right hand states refer to death from cardiovascular disease ("D-CVD"), cancer ("D-Can"), respiratory causes ("D-Res") and other causes ("D-Oth"). For persons in "T1D" and "T2D" the survival is just the probability of remaining in the state. For persons in state "no DM" at a given age the survival is the probability of being in either of the states "no DM", "T1D" and "T2D".*

For the tabulated data we fitted age-period-cohort models for all transition rates illustrated in figure ESM 1, using a Poisson likelihood for D with log person years ($\log(Y)$) as offset.

All analyses were made separately for men and women. We used natural splines (restricted cubic splines) for the effects of current age, current date (period) and date of birth (cohort).

1.5 Model based survival curves

From the parametric models for each of the 14 transitions (age-period-cohort models with smooth effects) for each sex, and from these derived the estimated cross-sectional age-specific rates at 1996-01-01, 1997-01-01,..., 2017-01-01, in ages 0–1200 months. Thus, in line with the normal demographic practice we used cross-sectional rates to compute measures relating to lifetime experience.

The cross-sectional rates were used to construct 1-month transition probabilities between the states, one per transition illustrated in figure 1. We used three different initial state occupancy vectors; one with probability 1 in state "no DM" (and hence 0 in the two other

states), one with probability 1 in state "T1D" and one with probability 1 in state "T2D". These were then successively multiplied by the transition probability matrices for each age, yielding the state probabilities at all ages.

The sum of the probabilities of being in any of the alive states ("noDM", "T1D", "T2D") at a given time were taken as the survival function for persons starting in each of the three transient states ("no DM", "T1D" and "T2D"). This calculation was repeated for persons starting at ages 0, 1, 2 etc. so we have survival functions conditional on being in any of the three states at these ages. The value of these survival functions were computed at 1 month age intervals till age 100 years (1200 months).

The expected lifetimes age were computed as the integral of these survival functions by adding the values of the survival function at different ages multiplied by the interval length (1 month).

The years of life lost to diabetes was computed as the difference in life expectancy between persons with diabetes and persons without.

Following Andersen [1] we used the differences in cumulative risks of each cause of death to decompose the total lifetime lost to each of the causes of death to type 1 diabetes, resp. type 2 diabetes.

1.6 Population related measures

The years of life lost to type 1 diabetes resp. type 2 diabetes are in principle unrelated to the Danish population in the sense that the measures applies to any population with incidence and mortality rates as the Danish, regardless of the age-composition of the population and patients.

But we also want to compute the population burden of diabetes in terms of the total number of years lost to diabetes in the Danish population. This can be done in (at least) two different ways:

1. the total future lifetime lost for persons alive with diabetes at a given time (the beginning of a given calendar year, say). This is the total `accumulated` future burden of diabetes among those currently alive with diabetes.

2. the total future lifetime lost among those diagnosed with diabetes during a given period (a calendar year, say). This is the *added* burden among the persons diagnosed during the last year, say.

1.7 Lifetime risk

The lifetime risk of type 1 resp. type 2 diabetes were computed by evaluating the probability of being in state T1D or T2D at age 100, using only the mortality rates from noDM, and ignoring the mortality rates from states T1D and T2D. This corresponds to ignoring anything that happens to diabetes patients after diagnosis — we are only interested in the probability of entering each of the T1D and T2D states.

2 Methodological issues

Most studies use the overall population mortality as basis for comparison (which is a reasonable approximation), and some use the non-diabetes mortality rates (which result in

an over-estimate of life time lost). Incidentally, the studies based on the NHIS [6, 3] by virtue of the data available use an empirical approximation to the correct survival probabilities for persons alive without diabetes at a given time — only mortality among persons surveyed were available, not the future diabetes occurrence.

Some studies [5, 4] indicate they used Chiang's method for calculation of the life table probabilities. This method dates back to 1968 and is aimed at compensating for irregular distribution of deaths across wide age-intervals, a natural consequence of the absence of computers in 1968. Notably it requires input of the average time lived in the interval before death for those who die in an interval, but none of the studies claiming to use Chiang's method detail how they estimated this quantity. Using a value of half the interval length will in most cases give results indistinguishable from just using the standard mathematical relationship of cumulative risk (= life table probability) as the exponential of minus the cumulative rate, particularly if rates are computed in small (1-year, say) intervals. These studies have used 5-year intervals which induce an extra inaccuracy relative to 1-year intervals. In our study we used 1 month intervals of age for calculation of transition probabilities between states.

The papers by Gregg *et al.* [3] and Narayan *et al.* [6] among others use an approach similar to ours by estimating rates in a multistate model and a Markov-chain approach to estimation of survival probabilities in different scenarios, the latter using a 1-year updating intervals. However, the updating interval should be chosen so small that the probability of transition from no diabetes to diabetes and further to death within a single interval is negligible. Which is not the cases in older ages in a 1-year interval, so these studies are likely to have a small extra bias from this.

Unlike the papers mentioned above, our study exploits the possibility from register data to build results on credible models for incidence and mortality rates (namely as smooth continuous functions of age and calendar time) as well as using modern computing to arrive at results based on continuous time models, through using 1-month updating intervals for the Markov chain. This is a major strength of our study and can be implemented in any study — using 100 1-year age classes or 1200 1-month age classes makes little difference on a modern computer.

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Table ESM 1: *Events (diabetes diagnoses and deaths) and person-years (in 1000s) in the Danish population in the 21 year study period 1996–2016, subdivided by current diabetes status.*
The three parts of the P-years column correspond to the person-years (in 1000s) in the three leftmost boxes (noDM, T1D, T2D) in figure ESM1. The 14 combinations of type of diabetes (2 types) and cause of death (4 causes) on one hand and status (noDM, T1D, T2D) on the other hand correspond to the events (arrows) in figure ESM1. Of course there are no diabetes events among persons with diabetes.

Status	Diabetes cases		Deaths by cause					
Period	T1D	T2D	CVD	Cancer	Respir	Other	All	P-years
No diabetes								
1996-1998	3,478	33,986	58,088	42,494	15,170	43,916	159,668	15,623.6
1999-2001	2,994	36,887	55,457	42,406	14,917	41,430	154,210	15,726.0
2002-2004	2,816	49,185	50,897	40,506	15,295	41,733	148,431	15,808.1
2005-2007	2,780	44,326	42,956	40,444	14,122	42,943	140,465	15,872.1
2008-2010	2,734	56,453	36,812	39,304	15,031	44,762	135,909	16,019.6
2011-2013	2,477	69,728	31,855	39,093	14,811	40,947	126,706	16,105.7
2014-2016	2,433	53,387	29,588	38,229	14,137	41,226	123,180	16,301.0
1996-2016	19,712	343,952	305,653	282,476	103,483	296,957	988,569	111,456.1
T1D								
1996-1998	.	.	868	290	137	671	1,966	68.1
1999-2001	.	.	997	365	130	643	2,135	71.2
2002-2004	.	.	835	333	175	860	2,203	73.1
2005-2007	.	.	610	397	137	950	2,094	74.4
2008-2010	.	.	501	402	183	803	1,889	73.3
2011-2013	.	.	348	284	157	643	1,432	71.0
2014-2016	.	.	243	237	113	450	1,043	70.0
1996-2016	.	.	4,402	2,308	1,032	5,020	12,762	501.1
T2D								
1996-2016	.	.	4,402	2,308	1,032	5,020	12,762	501.1
1996-1998	.	.	8,133	2,788	1,114	3,564	15,599	212.6
1999-2001	.	.	8,559	3,556	1,294	4,005	17,414	269.6
2002-2004	.	.	8,084	4,025	1,860	5,199	19,168	341.0
2005-2007	.	.	7,485	4,760	1,973	6,414	20,632	421.0
2008-2010	.	.	7,080	5,508	2,562	7,416	22,566	502.6
2011-2013	.	.	7,546	6,704	3,013	7,907	25,170	631.1
2014-2016	.	.	7,850	7,965	3,584	9,052	28,451	718.1
1996-2016	.	.	54,737	35,306	15,400	43,557	149,000	3,096.0

Table ESM 2: *Number of deaths in Denmark 1996–2016 by cause of death (10 groups)*

				Other causes						
	CVD	Cancer	Respir	Diab	Digest	Extern	Infect	Other	Renal	Urinal
All	360,278	322,704	118,944	27,196	55,029	54,769	15,277	192,737	6,989	9,831
1996	22,542	15,216	5,691	629	2,428	3,371	530	10,030	195	405
1997	22,001	15,258	5,431	1,093	2,847	3,536	374	8,718	190	444
1998	21,270	15,180	5,284	1,195	2,804	3,409	350	7,894	223	451
1999	21,458	15,445	5,628	1,367	2,886	3,441	463	7,330	242	460
2000	20,535	15,486	5,227	1,434	2,801	3,357	374	7,346	238	429
2001	20,915	15,506	5,363	1,378	2,814	3,082	390	7,695	246	432
2002	20,447	14,967	5,822	1,462	2,830	2,593	732	8,611	373	484
2003	19,834	14,926	5,860	1,360	2,742	2,543	845	8,280	439	514
2004	18,559	15,217	5,420	1,289	2,759	2,434	812	8,177	398	544
2005	17,642	15,286	5,228	1,333	2,867	2,582	725	8,135	359	540
2006	17,001	15,636	5,261	1,306	2,924	2,672	799	8,589	383	627
2007	16,080	15,128	5,661	1,311	2,677	2,525	874	10,130	402	508
2008	15,119	15,231	5,639	1,297	2,758	2,468	720	10,253	314	462
2009	14,852	15,096	6,149	1,349	2,769	2,270	831	10,315	333	493
2010	14,492	15,384	5,850	1,257	2,718	2,067	918	10,627	394	408
2011	13,475	15,529	5,846	1,377	2,478	2,198	812	9,562	334	458
2012	13,419	15,786	5,861	1,338	2,306	2,144	919	9,615	398	373
2013	12,878	15,414	6,126	1,327	2,203	2,098	1,010	10,073	398	463
2014	12,489	15,605	5,674	1,320	2,229	2,105	924	9,775	364	456
2015	12,805	15,658	5,973	1,372	2,112	1,951	969	10,507	355	463
2016	12,464	15,744	5,950	1,401	2,077	1,923	906	11,074	411	417

Table ESM 3: *Future years of life lost (1000s) among* currently prevalent diabetes patients *in Denmark at 1 January each year, and average years of life lost* per person *among these. Note that only every 3rd 1 January is shown.*

		Total YLL (1000s)			Average YLL	
	Date	T1D	T2D	DM	T1D	T2D
Men	1996	85.1	149.4	234.4	6.9	4.9
	1999	110.9	188.2	299.2	8.4	4.6
	2002	129.8	222.8	352.6	9.5	4.3
	2005	138.8	266.8	405.6	9.9	3.9
	2008	148.1	276.8	424.9	10.3	3.4
	2011	141.4	310.5	451.8	9.6	3.1
	2014	121.2	377.9	499.1	8.0	3.0
	2017	99.9	428.5	528.4	6.4	3.1
Women	1996	74.7	150.6	225.3	7.8	4.8
	1999	86.6	173.5	260.2	8.6	4.4
	2002	94.8	192.6	287.3	9.1	4.1
	2005	102.2	223.3	325.5	9.7	3.7
	2008	108.5	225.4	334.0	10.0	3.2
	2011	103.2	248.4	351.7	9.3	3.0
	2014	92.7	303.7	396.3	8.1	2.9
	2017	81.9	337.3	419.2	6.9	3.0
M+W	1996	159.8	300.0	459.7	7.3	4.9
	1999	197.6	361.8	559.3	8.5	4.5
	2002	224.6	415.4	639.9	9.3	4.2
	2005	241.0	490.1	731.1	9.8	3.8
	2008	256.7	502.2	758.8	10.2	3.3
	2011	244.6	558.9	803.5	9.5	3.0
	2014	213.9	681.5	895.4	8.0	3.0
	2017	181.8	765.8	947.6	6.6	3.0

Table ESM 4: *Future years of life lost among* persons diagnosed each year *in Denmark and average future years of life lost* per person *among these. Note that only every 3rd year is shown.*

		Total YLL			Average YLL	
	Year	T1D	T2D	DM	T1D	T2D
Men	1998	5,757	33,376	39,134	8.8	5.1
	2001	6,096	32,815	38,912	10.4	4.8
	2004	5,749	40,636	46,385	11.3	4.4
	2007	6,652	34,104	40,757	11.8	3.9
	2010	6,079	41,343	47,422	11.5	3.5
	2013	4,703	34,857	39,560	10.0	3.4
	2016	3,748	38,619	42,367	8.1	3.6
Women	1998	4,335	26,082	30,418	9.5	4.9
	2001	4,334	24,678	29,012	10.4	4.5
	2004	4,180	32,055	36,236	10.8	4.1
	2007	4,419	25,293	29,712	11.5	3.7
	2010	4,090	29,556	33,647	11.1	3.4
	2013	3,421	26,917	30,339	9.7	3.4
	2016	2,652	28,177	30,830	8.4	3.6
M+W	1998	10,093	59,460	69,553	9.1	5.0
	2001	10,431	57,494	67,925	10.4	4.7
	2004	9,929	72,693	82,622	11.1	4.3
	2007	11,072	59,397	70,470	11.7	3.8
	2010	10,170	70,900	81,070	11.4	3.4
	2013	8,125	61,775	69,900	9.9	3.4
	2016	6,401	66,797	73,198	8.2	3.6

Table ESM 5: *Years of life lost to type 1 diabetes in the Danish population by cause of death at different dates and ages. Dates refer to 1 January every 3rd year.*

		CVD		Cancer		Respir.		Other		All causes	
Date	Age	M	W	M	W	M	W	M	W	M	W
1996	20	3.4	6.2	−2.0	−1.3	0.4	−0.1	7.9	6.4	9.7	11.2
	30	3.5	6.2	−2.0	−1.1	0.4	−0.1	7.3	5.7	9.3	10.6
	40	3.7	6.1	−1.9	−1.0	0.4	−0.1	6.1	4.7	8.3	9.7
	50	4.0	5.7	−1.6	−0.8	0.5	−0.2	3.6	3.6	6.6	8.3
	60	4.2	5.0	−1.3	−0.7	0.4	−0.4	1.4	2.3	4.7	6.4
	70	3.4	3.7	−1.2	−0.4	0.1	−0.5	0.4	1.3	2.7	4.1
	80	1.7	1.8	−0.8	0.0	0.2	−0.4	−0.1	0.6	1.1	2.0
1999	20	4.4	6.2	−2.2	−1.0	0.0	0.0	9.4	6.5	11.6	11.8
	30	4.5	6.3	−2.1	−0.9	0.0	0.0	8.7	5.8	11.1	11.2
	40	4.6	6.2	−2.0	−0.7	0.0	0.0	7.4	4.9	10.0	10.3
	50	4.9	5.8	−1.7	−0.5	0.1	−0.1	4.9	3.8	8.2	9.1
	60	5.1	5.2	−1.4	−0.5	0.0	−0.2	2.3	2.6	6.1	7.1
	70	4.2	4.1	−1.2	−0.5	−0.2	−0.3	1.0	1.6	3.7	4.9
	80	2.3	2.2	−0.8	−0.1	0.0	−0.3	0.3	0.8	1.8	2.6
2002	20	4.3	5.7	−2.1	−0.6	−0.3	0.2	11.0	6.9	12.9	12.2
	30	4.4	5.7	−2.0	−0.4	−0.3	0.2	10.2	6.1	12.3	11.6
	40	4.6	5.7	−1.9	−0.3	−0.3	0.1	8.7	5.2	11.1	10.8
	50	4.8	5.4	−1.6	−0.1	−0.2	0.1	6.3	4.1	9.3	9.5
	60	4.9	4.9	−1.2	−0.2	−0.2	0.0	3.4	3.0	6.9	7.7
	70	4.1	4.0	−1.1	−0.5	−0.4	−0.1	1.8	2.0	4.4	5.4
	80	2.3	2.3	−0.8	−0.1	−0.1	−0.2	0.9	1.1	2.3	3.1
2005	20	2.5	4.2	−1.4	0.1	−0.2	0.3	12.6	8.0	13.5	12.7
	30	2.6	4.3	−1.3	0.2	−0.2	0.3	11.8	7.2	12.9	12.0
	40	2.7	4.2	−1.1	0.4	−0.2	0.3	10.2	6.2	11.6	11.2
	50	2.8	4.1	−0.8	0.6	−0.1	0.3	7.8	5.1	9.7	9.9
	60	3.0	3.7	−0.4	0.4	0.0	0.2	4.8	3.8	7.3	8.1
	70	2.4	3.2	−0.5	−0.2	−0.1	0.1	2.9	2.8	4.8	5.8
	80	1.3	1.9	−0.5	−0.1	0.1	0.0	1.6	1.7	2.6	3.5

Table ESM 5: *(cont.) Years of life lost to type 1 diabetes in the entire Danish population by cause of death at different dates and ages. Dates refer to 1 January every 3rd year.*

		CVD		Cancer		Respir.		Other		All causes	
Date	Age	M	W	M	W	M	W	M	W	M	W
2008	20	1.3	3.0	−0.3	0.5	0.1	0.5	12.8	8.9	13.9	12.9
	30	1.3	3.0	−0.2	0.7	0.1	0.5	12.0	8.1	13.2	12.2
	40	1.4	3.0	0.0	0.9	0.1	0.5	10.4	7.0	12.0	11.4
	50	1.5	2.9	0.3	1.0	0.2	0.4	8.1	5.8	10.1	10.2
	60	1.5	2.7	0.6	0.9	0.2	0.4	5.5	4.5	7.8	8.4
	70	1.2	2.3	0.4	0.1	0.3	0.3	3.4	3.5	5.3	6.2
	80	0.5	1.5	0.0	−0.1	0.4	0.2	2.0	2.3	2.9	3.9
2011	20	1.3	2.4	0.1	0.6	0.4	0.7	10.9	8.0	12.6	11.7
	30	1.3	2.5	0.2	0.7	0.4	0.7	10.2	7.3	12.0	11.1
	40	1.4	2.5	0.3	0.9	0.4	0.7	8.9	6.4	11.0	10.4
	50	1.4	2.4	0.6	1.0	0.4	0.6	7.0	5.3	9.4	9.4
	60	1.3	2.2	0.8	0.9	0.4	0.6	5.1	4.2	7.5	7.9
	70	0.9	1.9	0.5	0.1	0.5	0.5	3.3	3.3	5.2	5.9
	80	0.3	1.3	0.1	−0.2	0.6	0.5	1.9	2.2	2.8	3.8
2014	20	1.8	2.2	−0.4	0.4	0.6	0.9	8.4	6.6	10.4	10.0
	30	1.8	2.2	−0.3	0.4	0.6	0.9	7.9	6.0	10.0	9.5
	40	1.8	2.2	−0.2	0.6	0.6	0.8	7.0	5.3	9.1	9.0
	50	1.8	2.1	0.0	0.7	0.6	0.8	5.6	4.5	7.9	8.1
	60	1.5	2.0	0.0	0.6	0.5	0.7	4.3	3.6	6.4	6.9
	70	1.0	1.7	−0.1	0.1	0.6	0.7	3.0	2.9	4.5	5.4
	80	0.4	1.2	−0.3	−0.3	0.7	0.7	1.8	1.9	2.5	3.5
2017	20	2.1	1.9	−1.0	0.1	0.7	1.0	6.4	5.4	8.2	8.4
	30	2.1	1.9	−1.0	0.1	0.7	1.0	6.1	5.0	7.9	8.0
	40	2.1	1.9	−0.9	0.2	0.7	1.0	5.4	4.4	7.3	7.6
	50	2.0	1.9	−0.8	0.3	0.7	1.0	4.4	3.8	6.3	6.9
	60	1.7	1.7	−0.7	0.3	0.6	0.9	3.5	3.1	5.2	6.0
	70	1.2	1.5	−0.8	−0.1	0.6	0.8	2.7	2.5	3.7	4.7
	80	0.5	1.1	−0.6	−0.4	0.7	0.8	1.6	1.6	2.2	3.2

Table ESM 6: *Years of life lost to type 2 diabetes in the Danish population by cause of death at different dates and ages. Dates refer to 1 January every 3rd year.*

		CVD		Cancer		Respir.		Other		All causes	
Date	Age	M	W	M	W	M	W	M	W	M	W
1996	20	6.8	6.6	−0.6	1.0	−0.7	−0.1	6.4	3.8	11.9	11.3
	30	6.8	6.4	−0.4	1.0	−0.6	−0.1	5.2	3.3	10.9	10.6
	40	6.6	6.1	−0.3	1.0	−0.6	−0.2	3.8	2.6	9.5	9.5
	50	6.3	5.9	−0.2	0.7	−0.6	−0.2	2.2	1.7	7.7	8.1
	60	5.8	5.6	−0.3	0.2	−0.6	−0.3	0.8	0.8	5.7	6.3
	70	4.7	4.9	−0.3	0.0	−0.5	−0.3	−0.1	−0.1	3.8	4.5
	80	2.9	3.0	−0.3	0.0	−0.3	−0.1	−0.3	−0.3	2.0	2.5
1999	20	5.2	5.1	−0.3	1.1	−0.5	0.0	6.6	3.9	11.1	10.2
	30	5.2	4.9	−0.2	1.2	−0.5	0.0	5.5	3.5	10.0	9.6
	40	5.0	4.7	0.0	1.1	−0.4	0.0	4.1	2.8	8.7	8.6
	50	4.8	4.5	0.0	0.8	−0.4	0.0	2.7	2.0	7.1	7.3
	60	4.5	4.3	−0.1	0.4	−0.4	−0.1	1.3	1.2	5.2	5.7
	70	3.6	3.9	−0.2	0.0	−0.4	−0.2	0.4	0.3	3.4	4.0
	80	2.3	2.4	−0.2	0.0	−0.2	−0.1	0.0	0.0	1.9	2.3
2002	20	4.0	3.8	−0.1	1.2	−0.3	0.2	6.8	4.0	10.3	9.3
	30	3.9	3.7	0.0	1.2	−0.3	0.2	5.7	3.6	9.3	8.7
	40	3.8	3.5	0.2	1.2	−0.3	0.2	4.3	3.0	8.1	7.8
	50	3.6	3.4	0.2	0.9	−0.2	0.1	2.9	2.2	6.5	6.6
	60	3.3	3.2	0.1	0.5	−0.2	0.0	1.7	1.4	4.9	5.1
	70	2.6	2.9	−0.1	0.1	−0.2	−0.1	0.8	0.7	3.2	3.6
	80	1.7	1.9	−0.2	0.0	−0.1	0.0	0.4	0.3	1.8	2.1
2005	20	3.0	2.7	0.1	1.3	−0.2	0.3	6.4	3.9	9.4	8.3
	30	3.0	2.6	0.2	1.3	−0.1	0.3	5.4	3.5	8.5	7.8
	40	2.9	2.5	0.4	1.3	−0.1	0.3	4.1	2.9	7.3	7.0
	50	2.8	2.4	0.4	1.0	−0.1	0.3	2.8	2.3	5.9	5.9
	60	2.5	2.3	0.2	0.6	0.0	0.2	1.8	1.5	4.4	4.6
	70	2.0	2.0	0.0	0.2	0.0	0.1	1.0	0.9	3.0	3.2
	80	1.3	1.4	−0.2	0.0	0.0	0.0	0.5	0.5	1.7	1.9

Table ESM 6: *(cont.) Years of life lost to type 2 diabetes in the Danish population by cause of death at different dates and ages. Dates refer to 1 January every 3rd year.*

		CVD		Cancer		Respir.		Other		All causes	
Date	Age	M	W	M	W	M	W	M	W	M	W
2008	20	2.3	1.8	0.3	1.4	0.0	0.5	5.6	3.6	8.2	7.3
	30	2.3	1.8	0.5	1.4	0.0	0.5	4.6	3.2	7.4	6.9
	40	2.2	1.7	0.6	1.4	0.1	0.4	3.5	2.7	6.4	6.2
	50	2.1	1.6	0.6	1.1	0.1	0.4	2.4	2.1	5.1	5.2
	60	1.9	1.6	0.4	0.7	0.1	0.3	1.5	1.5	3.9	4.0
	70	1.5	1.4	0.1	0.2	0.1	0.2	0.9	0.9	2.6	2.7
	80	0.9	1.0	−0.1	0.0	0.1	0.1	0.5	0.6	1.4	1.6
2011	20	1.9	1.4	0.5	1.5	0.1	0.6	4.8	3.2	7.4	6.7
	30	1.9	1.4	0.6	1.5	0.1	0.6	4.0	2.8	6.7	6.3
	40	1.8	1.3	0.7	1.4	0.2	0.6	3.0	2.4	5.7	5.7
	50	1.7	1.3	0.7	1.2	0.2	0.5	2.0	1.9	4.6	4.8
	60	1.6	1.2	0.5	0.8	0.2	0.4	1.3	1.3	3.5	3.7
	70	1.2	1.1	0.2	0.3	0.2	0.3	0.8	0.8	2.5	2.5
	80	0.7	0.7	−0.1	0.0	0.2	0.2	0.5	0.6	1.3	1.5
2014	20	1.9	1.3	0.7	1.8	0.2	0.7	4.4	2.8	7.2	6.6
	30	1.9	1.2	0.8	1.7	0.2	0.7	3.6	2.5	6.5	6.2
	40	1.8	1.2	0.9	1.7	0.2	0.7	2.7	2.1	5.6	5.6
	50	1.7	1.1	0.9	1.4	0.2	0.6	1.8	1.7	4.6	4.8
	60	1.5	1.1	0.6	0.9	0.2	0.6	1.1	1.2	3.6	3.7
	70	1.2	0.9	0.3	0.5	0.2	0.4	0.8	0.7	2.5	2.6
	80	0.7	0.6	0.0	0.0	0.2	0.3	0.5	0.6	1.4	1.5
2017	20	1.9	1.2	1.0	2.1	0.2	0.8	4.1	2.5	7.2	6.5
	30	1.9	1.1	1.1	2.1	0.2	0.8	3.4	2.2	6.5	6.2
	40	1.8	1.1	1.1	2.0	0.2	0.8	2.6	1.9	5.7	5.7
	50	1.7	1.0	1.1	1.7	0.2	0.7	1.7	1.5	4.7	4.9
	60	1.6	1.0	0.8	1.2	0.2	0.7	1.1	1.0	3.7	3.8
	70	1.2	0.8	0.4	0.7	0.2	0.5	0.8	0.6	2.7	2.7
	80	0.8	0.6	0.0	0.2	0.2	0.3	0.6	0.5	1.6	1.6

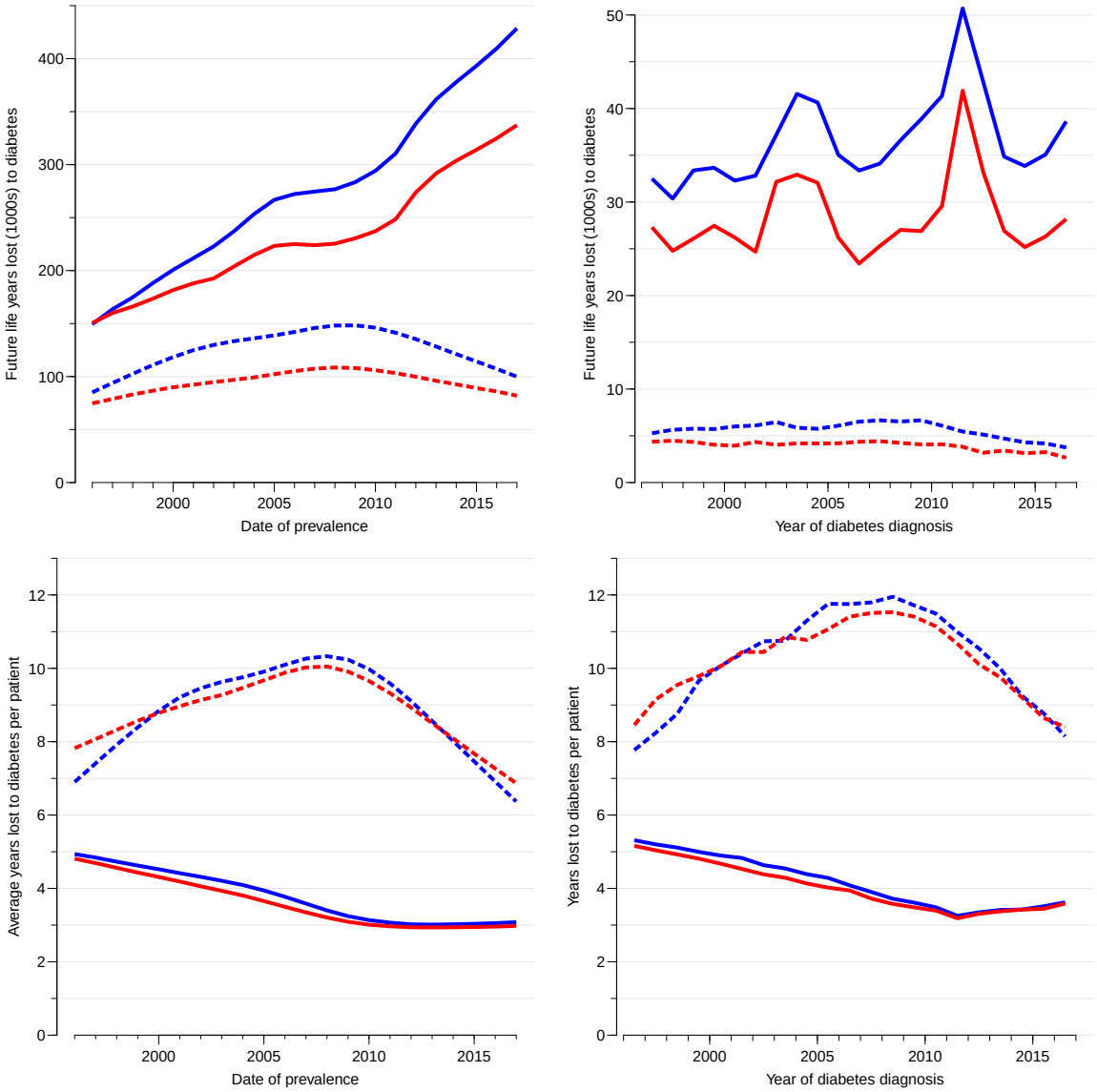

Figure ESM 2: *Upper panels:* Total *future years of life lost among all* currently prevalent *diabetes patients at each 1 January (left) and among* newly diagnosed *patients during each calendar year (right).*
Lower panels: Average *future years of life lost among currently prevalent diabetes patients each 1 January (left) and among patients diagnosed during each calendar year (right).*
Red lines are women, blue lines are men, broken lines are type 1 diabetes and full lines are type 2 diabetes.

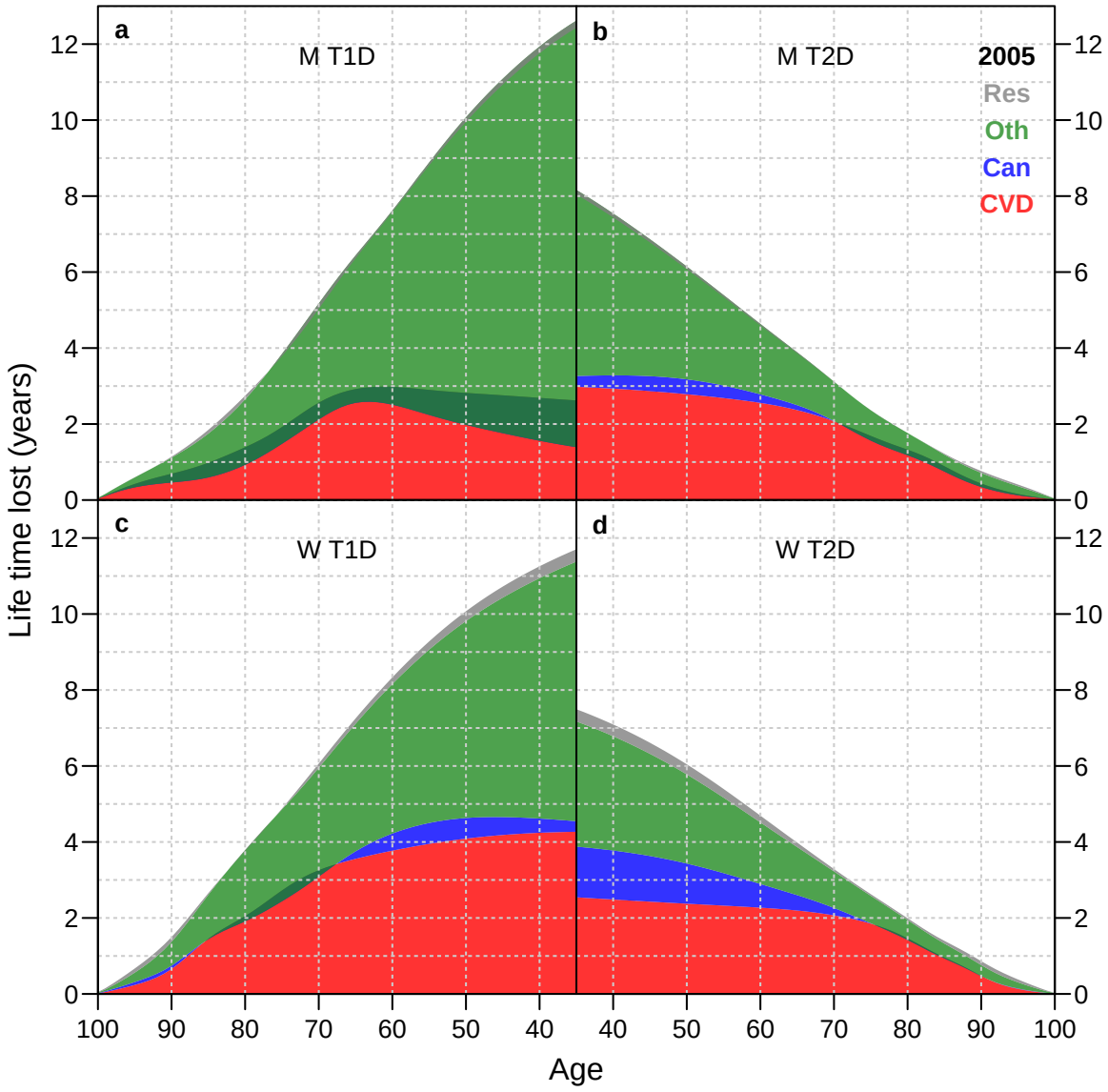

Figure ESM 3: *Years of life lost to different causes of death at 1 January 2005 by sex, type of diabetes and age.*
The dark green areas in panels a and c is equal to the negative *years of life lost to cancer for type 1 diabetes patients (it is the overlap of red, blue and green areas). This area is therefore part of both the CVD and the Other component.*
a: Men, type 1 diabetes; b: Men, type 2 diabetes; c: Women, type 1 diabetes; d: Women, type 2 diabetes.
Colors: gray: Respiratory causes; green: other causes; blue: cancer; red: CVD.

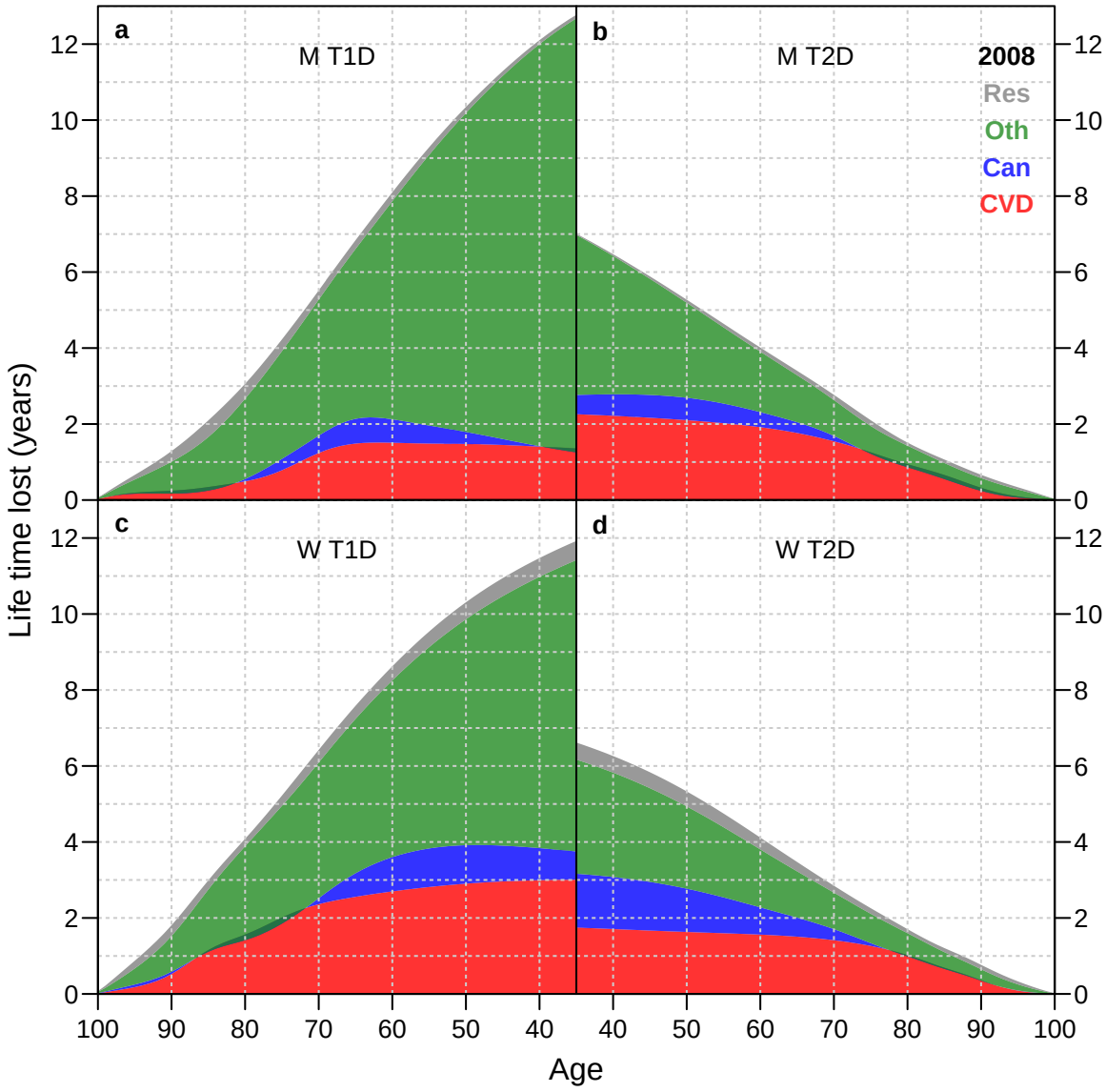

Figure ESM 4: *Years of life lost to different causes of death at 1 January 2008 by sex, type of diabetes and age.*
The dark green areas in panels a and c is equal to the negative *years of life lost to cancer for type 1 diabetes patients (it is the overlap of red, blue and green areas). This area is therefore part of both the CVD and the Other component.*
a: Men, type 1 diabetes; b: Men, type 2 diabetes; c: Women, type 1 diabetes; d: Women, type 2 diabetes.
Colors: gray: Respiratory causes; green: other causes; blue: cancer; red: CVD.

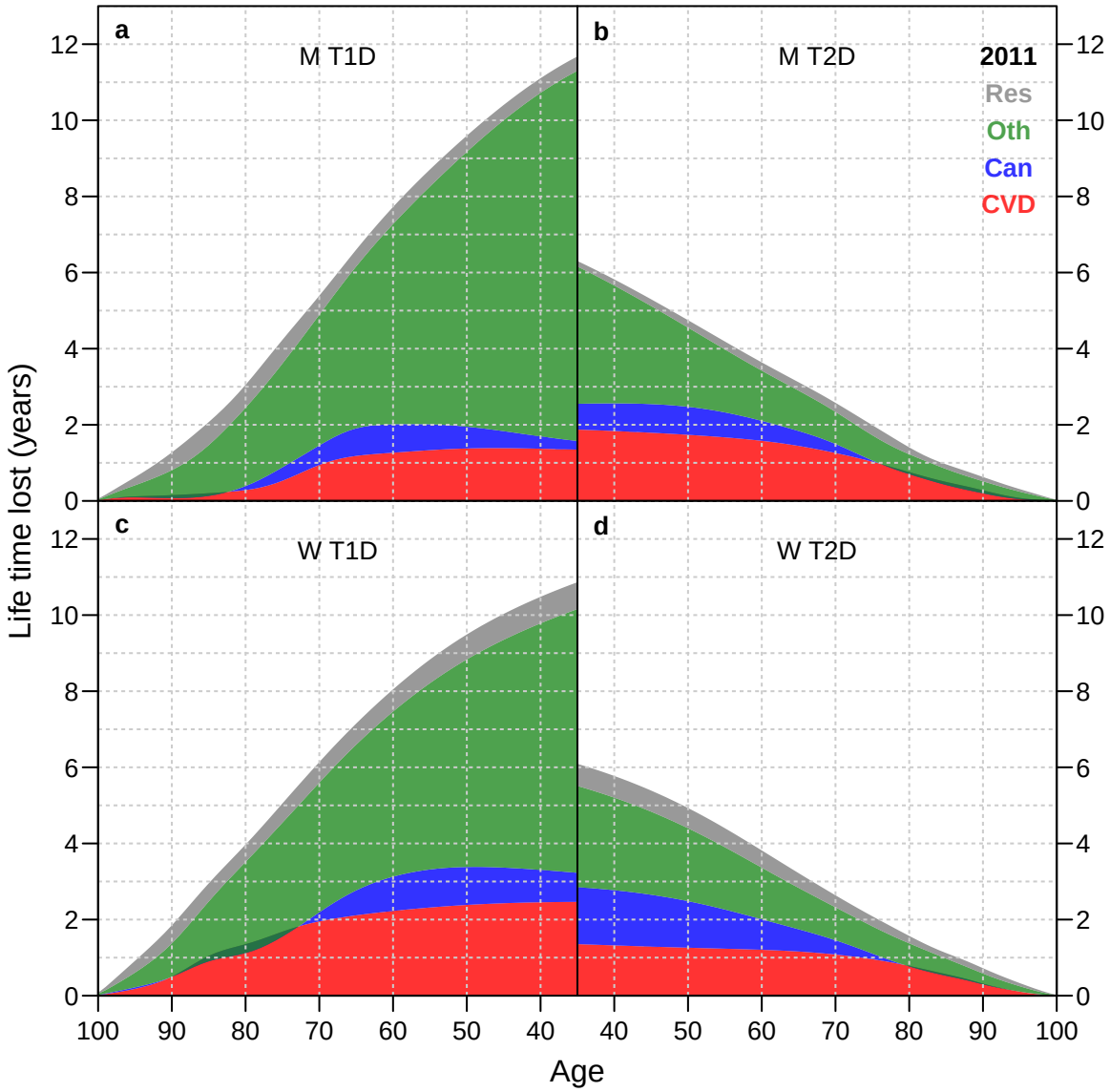

Figure ESM 5: *Years of life lost to different causes of death at 1 January 2011 by sex, type of diabetes and age.*
The dark green areas in panels a and c is equal to the negative *years of life lost to cancer for type 1 diabetes patients (it is the overlap of red, blue and green areas). This area is therefore part of both the CVD and the Other component.*
a: Men, type 1 diabetes; b: Men, type 2 diabetes; c: Women, type 1 diabetes; d: Women, type 2 diabetes.
Colors: gray: Respiratory causes; green: other causes; blue: cancer; red: CVD.

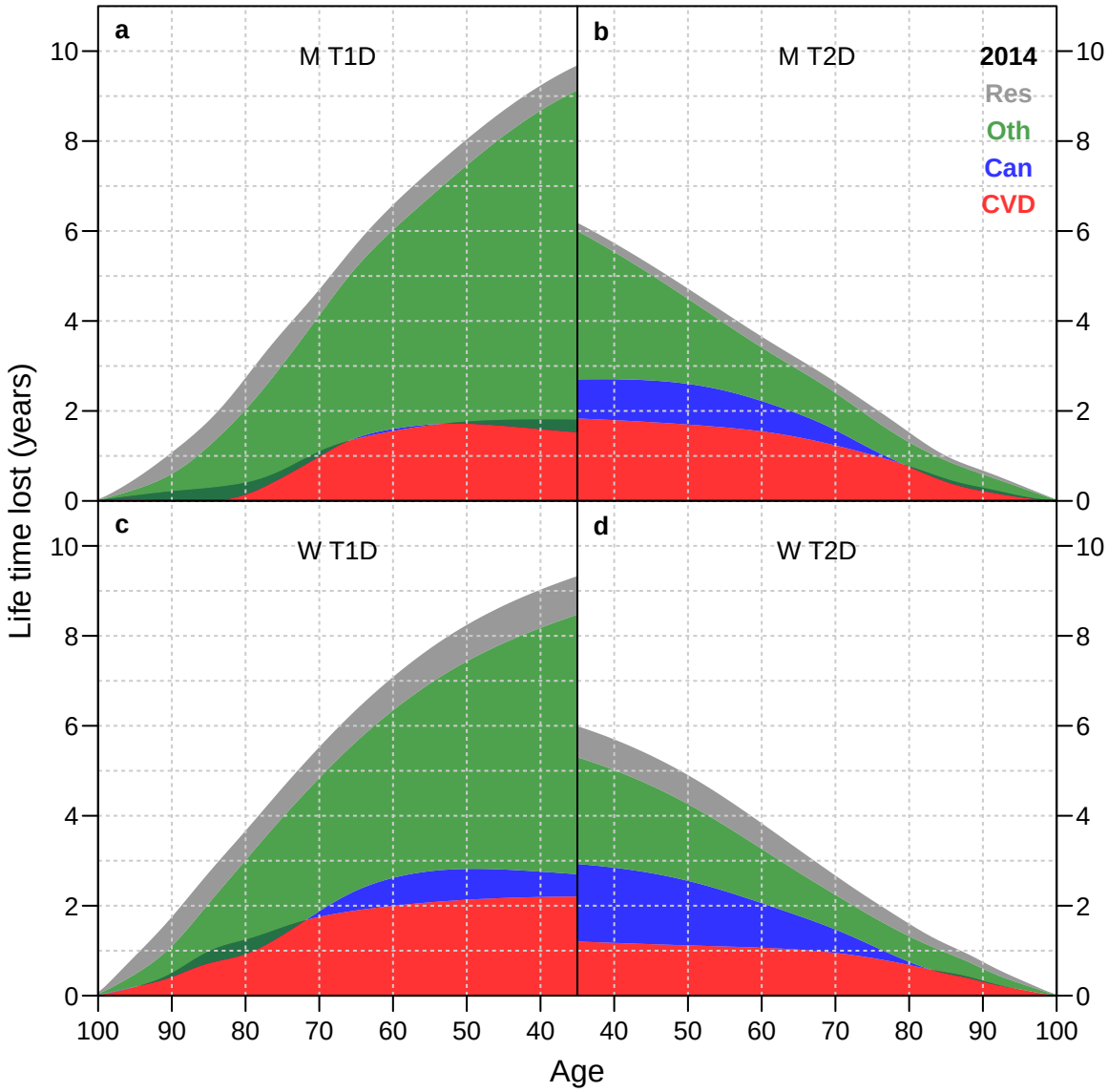

Figure ESM 6: *Years of life lost to different causes of death at 1 January 2014 by sex, type of diabetes and age.*
The dark green areas in panels a and c is equal to the negative *years of life lost to cancer for type 1 diabetes patients (it is the overlap of red, blue and green areas). This area is therefore part of both the CVD and the Other component.*
a: Men, type 1 diabetes; b: Men, type 2 diabetes; c: Women, type 1 diabetes; d: Women, type 2 diabetes.
Colors: gray: Respiratory causes; green: other causes; blue: cancer; red: CVD.