

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

SDCC

<http://bendixcarstensen.com/>

July 2019

Version 11 (3614 words)

Compiled Tuesday 9th July, 2019, 13:20

from: /home/bendix/sdc/DMreg/NewReg/art/DMDK/DMDK.tex

Bendix Carstensen Steno Diabetes Center Copenhagen, Gentofte, Denmark
Senior Statistician Clinical Epidemiology
 & Department of Biostatistics, University of Copenhagen
bcar0029@regionh.dk b@bxc.dk
<http://BendixCarstensen.com>

Pernille Falberg Rønn Steno Diabetes Center Copenhagen, Gentofte, Denmark
Post Doc Clinical Epidemiology
pernille.falberg.roenn@regionh.dk

Marit Eika Jørgensen Steno Diabetes Center Copenhagen, Gentofte, Denmark
Head Clinical Epidemiology
marit.eika.joergensen@regionh.dk

Contents

1	Abstract	2
2	Introduction	3
3	Material and methods	3
3.1	Register data	3
3.2	Tabulation of data	5
3.3	Statistical methods	5
3.4	Software and documentation	6
4	Results	6
4.1	Prevalence	6
4.2	Incidence	7
4.3	Mortality and Standardized Mortality Ratio	7
5	Discussion	8
5.1	Summary of findings	8
5.2	Comparison with other studies	9
5.3	Strengths and weaknesses	11
5.4	Conclusion and implications	11
6	Paraphernalia	11
	References	15

List of Tables

1	Persons, follow-up time and ages and dates of entry and follow-up from the Danish Diabetes Register.	16
2	Time trends in prevalence, incidence, mortality and SMR.	17

List of Figures

1	Age-specific prevalence of T1D and T2D in Denmark as of 1 January 1996, 2003,...,2017	18
2	Incidence rates of T1D at ages 10–60 and T2D at ages 40,...,90.	19
3	Mortality rates among T1D and T2D patients.	20
4	SMR among T1D and T2D patients.	21

Abbreviations

- APC — Age-Period-Cohort
- ATC — Anatomical therapeutic chemical classification
- CI — Confidence interval
- DADD — Danish adult diabetes database
- diaB — DiaBase
- DM — Diabetes mellitus
- ESM — Electronic supplementary material
- GP — General practitioner
- ICD — International classification of disease
- IDF — International Diabetes Federation
- NHS — National health service
- NHSR — National health services register
- NPR — National patient register
- M — Men
- MPR — Medicines products register (“prescription register”)
- OAD — Oral Antidiabetic Drug
- PCOS — Polycystic ovary syndrome
- PY — Person-years
- RKKP — Regionale Kliniske Kvalitets Databaser (Danish Regional Quality Databases)
- RR — Rate ratio
- SDCC — Steno Diabetes Center Copenhagen
- SMR — Standardized mortality ratio
- T1D — Type 1 diabetes
- T2D — Type 2 diabetes
- W — Women

Research in context

What is already known about this subject?

- Incidence rates of T2D have been increasing over the last decades, T1D diabetes in childhood too, but to a lesser extent than T2D
- There are indications that incidence rates of T2D has decreased recently or at least is showing a slower increase

What are the key questions?

- Is there a decrease of T2D around the time of the initiation of the HbA_{1c} criteria for diagnosing T2D?
- How is the development of incidence rates of T1D after age 30?
- What is the mortality difference between T1D and T2D patients?
- Is the mortality of diabetes patients relative to the population mortality still decreasing?

What are the new findings?

- Incidence rates of T2D showed a decrease around 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 T1D patients is some 70% higher than that of T2D patients, but decreasing over time
- Mortality of both T1D and T2D relative to the population mortality showed a stable decrease

How might this impact on clinical practice in the foreseeable future?

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

1 Abstract

Introduction The surveillance of the population distribution of prevalence incidence and mortality of diabetes is of major importance, both for quality control of prevention and care, as well as for planning purposes. The aim of the study was to produce an overview of prevalence, incidence and mortality of both T1D and T2D in Denmark, and the temporal trends in these.

Methods We compiled a Danish Diabetes Register based on existing population-based health care registers, including a classification of patients as type 1 diabetes (T1D) or type 2 diabetes (T2D), with coverage from 1996 to 2016. Based on this and complete population records for Denmark in period, we were able to devise detailed figures for prevalence, incidence and mortality by diabetes type.

Results We found that the overall prevalence of diabetes at the end of 2016 was 4.8% (T1D: 0.5%, T2D: 4.4%). The increase in prevalence since 1996 has mainly been in T2D; 0.5% per year for T1D and 5.5% per year for T2D.

Incidence rates of T1D were overall decreasing over time with an average decrease of 3.5% per year, but with an increase for persons under 25 years of age and a decrease for older persons. Incidence rates of T2D were increasing 2.5% per year until 2011, where we saw a decrease till 2014 and a new increase after that, similar in all ages.

Mortality rates were in general decreasing with calendar time, 0.3%/year for T1D and 2.9%/year for T2D. The overall mortality rate ratio between T1D and T2D was 1.9 for men and 1.6 for women.

For T1D patients, we found that at a given age, early diagnosis (that is, longer duration) was associated with smaller mortality. This was not the case for T2D patients, where duration of disease had only minor impact on mortality at any given age.

Finally, we found a decreasing SMR by calendar time, for T1D 2%/year and for T2D 0.5%/years.

Conclusion Based on a population register of diabetes patients we demonstrated that incidence and prevalence of diabetes is still increasing but mortality among diabetes patients in Denmark is decreasing and decreasing faster than the mortality among persons without diabetes. We established that T1D carries a 70% higher mortality than T2D.

Keywords: Type 1 diabetes, type 2 diabetes, prevalence, incidence rates, mortality rates, SMR, Denmark, time trends

2 Introduction

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

Recently there have been indications in the literature that incidence rates of diabetes have been declining in recent years [1, 2, 3, 4, 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 [6, 7] comparing the occurrence of T1D and T2D diabetes and how patients with the two diseases fare relative to each other with respect to mortality.

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 health care registers. Moreover, recent administrative developments in Denmark has 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) duration of diabetes.

3 Material and methods

3.1 Register data

Denmark has population-wide registers covering virtually all aspects of life, including health care; and all registers are linkable by a unique person id [8]. 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.

3.1.1 Diabetes data

We constructed a Danish diabetes register from existing Danish health care registers, using all available sources to obtain maximal sensitivity. Diabetes patients were defined using the earliest of the following as inclusion date (date of diagnosis):

- first diagnosis of diabetes (ICD-8: 249, 250; ICD-10: E10, E11; these *exclude* gestational diabetes) in the National Patient Register [9] (NPR; 1977–).
- first use of “podiatry for diabetes patients” in the National Health Services Register [10] (NHSR, 1990–).
- first date of purchase of any anti-diabetic medication (ATC A10xxx) in the Medicines Products Register [11] (“Prescription register”) (MPR, 1995–).
- earliest mentioned date of diagnosis in the Danish Adult Diabetes Database [12] (DADD, 2005–, a clinical quality data base, with annual status of patients reported from outpatient clinics and GPs).
- earliest date of eye examination recorded in the diaBase [13] (diaB, 2009–, a clinical quality data base for eye screening of diabetes patients).

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 oral antidiabetic drugs (OAD) before age 15
- Purchase of insulin before age 30
- DADD: classified as T1D in the majority 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 the majority of the patient’s records from NPR classify 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 1996-01-01 were considered incident cases of diabetes, whereas those included before were only considered prevalent cases as of 1996-01-01 with uncertain date of diagnosis.

Further details of the databases and the algorithm used are given in the ESM.

3.1.2 Population data

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

3.2 Tabulation of data

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

Follow-up time and new cases of T1D, T2D and deaths were tabulated by diabetes status (no DM, T1D, T2D), sex, age and date of diagnosis and date of birth in 1-year classes (Lexis triangles, [14]). For DM persons diagnosed after 1996 we further tabulated by duration of disease in 1-year intervals (the first year 3-month intervals)

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

3.3 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 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 using restricted cubic splines by 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 using Poisson models with log person time as offset and natural cubic spline effects of age and date of follow-up and date of birth (age-period-cohort (APC) models [14]), using 2015-01-01 as reference point for calendar time.

Mortality in T1D and T2D rates were additionally modeled by duration of diabetes. Since the constant and 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 etc. The mortality curves are thus showing the *joint* effect of current age, age at diagnosis and duration of disease (see *e.g.* [15], and the detailed account of this in the ESM section on statistical methods).

Since only persons included after 1996-01-01 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 1996-01-01 and for all patients (that is, also including the prevalent cases as of 1996-01-01).

We computed M/W mortality rate-ratios for each type of diabetes, and T1D/T2D

mortality rate-ratios for men and women separately.

The standardized mortality ratio (SMR) was modeled 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, resp. T2D and no DM.

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

3.4 Software and documentation

All registers mentioned were put at our disposal in deidentified, 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 version 12.4, including the %Lexis macro [16]; for statistical analyses and graphics we used **R** version 3.5.0 [17], using the Epi package, version 2.30 [18].

Documentation of the construction of the register and the analysis files of prevalence and follow-up can be found in <http://BendixCarstensen.com/DMreg/NewReg.pdf>, and a complete account of all statistical analyses based on these is available in <http://BendixCarstensen.com/DMreg/NewAna.pdf>.

4 Results

In the period 1996–2016, 448,445 persons were recorded in our register as diabetes patients in Denmark (table 1), about 9% as T1D and the rest as T2D, and 83,441 (19%) were prevalent cases as of 1996-01-01. The median age at diagnosis for T1D patients 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 1).

4.1 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 the Electronic Supplementary Material (ESM), tables ESM 1–2, and illustrated in figure ESM 1.

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 ESM 2) — an annual increase of 5.5% per year (table 2).

The fraction of T1D among all diabetes patients has consequently dropped from about 25% in 1996-01-01 to 10% at 2017-01-01 (table ESM 1).

For T1D the age-specific prevalence increased till about age 40 for men and about 30 for women (figure 1, panels a and b). T2D showed a peak age-specific prevalence at 2017-01-01 at age 80 at 19% for men and 16% for women (figure 1, panels c and d).

4.2 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 ESM 3). 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, more among older persons; the overall average a decrease of 3.5% per year (figure 2, panels a & b, figure ESM 2). For T2D the patterns were almost identical in different ages, with an increase till 2011, a down-turn until 2014 and an increase during the last 2 years of the study period (figure 2, panels c & d).

The APC models (figure ESM 3) showed that men had higher incidence rates than women, and also somewhat different age-patterns for T1D incidence rates in men and women. For men there was an increase to about age 18, a plateau and a slight increase to age 40, whereas women showed an increase till 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 ESM 2).

4.3 Mortality and Standardized Mortality Ratio

4.3.1 Mortality

Figure 3 shows the mortality for T1D and T2D patients 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 (ESM figures 4 & 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

more pronounced effect of duration (ESM figures 4 & 5).

We found that the M/W mortality RR (black curves in figure ESM 4) 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 till about 2005, but after this a consistent decrease (figure ESM 4), the latter 4.9% per year, whereas the mortality in T2D patients showed a consistent decrease over the entire study period of 2.9% per year (M: 3.3%/y, W:2.5%/y, table 2).

T1D vs. T2D mortality rate ratio We found a higher mortality among T1D patients relative to T2D (ESM figure 6); the first few years after diagnosis more than 2-fold, but at 10 years of duration the T1D/T2D mortality RR was about 1.7, and decreasing by duration (and hence by current age too). Overall the T1D vs. T2D mortality RR was 1.86 (1.79;1.93) for men and 1.55 (1.48;1.63) for women.

4.3.2 Standardized Mortality Ratio

Figure 4 shows the Standardized Mortality Ratio (SMR) — the mortality in diabetes patients relative to the mortality among persons without diabetes.

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 til 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 2) 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 larger than for men, but we saw only a moderate decline of 0.6%/year (table 2).

5 Discussion

5.1 Summary of findings

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

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 diabetes patients. Second, the incidence of T1D increased slightly in the younger age groups (approx. 2%/year) and declined in the older age groups (approx. 5%/year) over the study period. Third, the T2D incidence increased till 2011, declined till 2014, but seems to increase again after 2015. Fourth, the mortality of T1D patients is more than 50% higher than that of T2D patients. Finally, we found an excess mortality for T1D and T2D compared to the general population, highest for T1D.

5.2 Comparison with other studies

5.2.1 Prevalence and incidence

The overall prevalence estimates by 2017-01-01 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 US [19, 4, 5].

Most studies in T1D have reported the prevalence and incidence in children and youth [19, 20, 21], and only few [21, 22] have included older age groups as done in our study. The peak T1D incidence rates of 0.35 in men and 0.25 in women per 1,000 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, 22, 23, 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 to 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 1983–2007, 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 health care 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 T2D patients as T1D patients 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 265,728 by 2017-01-01, 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 have been reported in studies from Scotland[2, 3], USA[1, 28] and Sweden [4], but in contrast to our study the decline / plateauing happened earlier.

A register-based study from Norway recently conducted by Ruiz *et al.* [5] found a decline in T2D incidence in the period 2009–2014 which after 2012 seemed to level off. Both in Norway and Denmark the recommendation of HbA_{1c} 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.

5.2.2 Mortality and SMR

A decline in mortality among patients with diabetes have been reported in several countries [2, 3, 29, 30, 31]. 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.

We found that mortality rates of T1D are higher than those of T2D for patients of similar age, but with RR dissimilar between men (RR 1.84) and women (RR 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 1997–2010 for both T1D and T2D patients with a larger decrease than found in the general population [30]. Similar trends have been observed in USA [29] and Scotland [2, 3], which is consistent with our finding of an SMR decline for T2D of 0.6% per year.

Early age at diagnosis (and hence longer duration of diabetes) was associated with a smaller mortality among T1D patients in our study but a larger mortality among T2D patients, although the latter effect was 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 [34], but it was not clear how this study included duration and current age, which may have affected the reported effect of age at diagnosis.

5.3 Strengths and weaknesses

The major strengths of our study is that it covers the entire Danish population, the long coverage period (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 data base is that inclusion date (which is used as proxy for date of diagnosis) is based solely on administrative records.

While the classification of patients as T1D or T2D is a strength, the limited coverage of the DADD (2005 ff.) most likely *underestimates* the number of T1D patients 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 is increasing with increasing duration.

Furthermore, T2D incidence among women under 40 may be underestimated due to the classification as possible PCOS patients if metformin only is used in the age range 18–40.

5.4 Conclusion and implications

During a 21-year period we observed increasing prevalence and incidence rates but with a decreasing incidence of T2D from 2012, while the incidence for T1D remained more stable over the period. The decline in mortality were 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, diabetes patients still experience an excess mortality relative to persons without diabetes, highest for T1D patients, which can only partially be attributed to differences in disease duration. The excess mortality underlines the need for continuous improvements in prevention and treatment of complications especially among T1D patients.

6 Paraphernalia

6.0.1 Acknowledgments

We are grateful to the Danish Clinical Registries (RKKP) for providing access to the DADD and diaB for the construction of the diabetes register. We appreciate the meticulous and speedy support of the Research Service of Statistics Denmark.

6.0.2 Data availability

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.

6.0.3 Funding

The substudy regarding T1D was funded by Sanofi Aventis. The company had no influence on study design or analyses. The remainder of the study was funded through the core research budget of SDCC.

6.0.4 Duality of interest

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, Astra Zeneca and Sanofi Avensis,

6.0.5 Contribution statement

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.

References

- [1] L. S. Geiss, J. Wang, Y. J. Cheng, T. J. Thompson, L. Barker, Y. Li, A. L. Albright, and E. W. Gregg. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. *JAMA*, 312(12):1218–1226, Sep 2014.
- [2] S. H. Read, J. J. Kerssens, D. A. McAllister, H. M. Colhoun, C. M. Fischbacher, R. S. Lindsay, R. J. McCrimmon, J. A. McKnight, J. R. Petrie, N. Sattar, and S. H. Wild. Trends in type 2 diabetes incidence and mortality in Scotland between 2004 and 2013. *Diabetologia*, 59(10):2106–2113, 10 2016.
- [3] S. H. Read, J. J. Kerssens, D. A. McAllister, H. M. Colhoun, C. M. Fischbacher, R. S. Lindsay, R. J. McCrimmon, J. A. McKnight, J. R. Petrie, N. Sattar, and S. H. Wild. Erratum to: Trends in type 2 diabetes incidence and mortality in Scotland between 2004 and 2013. *Diabetologia*, 59(11):2492, 11 2016.
- [4] A. Norhammar, J. Bodegard, T. Nystrom, M. Thuresson, J. W. Eriksson, and D. Nathanson. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. *Diabetologia*, 59(8):1692–1701, 08 2016.
- [5] P. L. D. Ruiz, L. C. Stene, I. J. Bakken, S. E. Haberg, K. I. Birkeland, and H. L. Gulseth. Decreasing incidence of pharmacologically and non-pharmacologically treated type 2 diabetes in Norway: a nationwide study. *Diabetologia*, Jul 2018.
- [6] G. Xu, B. Liu, Y. Sun, Y. Du, L. G. Snetselaar, F. B. Hu, and W. Bao. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. *BMJ*, 362:k1497, Sep 2018.
- [7] K. M. Bullard, C. C. Cowie, S. E. Lessem, S. H. Saydah, A. Menke, L. S. Geiss, T. J. Orchard, D. B. Rolka, and G. Imperatore. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016. *MMWR Morb. Mortal. Wkly. Rep.*, 67(12):359–361, Mar 2018.
- [8] Pedersen C.B. The Danish civil registration system. *Scand J Public Health*, 39 (7 suppl):22–25, July 2011.
- [9] E. Lynge, J. L. Sandegaard, and M. Rebolj. The Danish National Patient Register. *Scand J Public Health*, 39(7 Suppl):30–33, Jul 2011.
- [10] J. S. Andersen, N. de F. Olivarius, and A. Krasnik. The Danish National Health Service Register. *Scand J Public Health*, 39(7 Suppl):34–37, Jul 2011.
- [11] H. W. Kildemoes, H. T. Sørensen, and J. Hallas. The Danish National Prescription Registry. *Scand J Public Health*, 39(7 Suppl):38–41, Jul 2011.
- [12] M. E. Jørgensen, J. K. Kristensen, G. Reventlov Husted, C. Cerqueira, and P. Rossing. The Danish Adult Diabetes Registry. *Clin Epidemiol*, 8:429–434, 2016.

- [13] G. S. Andersen, Z. Kamper-Jørgensen, B. Carstensen, M. Nørredam, I. C. Bygbjerg, and M. E. Jørgensen. Diabetes among migrants in Denmark: Incidence, mortality, and prevalence based on a longitudinal register study of the entire Danish population. *Diabetes Res. Clin. Pract.*, 122:9–16, Sep 2016.
- [14] B Carstensen. Age-Period-Cohort models for the Lexis diagram. *Statistics in Medicine*, 26(15):3018–3045, July 2007.
- [15] L. Huo, D. J. Magliano, F. Ranciere, J. L. Harding, N. Nanayakkara, J. E. Shaw, and B. Carstensen. Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997-2011. *Diabetologia*, Feb 2018.
- [16] B Carstensen and P Dickman. %lexis macro for splitting follow-up. <http://bendixcarstensen/Lexis/Lexis.sas>, 2003.
- [17] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2018.
- [18] Bendix Carstensen, Martyn Plummer, Esa Laara, and Michael Hills. *Epi: A Package for Statistical Analysis in Epidemiology*, 2018. R package version 2.32.
- [19] D. Dabelea, E. J. Mayer-Davis, S. Saydah, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA*, 311(17):1778–1786, May 2014.
- [20] V. Harjutsalo, R. Sund, M. Knip, and P. H. Groop. Incidence of type 1 diabetes in Finland. *JAMA*, 310(4):427–428, Jul 2013.
- [21] G. G. Dahlquist, L. Nystrom, and C. C. Patterson. Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends. *Diabetes Care*, 34(8):1754–1759, Aug 2011.
- [22] M. Thunander, C. Petersson, K. Jonzon, J. Fornander, B. Ossiansson, C. Torn, S. Edvardsson, and M. Landin-Olsson. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes Res. Clin. Pract.*, 82(2):247–255, Nov 2008.
- [23] D. M. Maahs, N. A. West, J. M. Lawrence, and E. J. Mayer-Davis. Epidemiology of type 1 diabetes. *Endocrinol. Metab. Clin. North Am.*, 39(3):481–497, Sep 2010.
- [24] Y. Berhan, I. Waernbaum, T. Lind, A. Mollsten, G. Dahlquist, et al. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. *Diabetes*, 60(2):577–581, Feb 2011.
- [25] P. E. Wandell and A. C. Carlsson. Time trends and gender differences in incidence and prevalence of type 1 diabetes in Sweden. *Curr Diabetes Rev*, 9(4):342–349, Jul 2013.
- [26] E. A. Gale and K. M. Gillespie. Diabetes and gender. *Diabetologia*, 44(1):3–15, Jan 2001.

- [27] International Diabetes Federation. IDF Diabetes Atlas. <https://reports.instantatlas.com/report/view/704ee0e6475b4af885051bcec15f0e2c/DNK>. Accessed November 2018.
- [28] W. Weng, Y. Liang, E. S. Kimball, T. Hobbs, S. X. Kong, B. Sakurada, and J. Bouchard. Decreasing incidence of type 2 diabetes mellitus in the United States, 2007-2012: Epidemiologic findings from a large US claims database. *Diabetes Res. Clin. Pract.*, 117:111–118, Jul 2016.
- [29] E. W. Gregg, Y. J. Cheng, S. Saydah, C. Cowie, S. Garfield, L. Geiss, and L. Barker. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. *Diabetes Care*, 35(6):1252–1257, Jun 2012.
- [30] Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, and Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in australia: 1997-2010. *Diabetes Care*, 37:2579–2586, 2014.
- [31] M. Lind, L. A. Garcia-Rodriguez, G. L. Booth, L. Cea-Soriano, B. R. Shah, G. Ekeroth, and L. L. Lipscombe. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. *Diabetologia*, 56(12):2601–2608, Dec 2013.
- [32] E. Morgan, C. R. Black, N. Abid, C. R. Cardwell, D. R. McCance, and C. C. Patterson. Mortality in type 1 diabetes diagnosed in childhood in Northern Ireland during 1989-2012: A population-based cohort study. *Pediatr Diabetes*, 19(1):166–170, 02 2018.
- [33] A. M. Secrest, D. J. Becker, S. F. Kelsey, R. E. LaPorte, and T. J. Orchard. All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: the Allegheny County type 1 diabetes registry. *Diabetes Care*, 33(12):2573–2579, Dec 2010.
- [34] A. Rawshani, N. Sattar, S. Franzen, A. Rawshani, A. T. Hattersley, A. M. Svensson, B. Eliasson, and S. Gudbjornsdottir. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*, 392(10146):477–486, Aug 2018.

Table 1: *Persons, follow-up time and ages and dates of entry and follow-up from the Danish Diabetes Register. Includes also persons over 100 years of age and time during nonresidency in Denmark. Medians and inter-quartile ranges (IQR, 25th and 75th percentiles). <1996 refer to the prevalent cases as of 1st January 1996; 1996+ refer to diabetes cases included in the register after this date.*

No. persons	Sex	T1D			T2D		DM
< 1996	M	12,378			30,338		42,716
	W	9,596			31,129		40,725
	M+W	21,974			61,467		83,441
1996+	M	11,646			192,418		204,064
	W	8,173			152,767		160,940
	M+W	19,819			345,185		365,004
Total	M+W	41,793			406,652		448,445

		T1D			T2D		
		Median	IQR		Median	IQR	
Date of inclusion ^{1,2}							
1996+	M	2005.7	2000.5	2010.9	2008.5	2003.1	2012.4
	W	2005.6	2000.4	2011.0	2008.3	2002.8	2012.3
Age at inclusion ¹							
1996+	M	30.7	15.7	47.6	62.1	53.0	70.6
	W	26.8	12.4	48.5	64.6	54.1	74.2
Person-years							
< 1996	M	21.0	9.5	21.0	8.9	3.6	18.2
	W	21.0	9.3	21.0	9.1	3.8	18.9
1996+	M	8.9	4.3	14.5	6.0	3.0	10.5
	W	9.3	4.4	14.9	6.1	3.1	10.9
Date of follow-up ^{2,3}							
< 1996	M	2006.5	2000.7	2006.5	2000.4	1997.8	2005.1
	W	2006.5	2000.6	2006.5	2000.6	1997.9	2005.5
1996+	M	2011.0	2008.0	2013.9	2012.5	2008.8	2014.6
	W	2011.0	2008.1	2014.0	2012.3	2008.7	2014.6
Age at follow-up ³							
< 1996	M	53.5	41.3	65.3	70.9	62.5	78.2
	W	55.5	41.3	71.0	76.0	66.6	82.7
1996+	M	36.5	20.6	52.4	65.9	57.1	73.9
	W	32.4	17.4	53.8	68.4	58.2	77.7

¹ Persons included before 1996 do not have a reliable date of inclusion, hence neither date nor age at inclusion can be meaningfully computed.

² Dates are coded so that 1st January 2006 is 2006.000 and 31st December 2006 is 2006.997.

³ Median and IQR for the median date/age of follow-up for each person.

Table 2: *Average change (%/year) in prevalence, incidence, mortality and SMR of diabetes in Denmark over the period 1996–2016.*

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

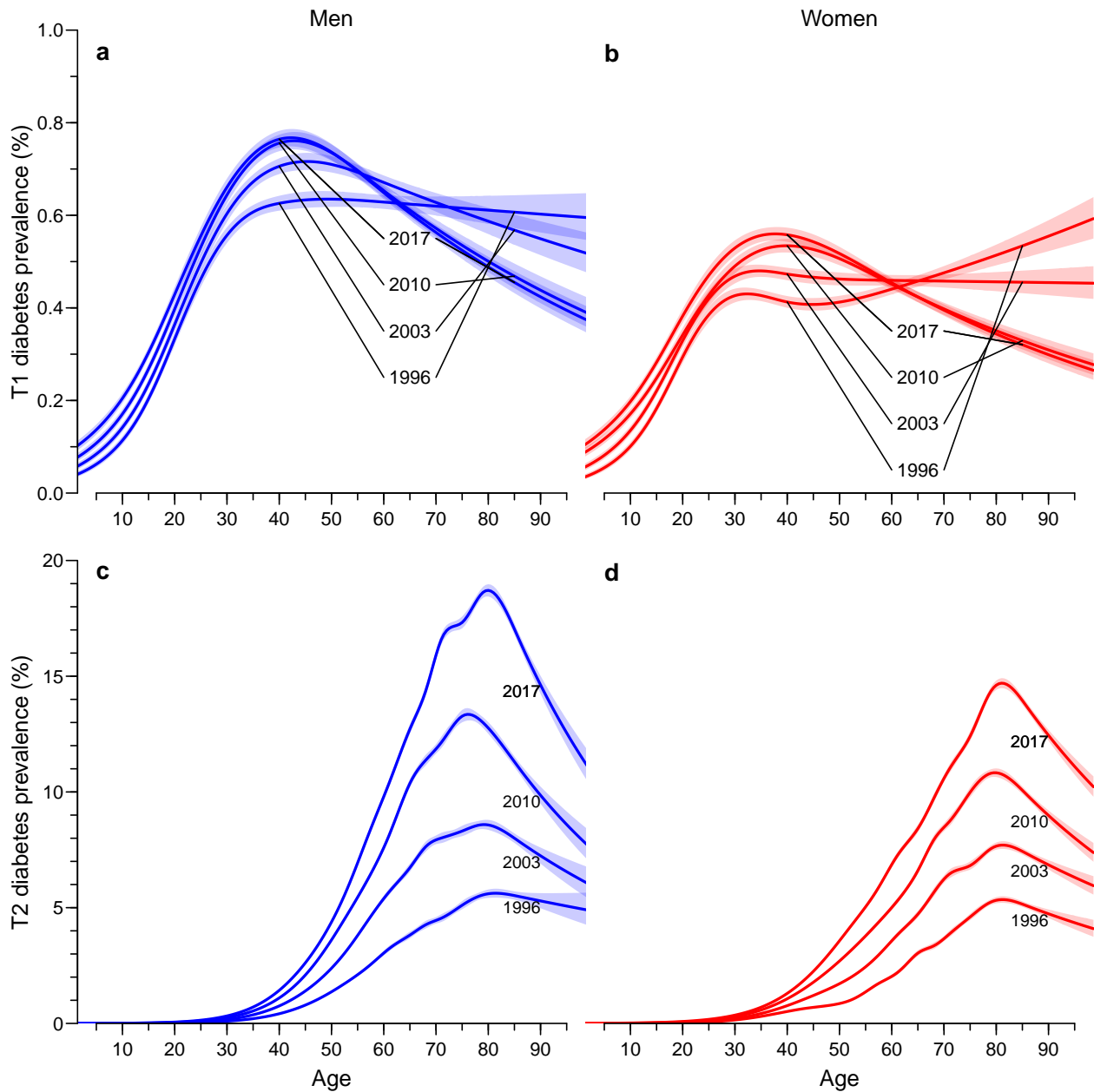


Figure 1: Age-specific prevalence of T1D (a,b) and T2D (c,d) in Denmark as of 1 January 1996,2003,...,2017. Note the different y-axes in the upper and lower panels. Blue curves are men, red curves women; shaded areas represent 95% confidence intervals. a: men, T1D; b: women, T1D; c: men, T2D; d: women, T2D.

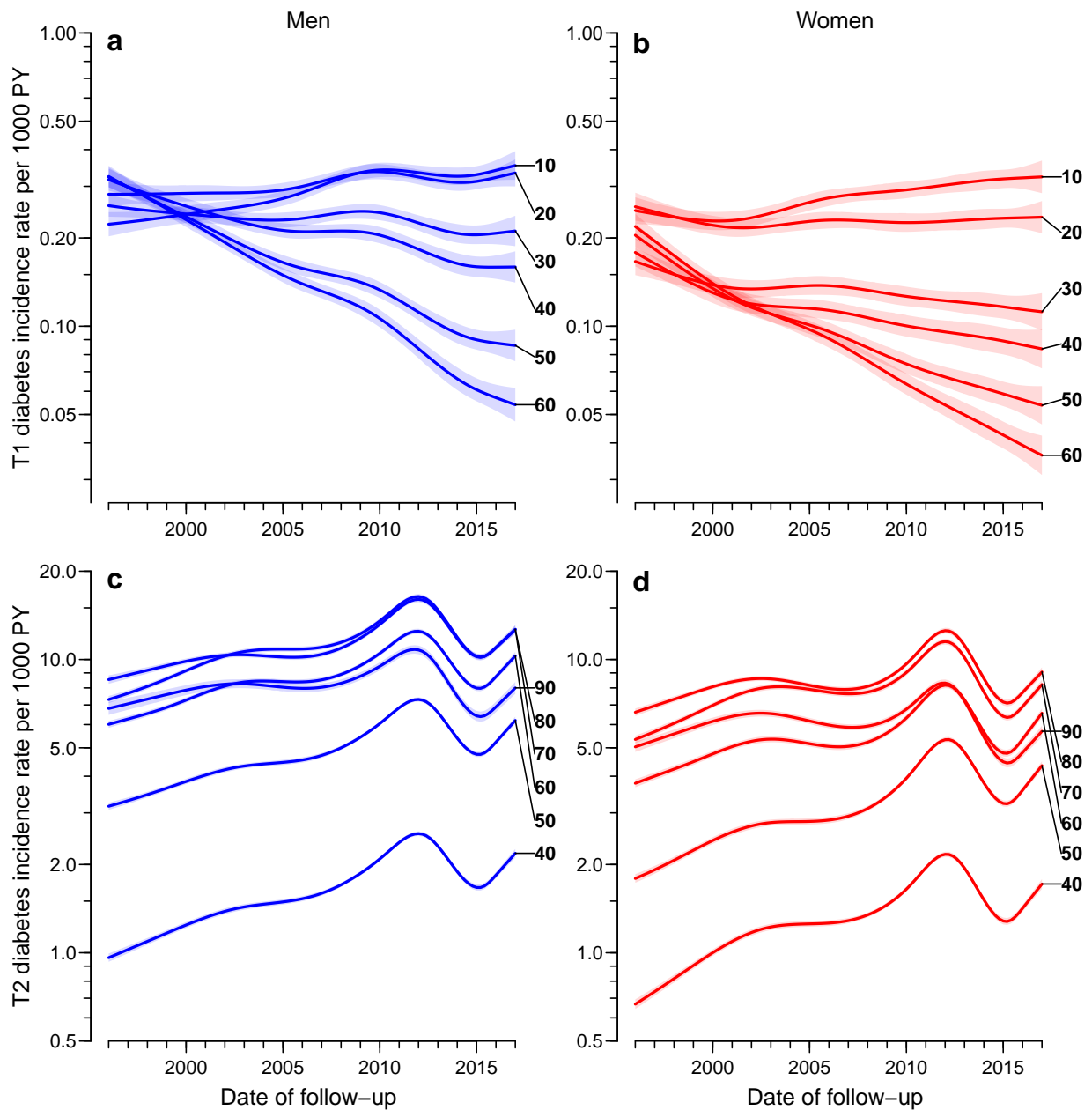


Figure 2: Age-specific incidence rates in different ages as of 1 January 2015, derived from Age-Period-Cohort models. Note the different y-axes in the upper and lower panels but that the relative extent of the axes are the same for T1D and T2D. Blue curves are men, red curves women; shaded areas represent 95% confidence intervals. a: men, T1D; b: women, T1D; c: men, T2D; d: women, T2D

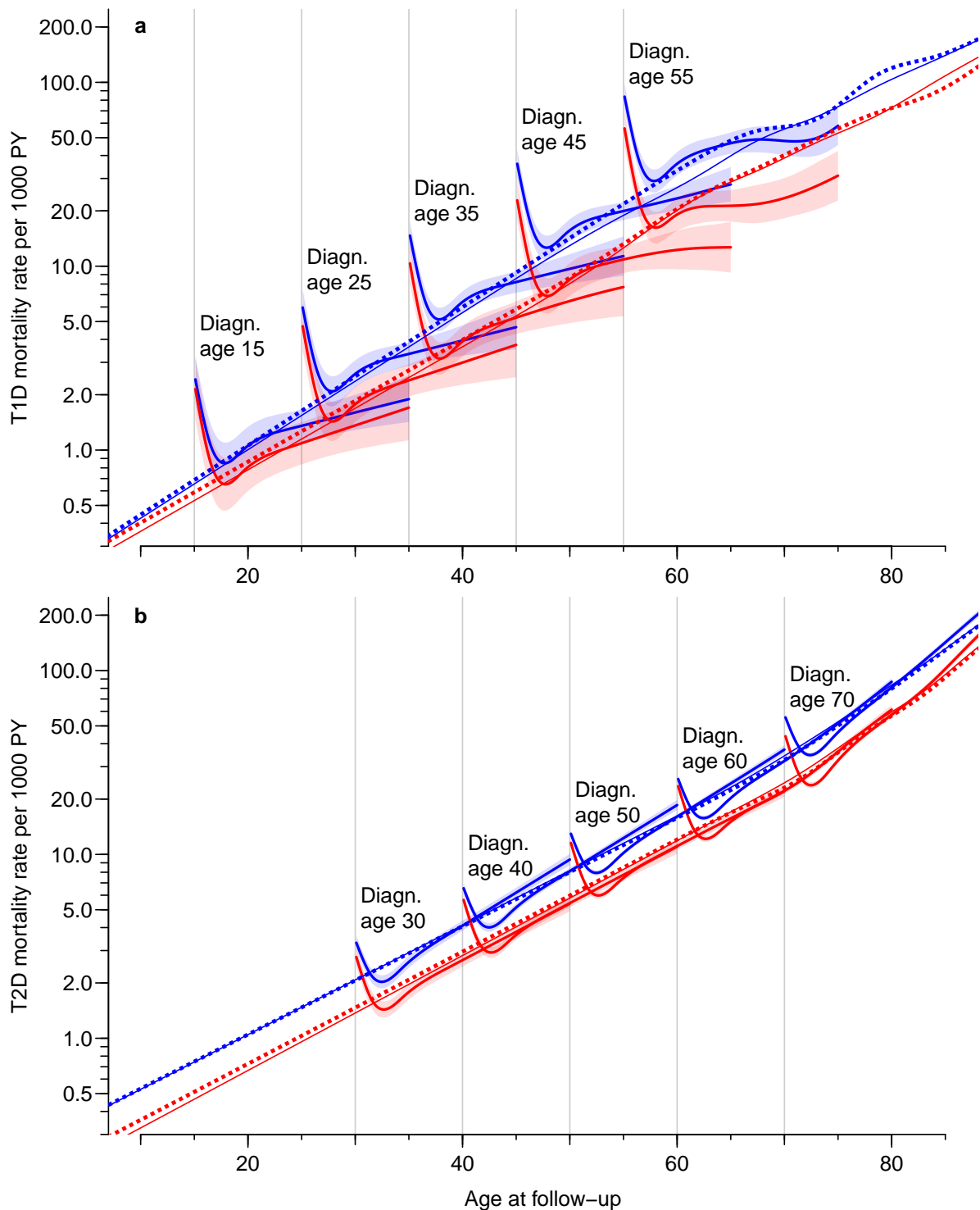


Figure 3: Age-specific mortality rates as of 2015-01-01 for T1D (upper panel) and T2D (lower panel). Each curve represents the mortality among patients diagnosed in ages 15, 25, 35, 45, 55 (T1D) respectively 30, 40, 50, 60, 70 (T2D). Each curve thus represents the joint effect of attained age and duration of diabetes for a given age at diagnosis.

Thick dotted curves are from a model ignoring age at diagnosis and duration of diabetes; thin full lines includes prevalent cases as of 1996-01-01 in the model.

Blue curves are men, red curves women.

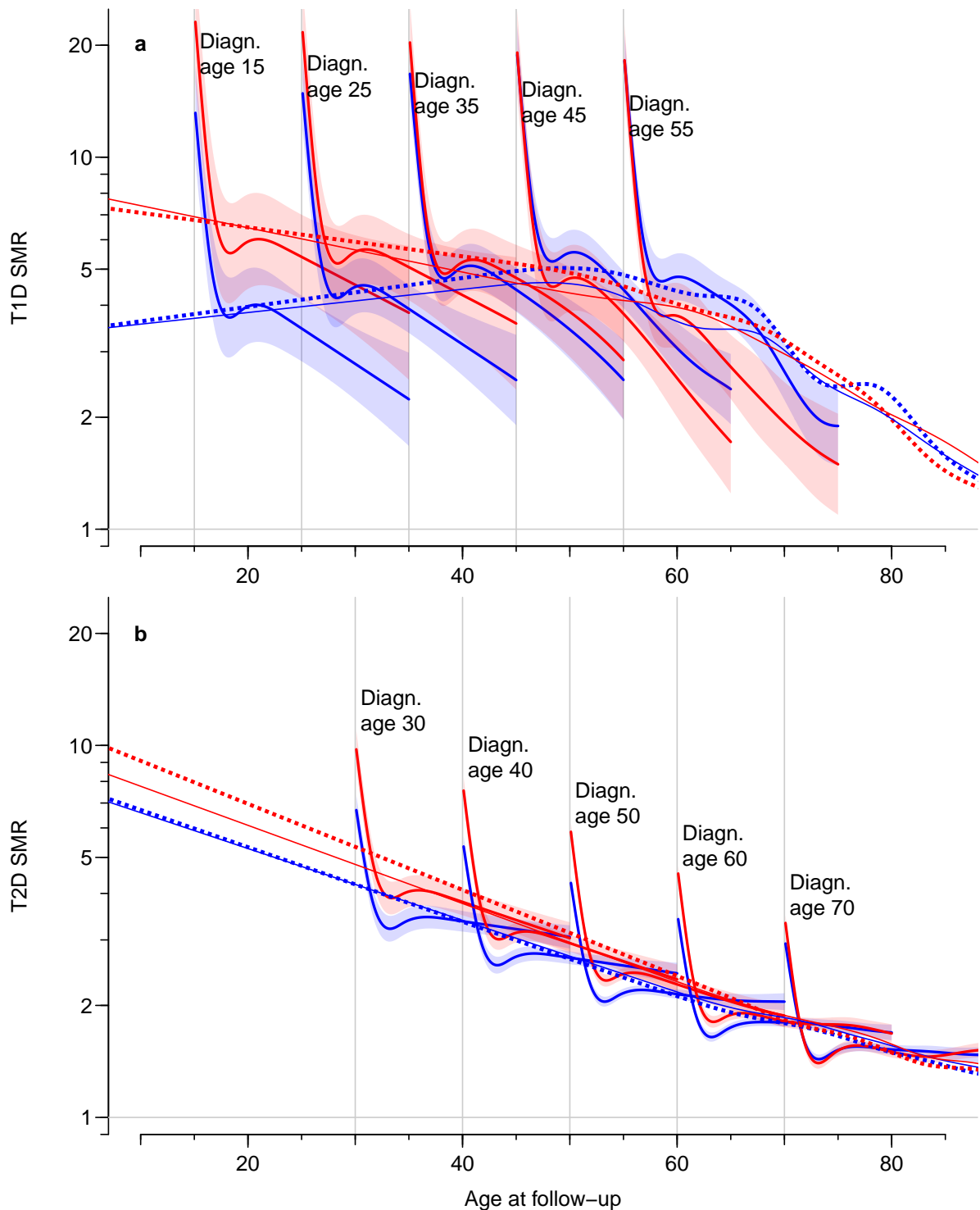


Figure 4: Age-specific SMR (rate-ratio relative to non-DM population) as of 2015-01-01 for T1D (upper panels) and T2D (lower panels). Each curve represents the SMR among patients diagnosed in ages 15, 25, 35, 45, 55 (T1D) respectively 30, 40, 50, 60, 70 (T2D). Each curve thus represents the joint effect of attained age and duration of diabetes for a given age at diagnosis.

Thick dotted curves are from a model ignoring age at diagnosis and duration of diabetes; thin full curves additionally includes prevalent cases as of 1996-01-01.

Blue curves are men, red curves women, and shaded areas represent 95% confidence intervals.

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

Electronic Supplementary Material

SDCC

<http://bendixcarstensen.com/>

March 2019

Version 3

Compiled Tuesday 9th July, 2019, 13:20

from: /home/bendix/sdc/DMreg/NewReg/art/DMDK/ESM.tex

Bendix Carstensen Steno Diabetes Center Copenhagen, Gentofte, Denmark
Senior Statistician Clinical Epidemiology
 & Department of Biostatistics, University of Copenhagen
bcar0029@regionh.dk b@bxc.dk
<http://BendixCarstensen.com>

Contents

1	Material and methods	1
1.1	Register data	1
1.1.1	Diabetes data	1
1.1.2	Population data	3
1.2	Tabulation of data	3
1.2.1	Prevalence	3
1.2.2	Follow-up	3
1.3	Statistical methods	4
1.3.1	Prevalence	4
1.3.2	Incidence rates	4
1.3.3	Mortality rates	4
1.3.4	Age, duration and age at diagnosis	5
1.3.5	Mortality data range	6
1.3.6	Standardized Mortality Ratio (SMR)	6
1.4	Sensitivity analyses	6
	References	7

List of Tables

1	Number of prevalent diabetes patients in Denmark at 1 January each year 1996–2017 by diabetes type and sex.	8
2	Crude prevalence (%) of diabetes in Denmark at 1 January 1996–2017 by diabetes type and sex.	9
3	Number of incident diabetes cases during each year 1996–2016 by diabetes type and sex.	10
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.	11
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.	12

List of Figures

1	Age-specific number of diabetes in Denmark as of 1 January 2017 by type	13
2	Age-specific average annual change in incidence rates of T1D and T2D in Denmark 1996–2016.	14
3	Incidence rates of T1D and T2D: Age-Period-Cohort model effects.	15
4	Mortality, and RR relative to 2015-01-01 and birth cohort residuals.	16
5	Mortality, and RR relative to 2015-01-01 and birth cohort residuals, with follow-up restricted to 2005+.	17
6	T1D versus T2D mortality RR at 2015	18
7	SMR, SMR-ratios relative to 2015-01-01 and birth cohort residuals.	19

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 health 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 40th 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, calendar 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; entry 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:

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

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

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

Thus, even if duration is not formally included in the model we may claim that it 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:

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

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 $a - e_0$:

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

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

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

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.

References

- [1] Pedersen C.B. The Danish civil registration system. *Scand J Public Health*, 39 (7 suppl):22–25, July 2011.
- [2] E. Lynge, J. L. Sandegaard, and M. Rebolj. The Danish National Patient Register. *Scand J Public Health*, 39(7 Suppl):30–33, Jul 2011.
- [3] J. S. Andersen, N. de F. Olivarius, and A. Krasnik. The Danish National Health Service Register. *Scand J Public Health*, 39(7 Suppl):34–37, Jul 2011.
- [4] H. W. Kildemoes, H. T. Sørensen, and J. Hallas. The Danish National Prescription Registry. *Scand J Public Health*, 39(7 Suppl):38–41, Jul 2011.
- [5] M. E. Jørgensen, J. K. Kristensen, G. Reventlov Husted, C. Cerqueira, and P. Rossing. The Danish Adult Diabetes Registry. *Clin Epidemiol*, 8:429–434, 2016.
- [6] G. S. Andersen, Z. Kamper-Jørgensen, B. Carstensen, M. Nørredam, I. C. Bygbjerg, and M. E. Jørgensen. Diabetes among migrants in Denmark: Incidence, mortality, and prevalence based on a longitudinal register study of the entire Danish population. *Diabetes Res. Clin. Pract.*, 122:9–16, Sep 2016.
- [7] B Carstensen. Age-Period-Cohort models for the Lexis diagram. *Statistics in Medicine*, 26(15):3018–3045, July 2007.
- [8] L. Huo, D. J. Magliano, F. Ranciere, J. L. Harding, N. Nanayakkara, J. E. Shaw, and B. Carstensen. Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997-2011. *Diabetologia*, Feb 2018.

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.*

Date	T1D		T2D		%T1		All DM		
	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.*

Date	T1D		T2D		All DM		
	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.*

Period	T1D		T2D		All DM		
	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.*

Period	T1D		T2D		All DM			non-DM
	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.*

Period	T1D		T2D		All DM			non-DM
	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

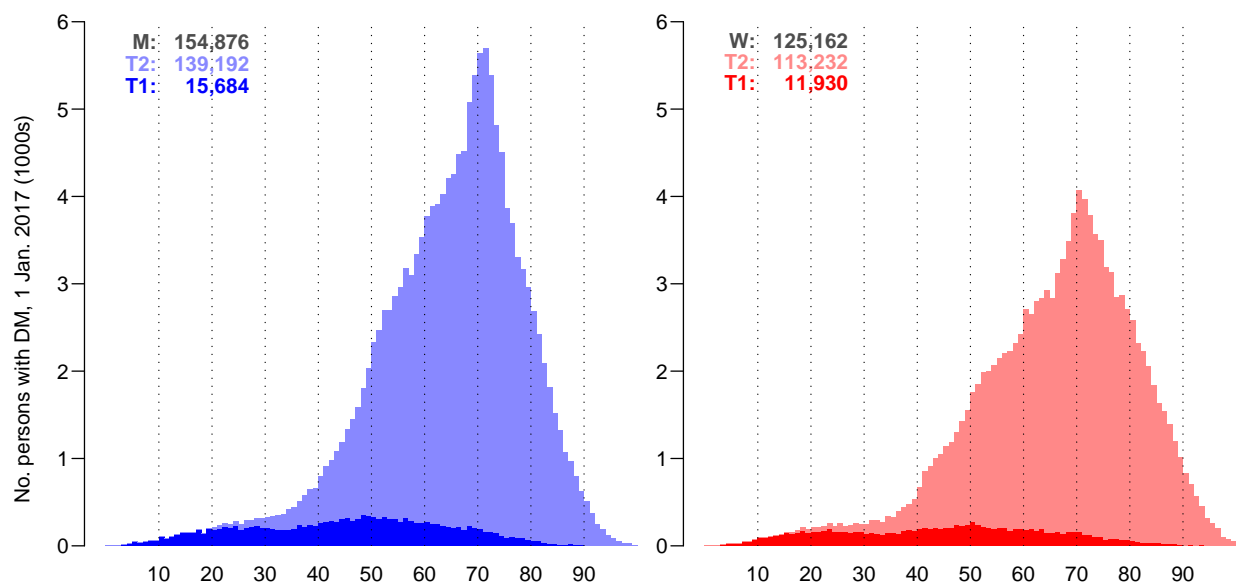


Figure ESM1: Number of T1D (dark color) and T2D (bright color) patients in Denmark as of 1 January 2017, the blue bars are men, red bars are women. The numbers in the corner of the plots indicate the number of prevalent cases, the black numbers are the total number of prevalent cases.

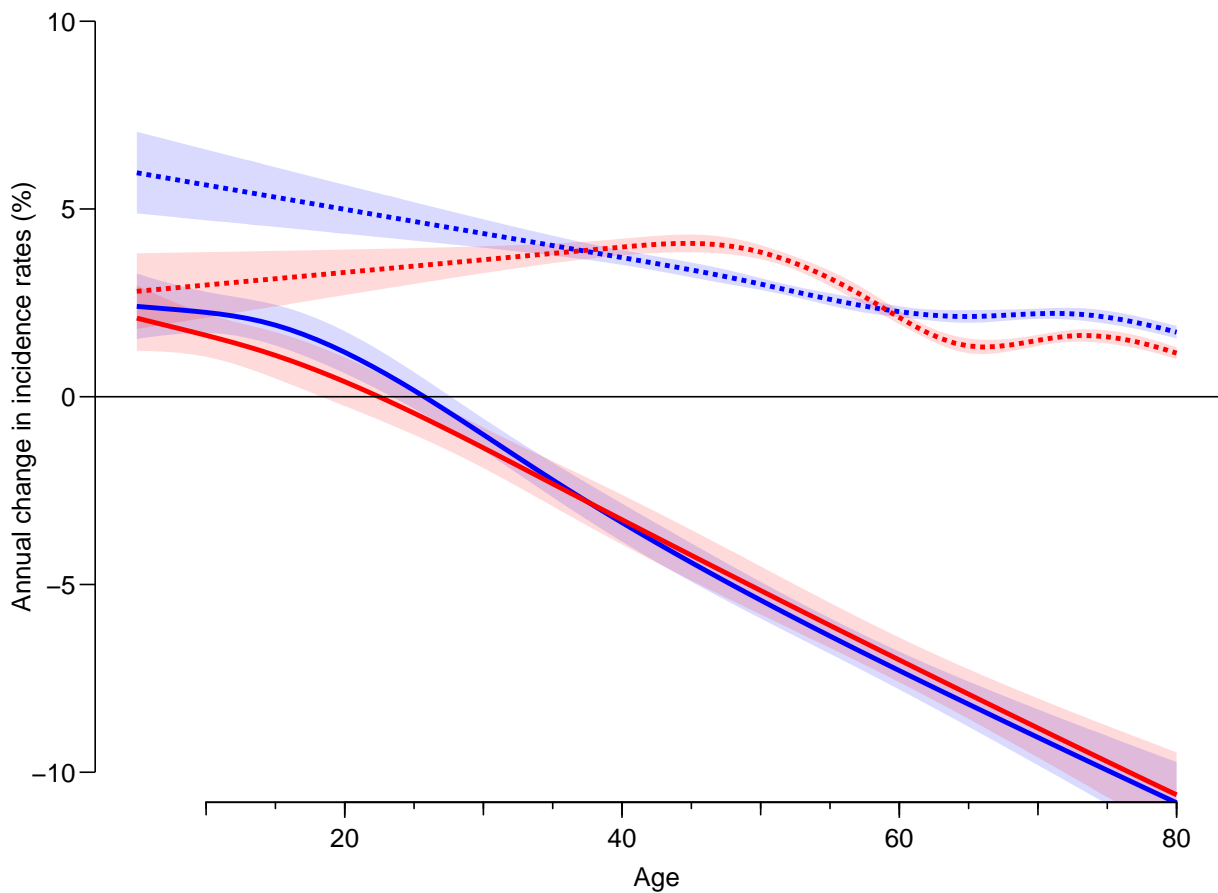


Figure ESM 2: *Age-specific average annual change in incidence rates of T1D and T2D in Denmark 1996–2016; a.k.a. “local drifts”. Estimates are from models with a smooth effect of age and an interaction between a smooth age term and a linear calendar time term (varying coefficients model). Full lines 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.

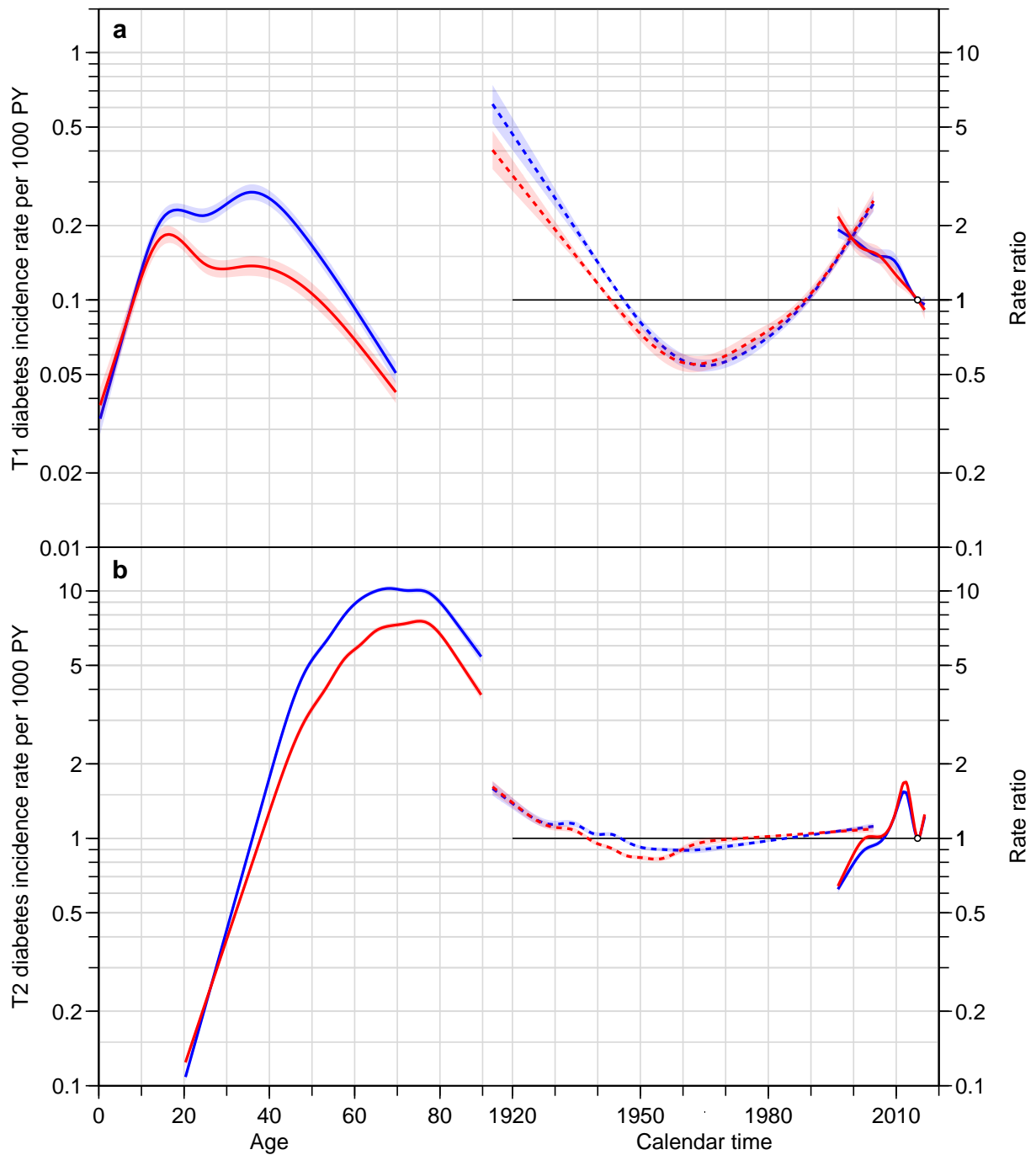


Figure ESM 3: *Estimates of effects from Age-Period-Cohort models for diabetes incidence rates in Denmark, using smooth effects of age, period and cohort (restricted cubic splines): Age-specific incidence rates (leftmost curves) as of 1 January 2015, period effects relative to this (rightmost curves, 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.

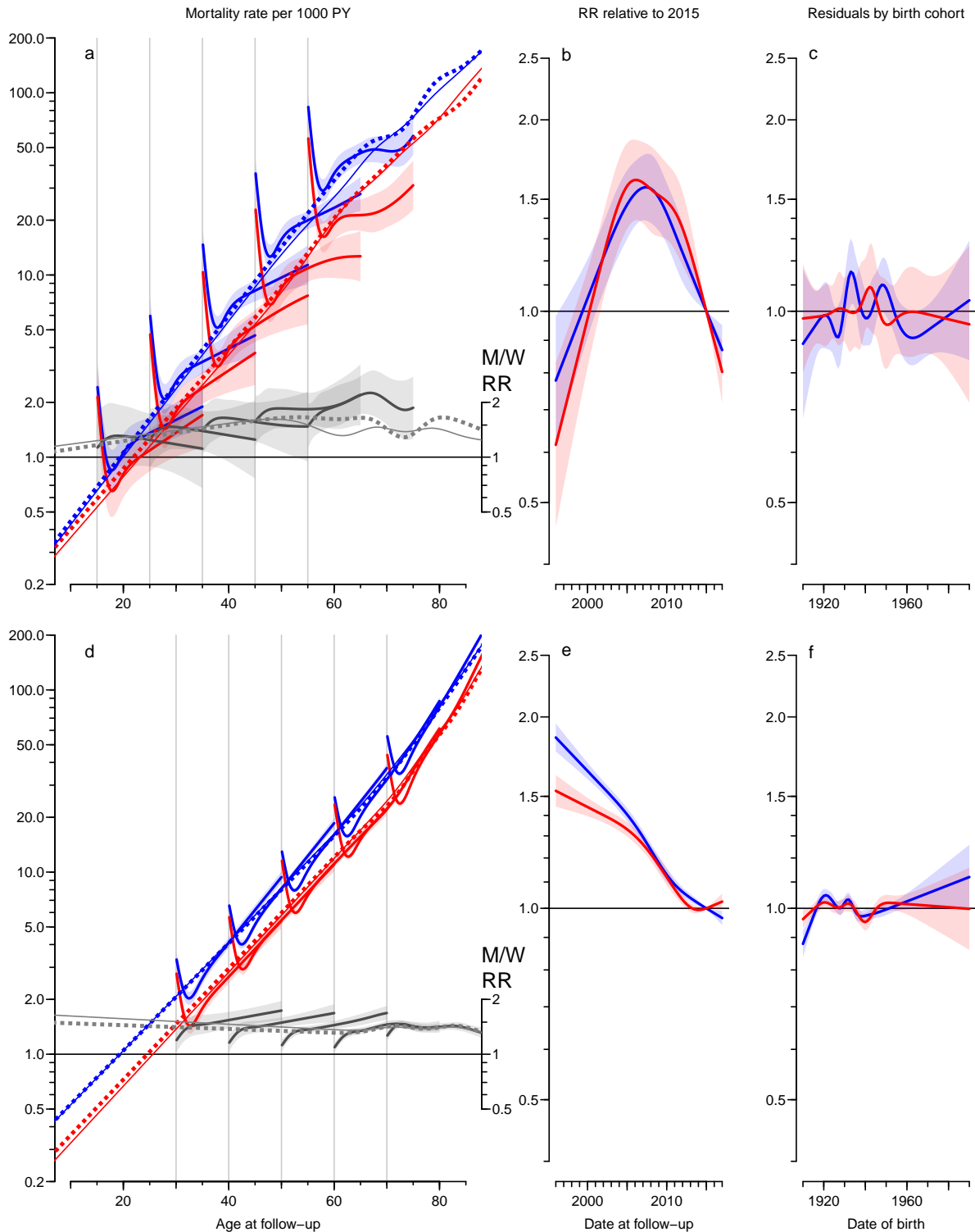


Figure ESM4: Mortality (a,c), and RR relative to 2015-01-01 (b,d) and birth cohort residuals (c,f). Upper panels (a,b,c) are T1D and lower panels (d,e,f) are T2D. Leftmost plot shows the mortality rates at 2015-01-01 for persons diagnosed in ages 15, 25, ..., followed for 0–20 years of diabetes duration. 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.

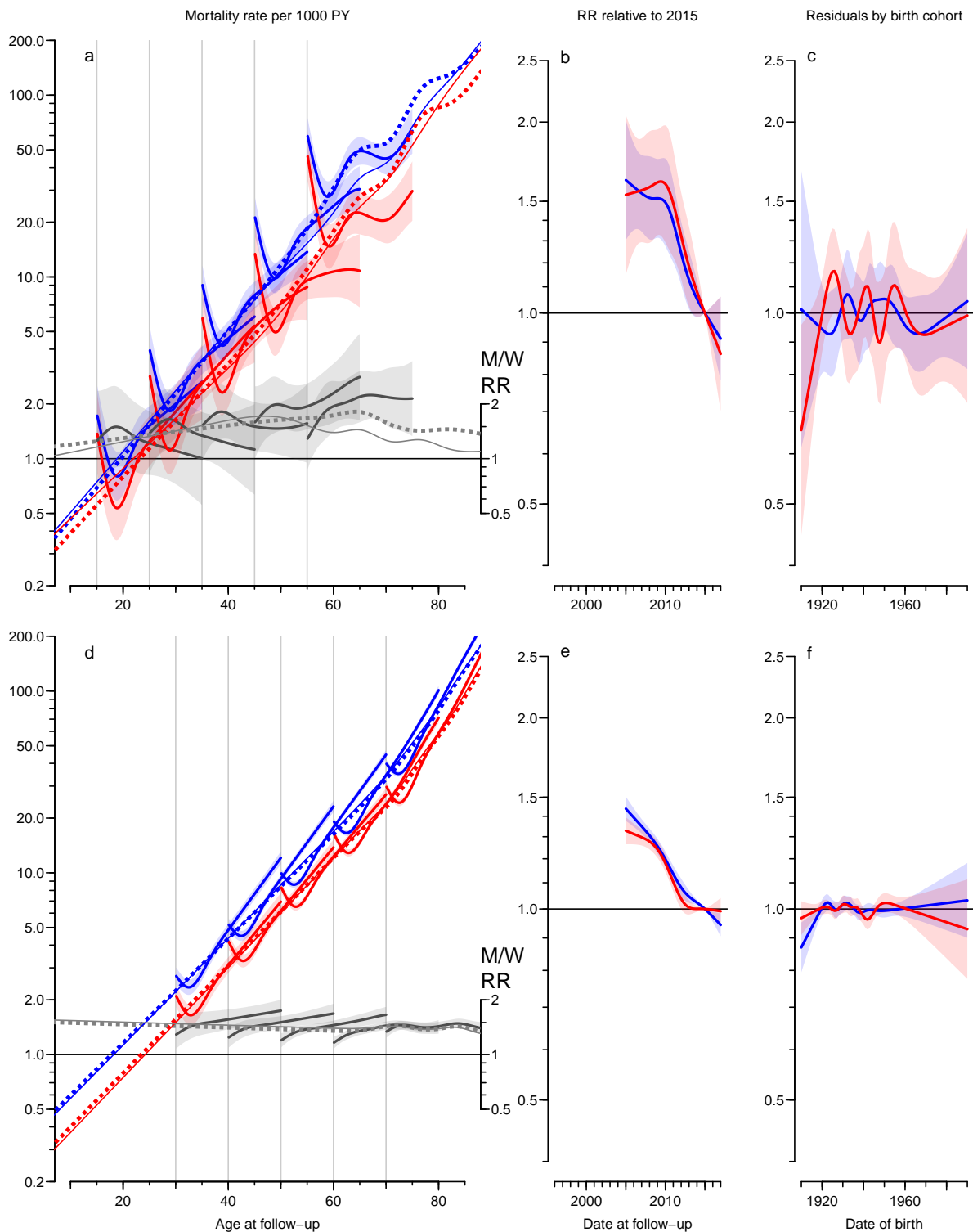


Figure ESM5: Mortality (a,c), and RR relative to 2015-01-01 (b,d) and birth cohort residuals (c,f), based on follow up after 2005 only. Upper panels (a,b,c) are T1D and lower panels (d,e,f) are T2D. Leftmost plot shows the mortality rates at 2015-01-01 for persons diagnosed in ages 15, 25, ..., followed 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.

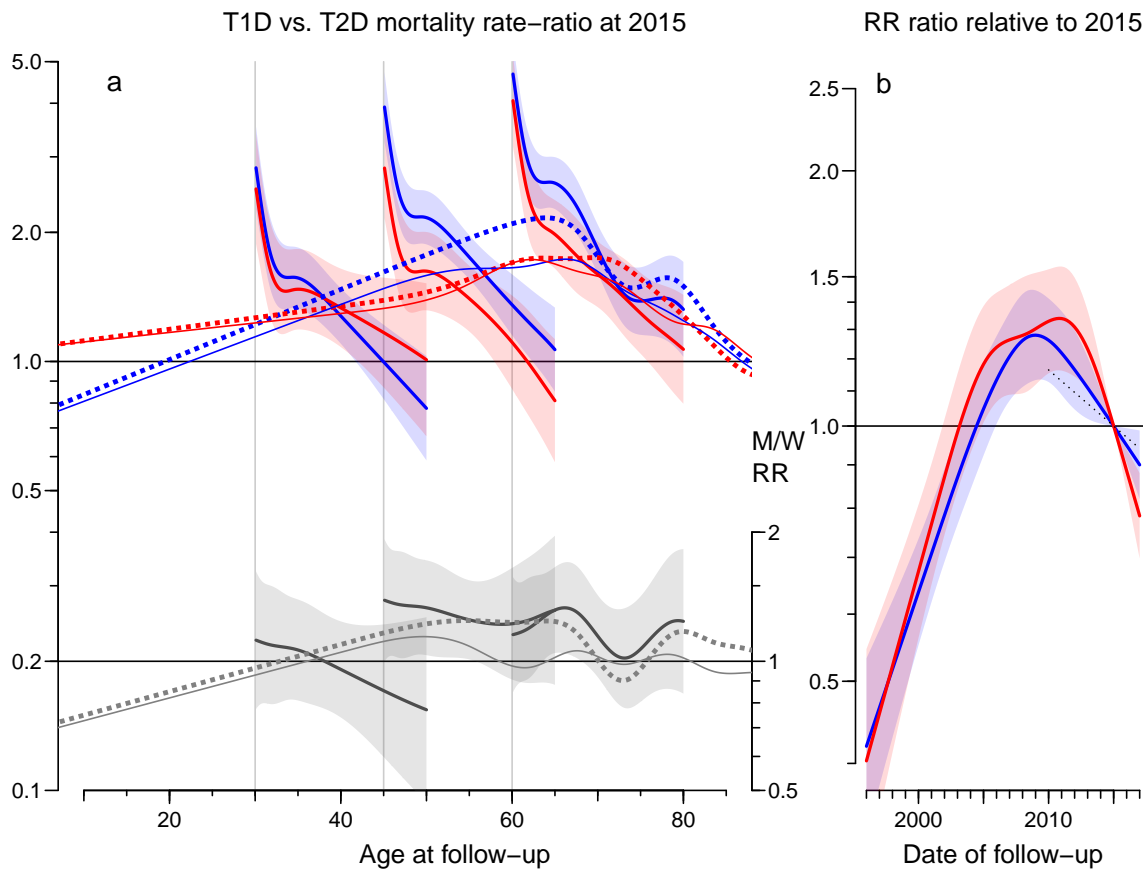


Figure ESM 6: *T1D versus T2D mortality RR at 2015-01-01. Leftmost plot shows the mortality RR at 2015-01-01 for persons diagnosed in ages 30, 45 and 60 years. Broken lines in leftmost plot are mortality RRs modeled ignoring age at diagnosis and duration of diabetes. Thin full lines are overall mortality 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.

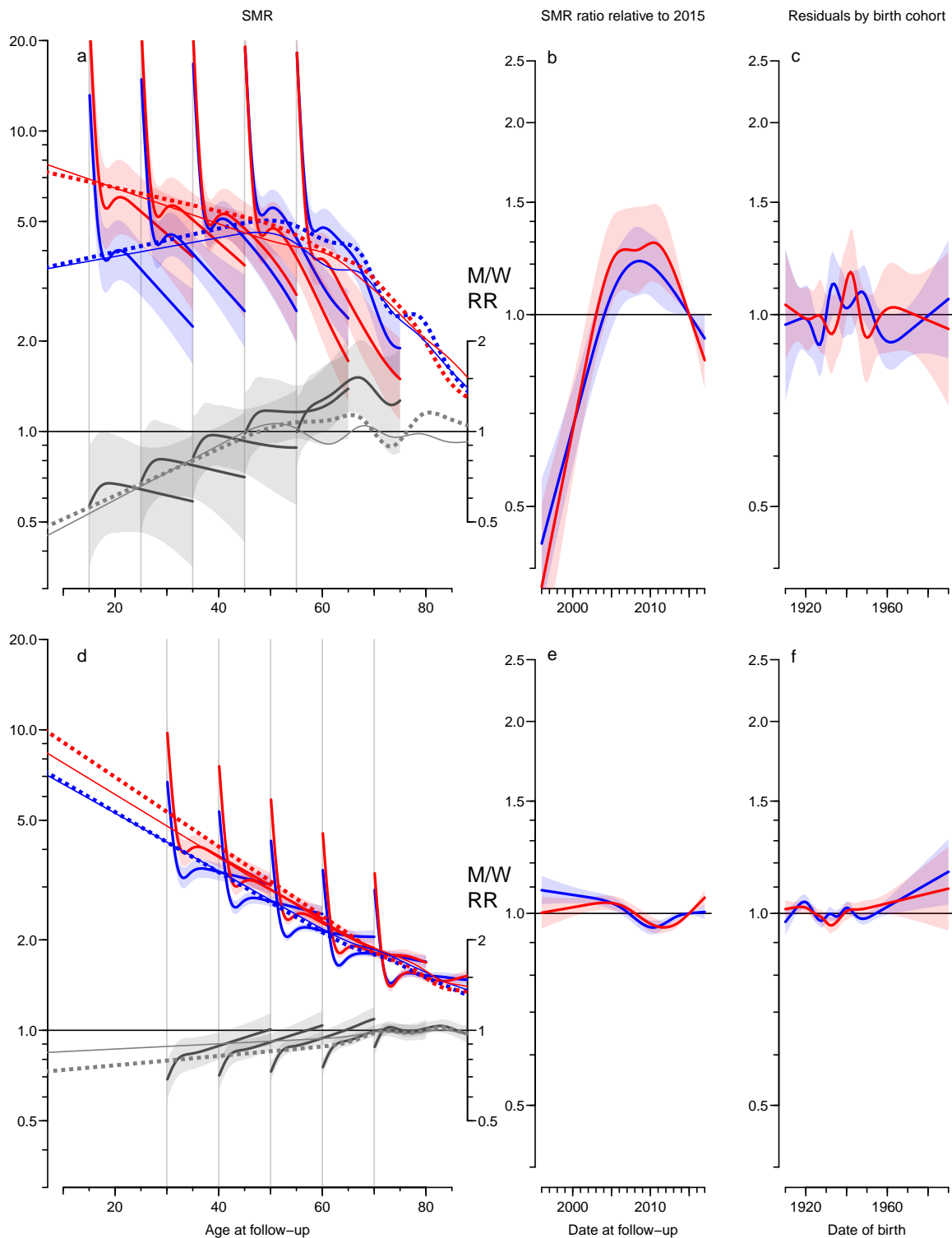


Figure ESM7: SMR (a,c) SMR-ratios relative to 2015-01-01 (b,d) and birth cohort residuals (c,f). The leftmost plots (a,c) shows the mortality rates at 2015-01-01 for persons diagnosed in ages 15, 30, 45, 60 and 75 followed for 0–20 years of diabetes duration. Broken lines in leftmost plot are SMR modeled 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.