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

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

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

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

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Abbreviations

APC — Age-Period-Cohort
DM — Diabetes mellitus
ESM — Electronic supplementary material
M — Men
SDCC — Steno Diabetes Center Copenhagen
T1D — Type 1 diabetes
T2D — Type 2 diabetes
W — Women

1 Abstract

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

Research Design and Methods From population-based registers of Denmark we derived diabtes incidence and mortality rates and mortality rates for persons without diabetes for the period 1996-2016. Rates were modeled by smooth parametric terms using Poissin 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 towards 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 diabetes patients 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.

2 Introduction

Diabetes (DM) is among the leading causes of death in Europe with diabetic macro- and microvascular complications resulting in increased disability and enormous health care 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 health care system) that the likely number of diabetes patients 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 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 to 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 [5, 6, 7] and type 2 diabetes [8, 9, 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:

$$\text{prevalence} = \text{incidence} \times \text{duration} = \text{incidence}/\text{mortality}$$

so both increasing incidence and decreasing mortality contributes 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 be regarded as a *qualitative* statement about the relationship.

A number of papers have pointed this qualitative relationship out [11, 12], but so far the only study that has attempted a quantification is Evans *et al.* [13], however not quantifying effects by age, and using a very crude age adjustment with 20 year age-classes.

There have been numerous reports predicting the future burden of diabetes [14, 15, 16, 17, 18], some even as far as 2050 (or further) [19, 20, 21], all ending with substantial predicted increases in numbers, mostly in the range 40–60% for the period 2015–2030.

In this work we used the Danish Diabetes Register [22] 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 diabetes patients.

3 Material and methods

3.1 Data

We used data from the Danish diabetes register [22] to compute prevalence and incidence of diabetes and mortality among persons with and without diabetes for the period 1996–2016.

As we are concerned with the total number of persons with diabetes in Denmark we did not distinguish between T1D and T2D.

3.2 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 1996-01-01 in 1-month age intervals, we used the estimated incidence and mortality rates to compute the prevalence in steps of one month for successive dates in the period of interest. The technicalities of this is given in the Electronic Supplementary Material (ESM).

Components of prevalence

Starting with the prevalences at 1996-01-01 we used estimated incidence and mortality rates for the period to 2016 to predict prevalence as of 2017-01-01. This was done in steps of 1 month of time and age, predicting the fraction of persons at a given date and age-interval, that will get diabetes resp. die in each 1 month interval. As a check of models we compared these with observed prevalences. We repeated the exercise using either incidence or mortality rates or both fixed at the 1996 level.

Differences in predicted age-specific prevalences at the end between the scenarios correspond to the contribution from the period changes in incidence resp. mortality. The difference between the scenario with both incidence and mortality fixed at 1996 level and the prevalence as of 1996-01-01 is the effect of epidemiological imbalance at 1996-01-01 — the change in prevalence attributable to the imbalance between incidence and mortality at that time. This way we subdivided the prevalence at 2017 in 4 parts: attributable to 1) decreasing mortality (Mort), 2) increasing incidence (Inc), 3) incidence/mortality imbalance as of 1996 (Imbal) and 4) the prevalence as of 1996 (Org). A detailed account of this is in the ESM.

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 2017-01-01 and predicting in 1-month steps till 2040 as described above. Multiplying the projected age-specific prevalences by the predicted population size 2017–2040 from Statistics Denmark we obtained the predicted *number* of diabetes patients for the period 2017–2040. A detailed account of this procedure can be found in the ESM.

4 Results

In the study period, during some 115 mil. person-years, there were 363,664 new cases of diabetes and about 1.15 mil. deaths, of which 161,762 were among diabetes patients (table ESM 1). There was a marked decrease in the number of new diabetes cases after 2012 and an increase again in 2015 and 2016 [22].

4.1 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 *de*creasing; 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).

4.2 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 (figure ESM 3). Thus the prediction modeling of the incidence and mortality rates method is sufficiently accurate to yield credible results for the scenarios considered.

The components of the prevalences as derived from the models are shown in figure ESM 4, 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 diabetes patients were dying—the socalled epidemiological imbalance.

Figure 1 shows the *number* of diabetes patients 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- 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 **??**, and not surprisingly, the mortality decrease has 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 **??**).

4.3 Future prevalence

At 2017-01-01 there were 280,130 prevalent cases of DM in the Danish population, corresponding to 4.8% of the population [22].

The incidence rates showed an increase till around 2011, then a decrease from 2012 to 2014 and an increase again from 2015 (figure **??**). It was therefore difficult to make any single soundly founded projections for the time beyond 2017-01-01, so we used 6 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 diabetes patients from 2017 to 2030.

The other prediction scenarios have deliberately been chosen to be on the low side (fixed rates, *i.e.* 0% annual increase) or high side (6% annual increase), and they produce estimates quite far from the attenuation estimate of prevalent number of diabetes patients by 2030 (392,000, resp. 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 figures ESM 9–11.

5 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.

The finding of a decline in diabetes-related mortality is encouraging, although the resulting increase in diabetes prevalence obviously challenges the health care 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 versus 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.* [26] 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. 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.* [13] used Tayside (Scotland) data to attempt a quantification of the relative contributions of incidence and mortality. 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 [19, 17]. This corresponds to a crude prevalence of 7.7%, up from 5.0% in 2017. Our sensitivity analyses 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 were merely included in table 2 to demonstrate their limited usefulness.

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

Andersson *et al.* [17] used simple annual changes in incidence and mortality rates for prediction of the number of diabetes patients in Sweden and arrived at some 50% increase in the number over the period 2013–30 (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). Holman *et al.* [14] 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.

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 — implemented in our attenuation assumption. This was done in order not to over-emphasize 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 (ESM figures 5–7)

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 straight-forward 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.

6 Conclusion

We showed that the increasing prevalence of diabetes is influenced by the decline in mortality affecting primarily the oldest part of the population. But the major drivers of the prevalence increase was 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 diabetes patients 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 diabetes patients were 54.6%; in 2030 it was predicted to be 56.1%, a very modest increase. The proportion of diabetes patients 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 endeavour will naturally entail a substantial component of arbitrary assumptions, and ours is no exception.

7 Paraphernalia

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.

Funding

The study was solely funded through the core research budget of SDCC.

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 ANGEN AB, Astra Zeneca and Sanofi Avensis,

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 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.

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Table 1: *Average annual change (%) in diabetes incidence and mortality rates in Denmark in the period 1996–2016 incl.*

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

Table 2: *Predicted number of prevalent diabetes patients and prevalence 2017–2040, using six different prediction scenarios for incidence rates: naïve prediction from a splines-based APC-model, attenuation with halving of rate change per 5 years, fixing rates at the level of 2017-01-01 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.*
The bold face 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.

					Fixed annual incidence increase							
Date	APC-naïve		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

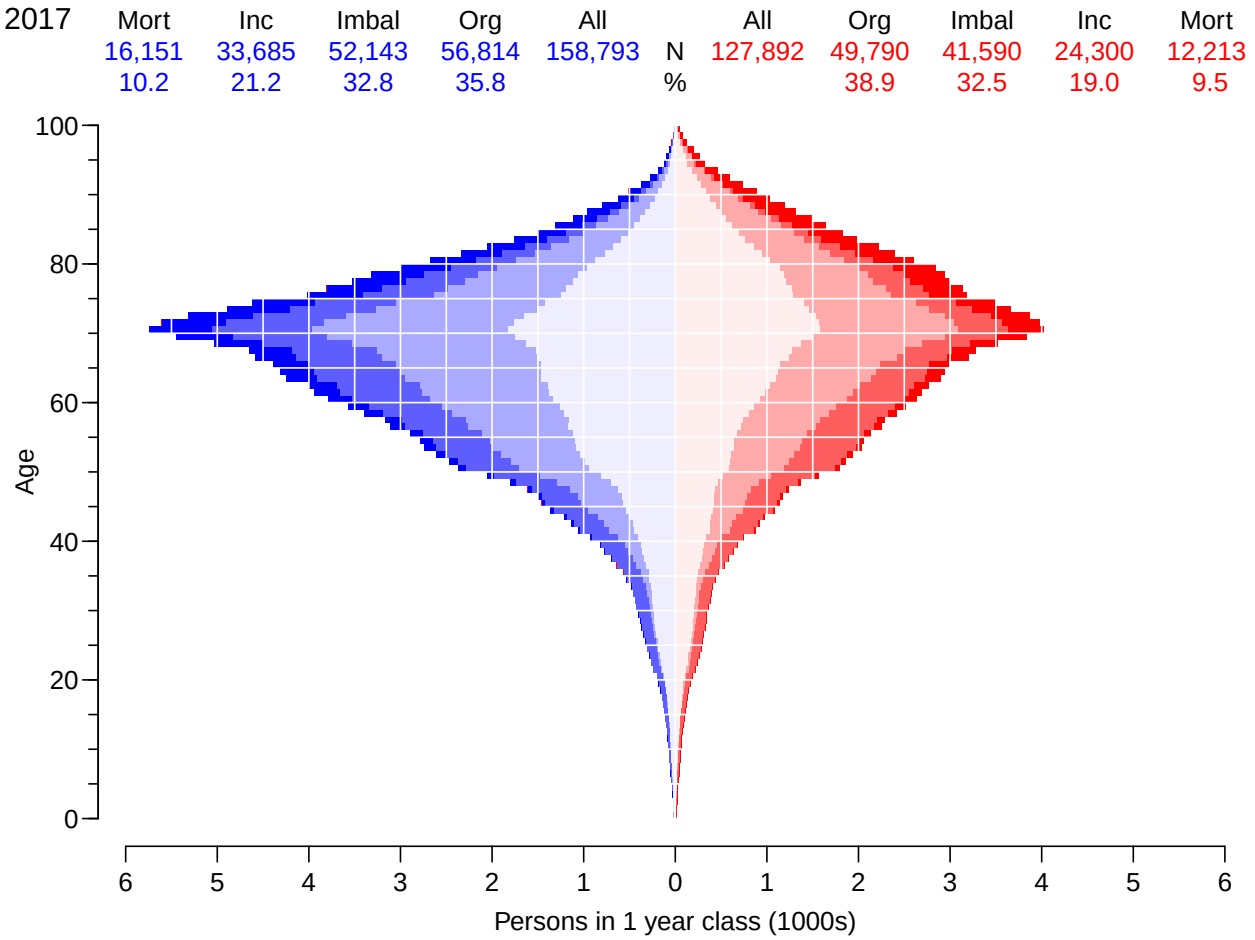

Figure 1: *Age-distribution of persons with diabetes in Denmark as of 1 January 2017 according to components of the changes in diabetes prevalence 1996–2016. Figures at the top is the number, resp. percentages attributable to the four factors. The coloured areas are no. of cases attributable to Mort: 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.*

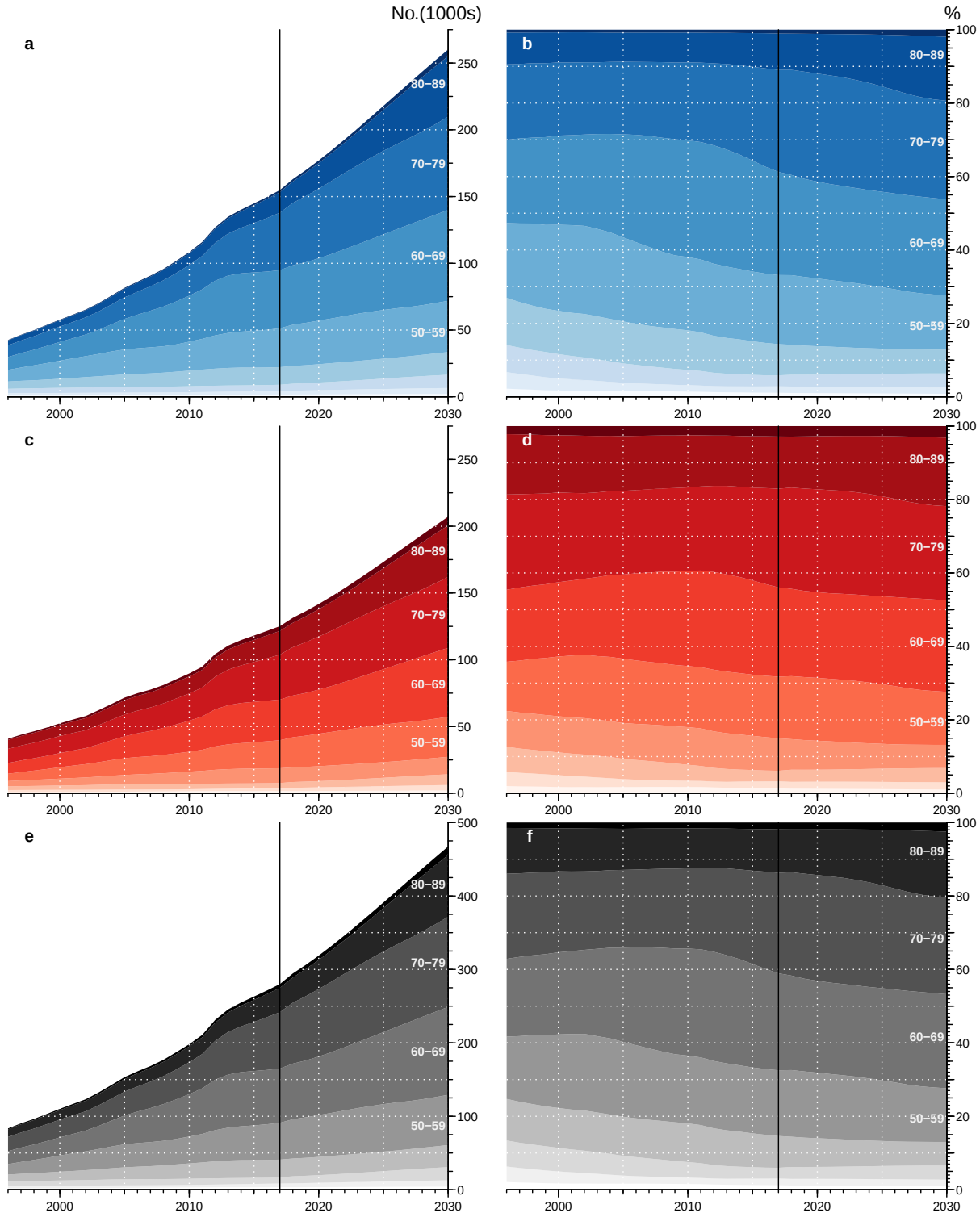

Figure 2: *Observed and predicted no.of diabetes patients 1996–2030. Left panels are number of men (a), women (c) and total no. diabetic persons (e); right panels shows age-distributions in 10-year classes for men (b), women (c) and all (f). Blue is men, red is women and gray both sexes combined, different shades correspond to 10-year age-classes. The black vertical line delineates the observed (data) from the prediction.*

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

Electronic Supplementary Material

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

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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

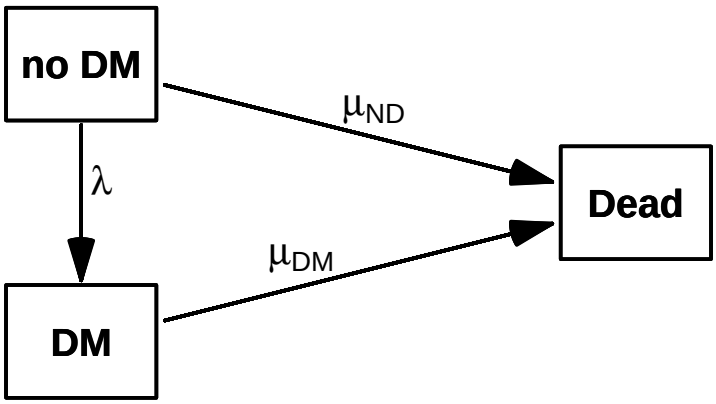

Figure ESM 1: *States and transition rates used: λ: Incidence rate, μ_{nD}: mortality rate in persons without diabetes, μ_{DM}: mortality rate in persons with diabetes. Prevalence of diabetes is the fraction in state "DM" relative to all in states "noDM" and "DM".*
Each rate is modeled separately for 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.

1.2 Prevalence and rates 1996–2016(7)

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 )
```

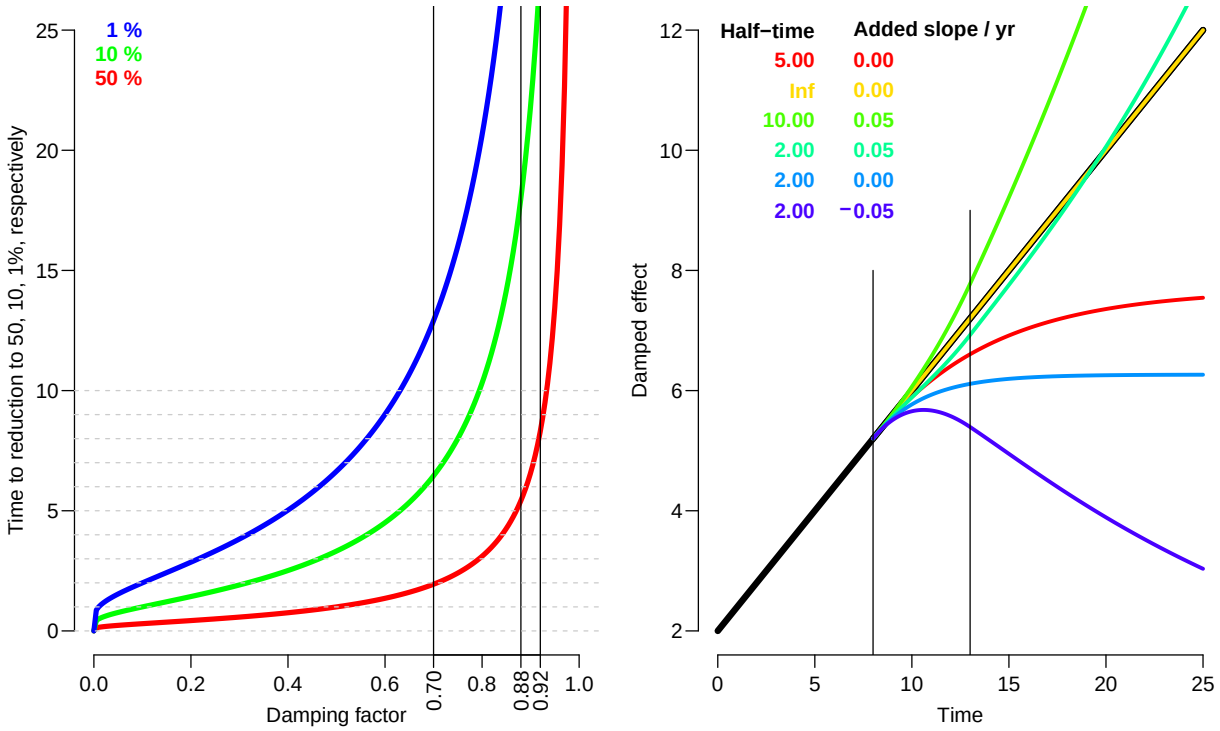

Figure ESM 2: *The left panel shows the time to reduction of the slope of a curve to 50, 10 and 1% of the original for different values of the damping factor. The right hand panel illustrates the* `damp` *function for attenuation of effects and addition of linear terms for various combinations of the 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

[1] B Carstensen. Age-Period-Cohort models for the Lexis diagram. *Statistics in Medicine*, 26(15):3018–3045, July 2007.

[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

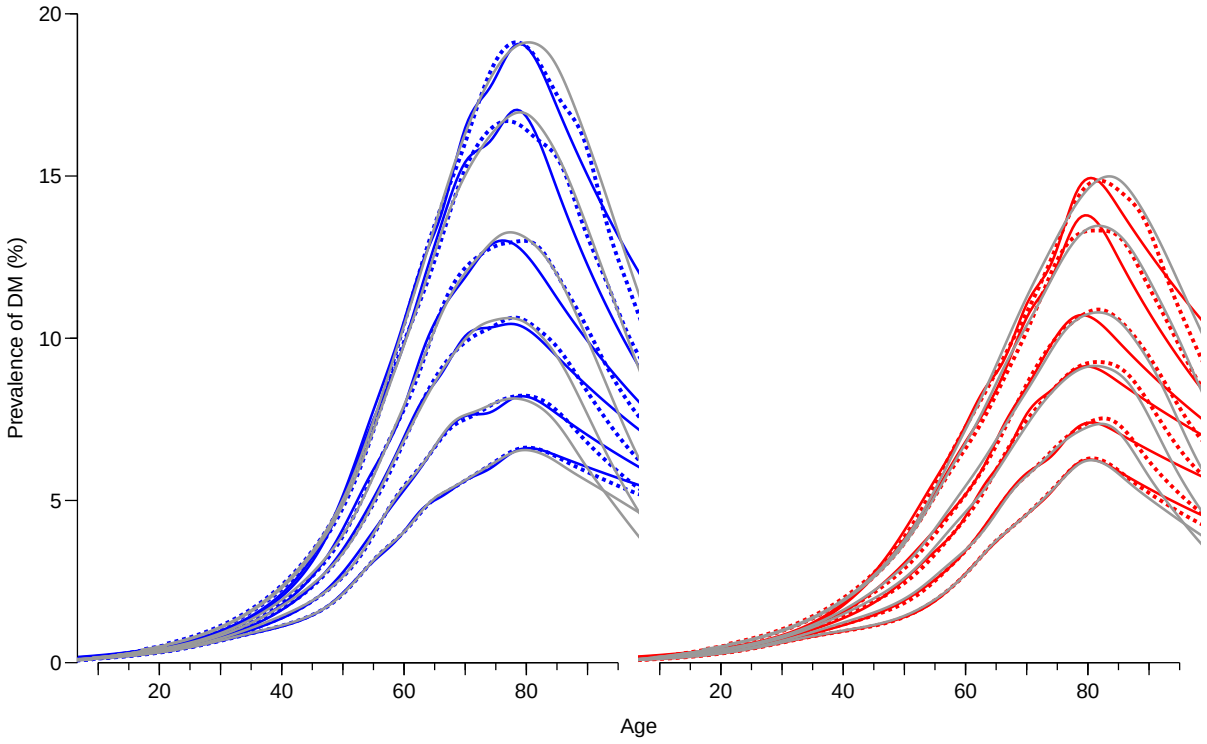

Figure ESM 3: *Observed (full lines) and predicted (broken lines) prevalence of DM in Denmark (from low to high) 1997, 2001,ldots,2017. The observed prevalences are smoothed using natural splines. The predicted prevalences are based on the prevalences as of 1995 and estimated rates from age-period-cohort 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.*

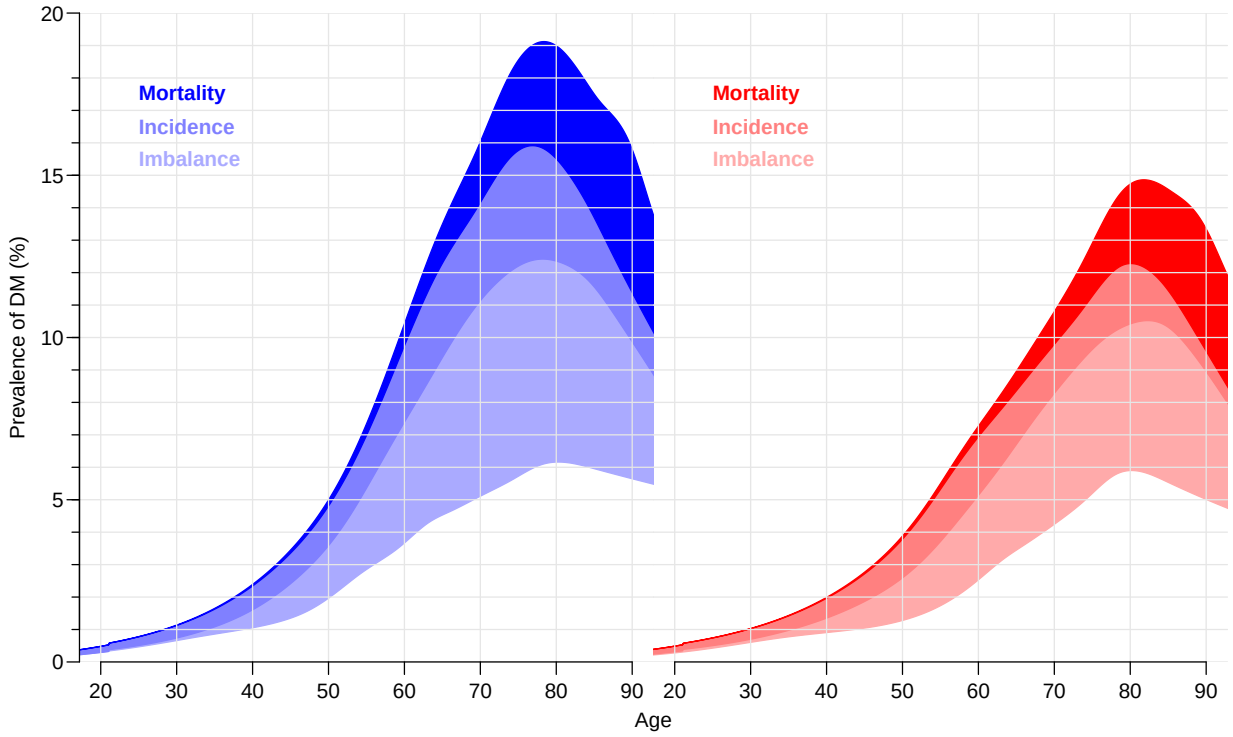

Figure ESM 4: *Age-specific prevalence as of 1 January 2017 subdivided by the components of the changes in diabetes prevalence in the period 1996–2016, based on prevalence in 1996 and models for incidence and mortality in the period. Men in blue, women in red. The white area at the bottom represents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

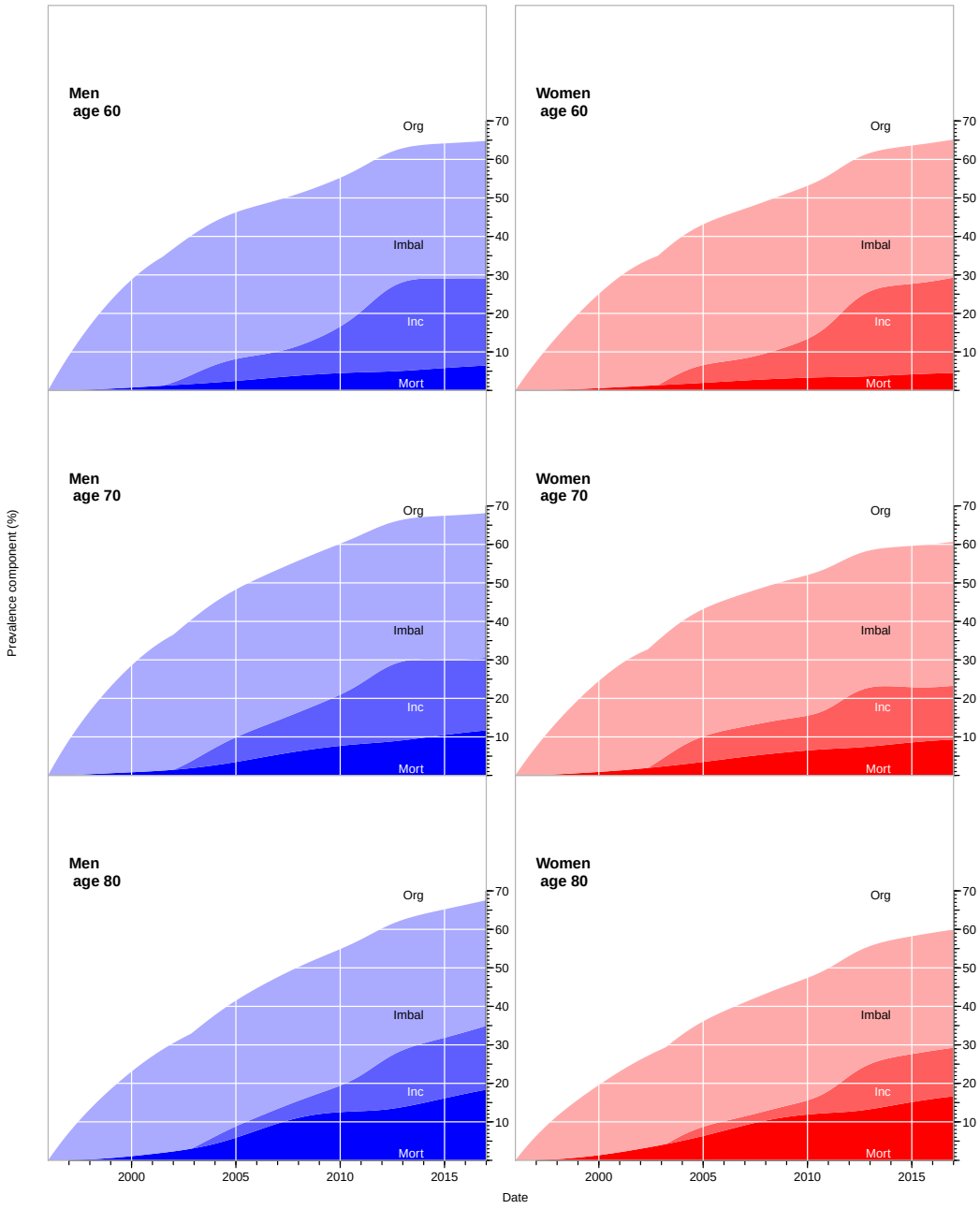

Figure ESM 5: *Fraction of the prevalent cases at different times attributable to a) declining mortality (bottom, full color), b) increasing incidence (middle, pale color) and c) incidence/mortality imbalance 1996 (top, weak color). The white areas above the curves correspond to the fraction of the cases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

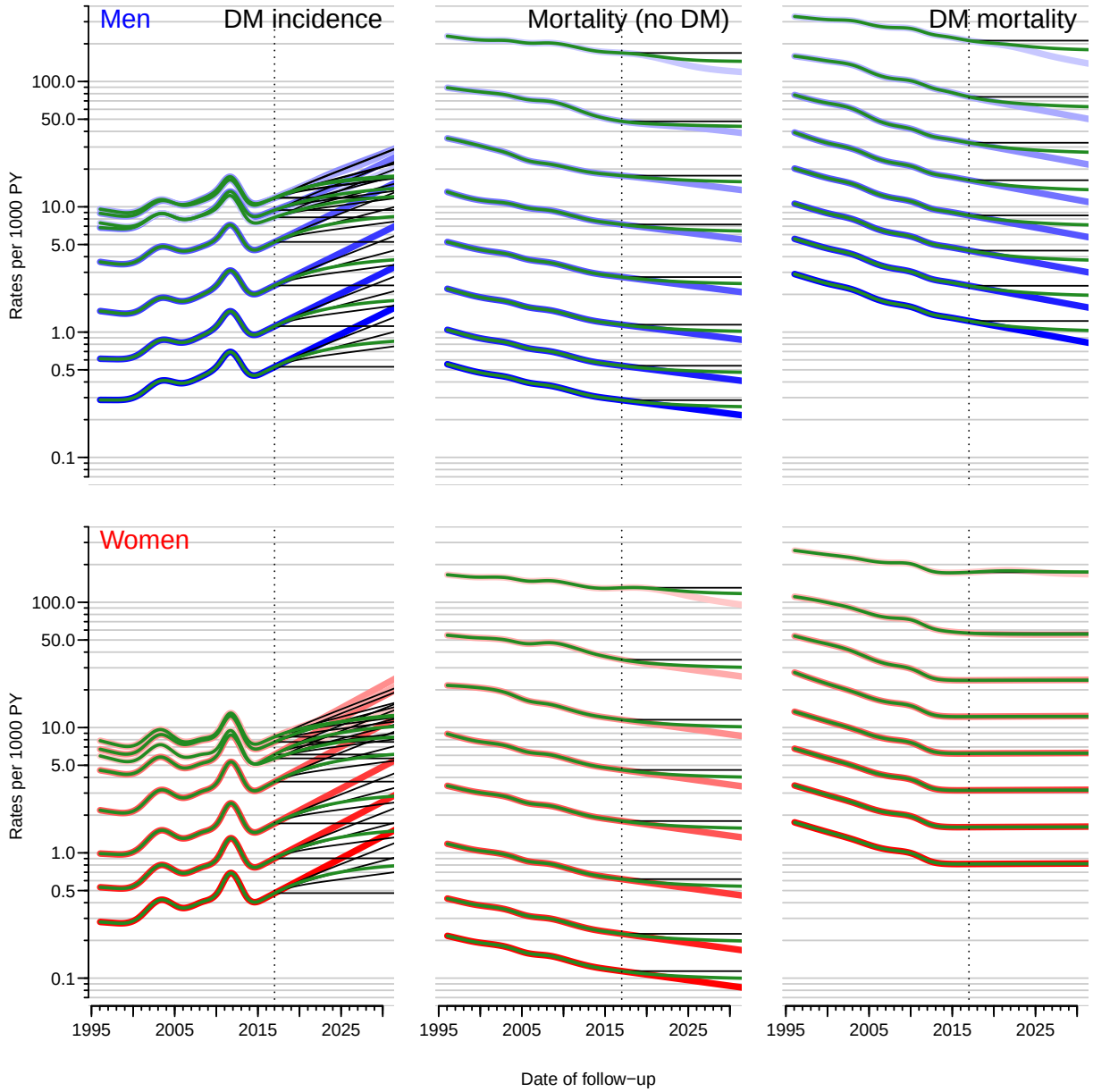

Figure ESM 6: *Observed and predicted incidence and mortality rates 1996–2030 for ages 20, 30,...,90. The naïve prediction based on natural spline models are shown in blue for men and red for women. The black predictions are rates fixed at the level of 2017-01-01. Green predictions are attenuated rates (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.*

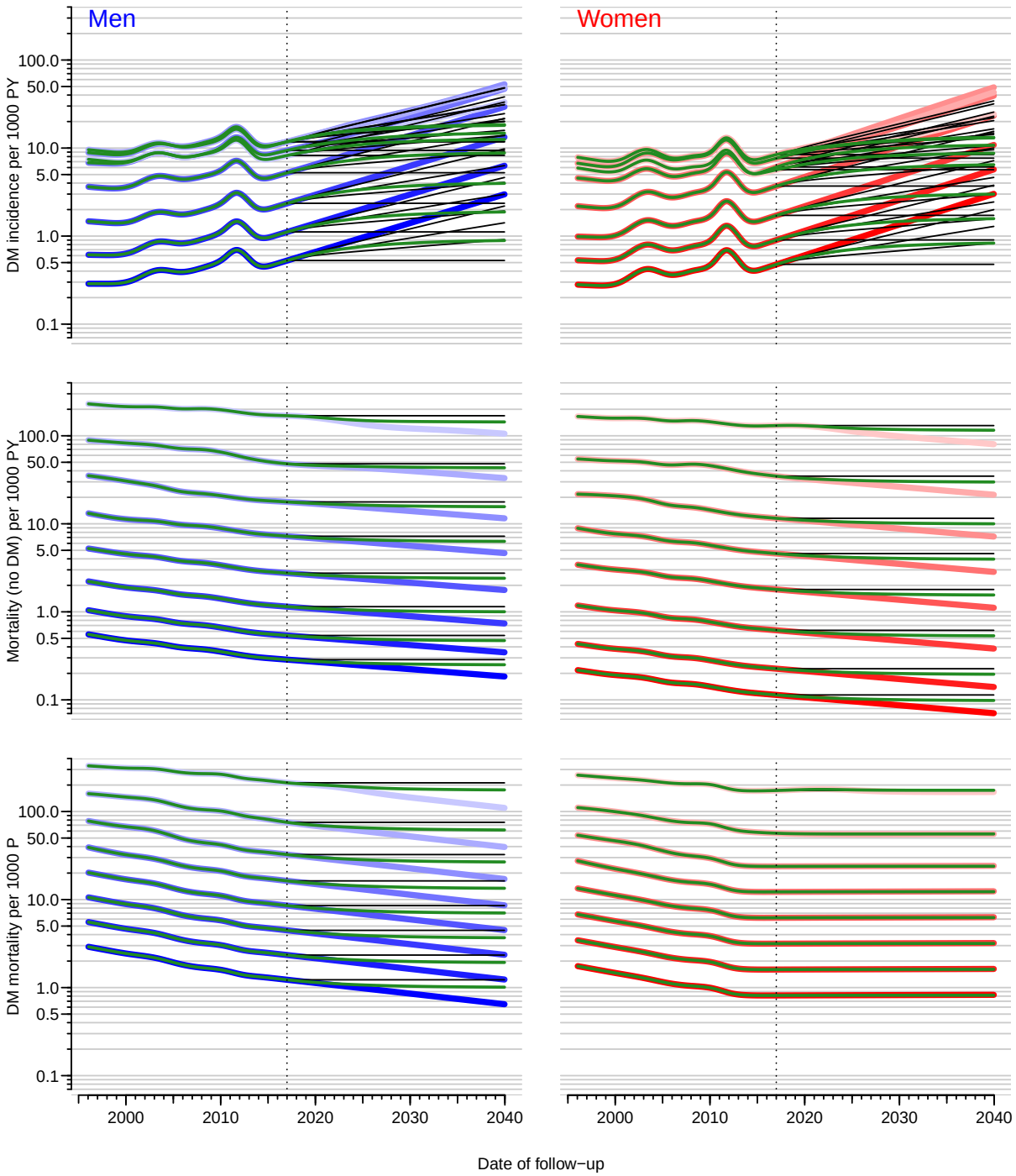

Figure ESM7: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2040 for ages 20, 30,...,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

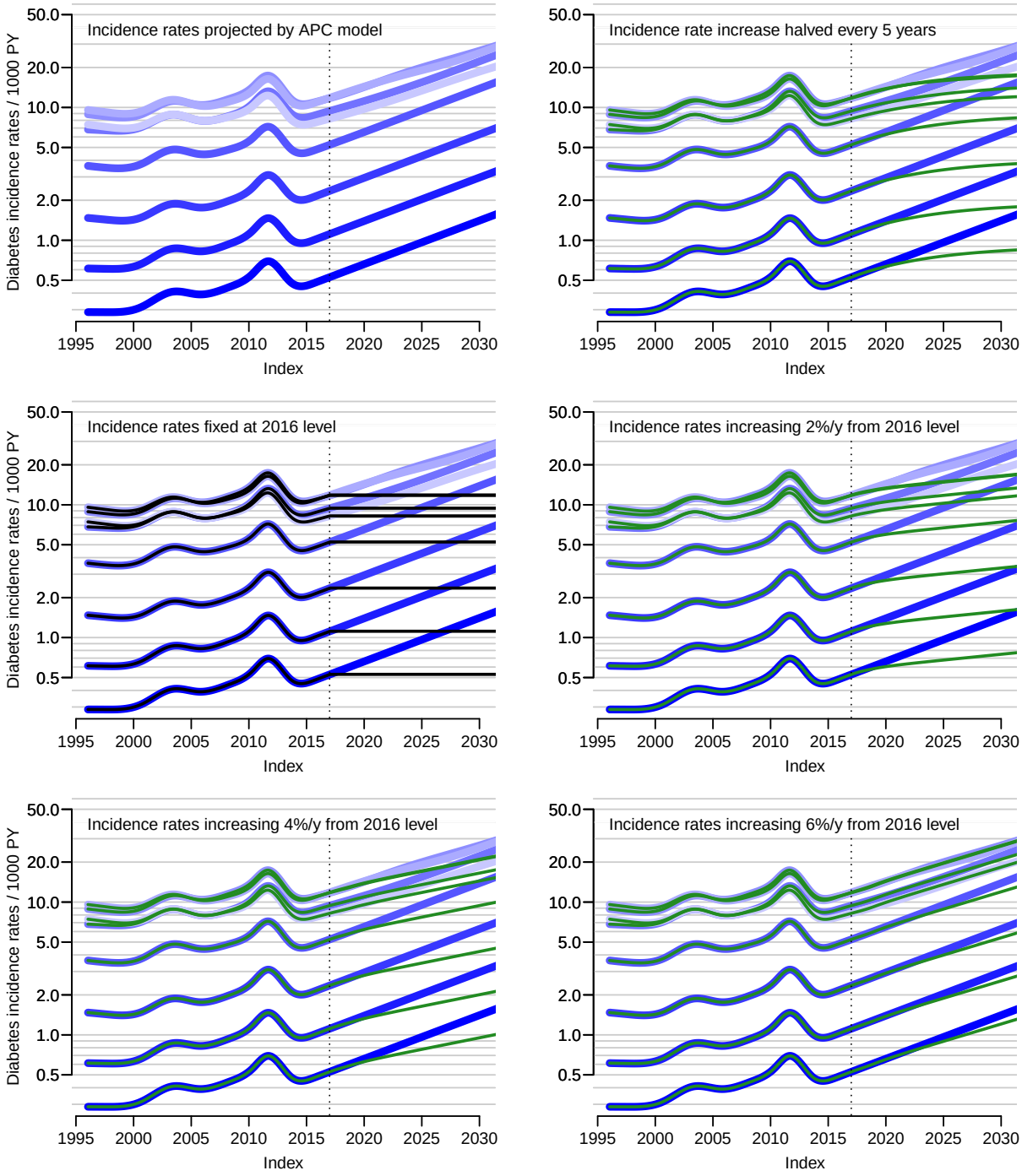

Figure ESM 8: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2030 for man at ages 20, 30,. . . ,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

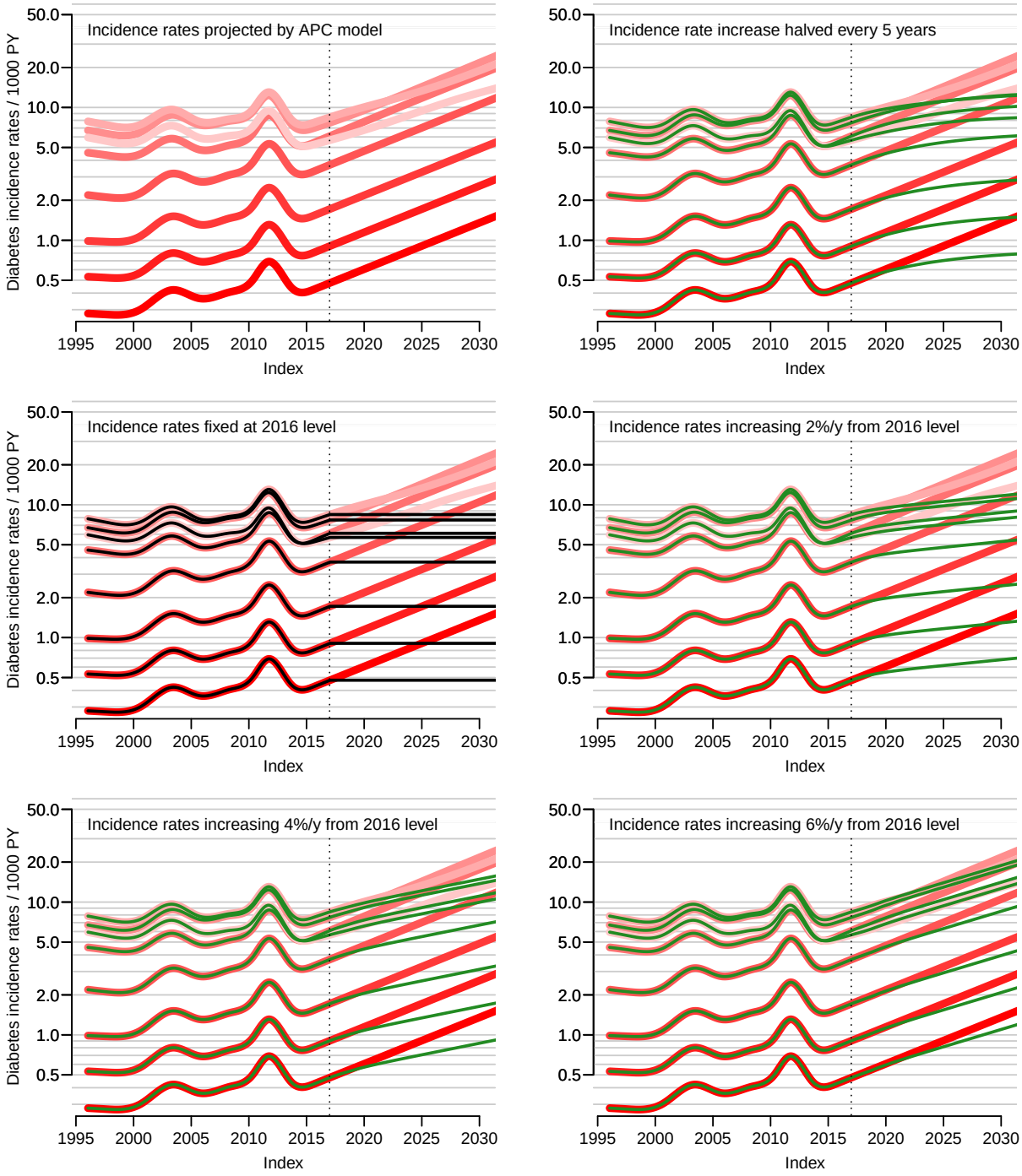

Figure ESM9: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2030 for women at ages 20, 30,...,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

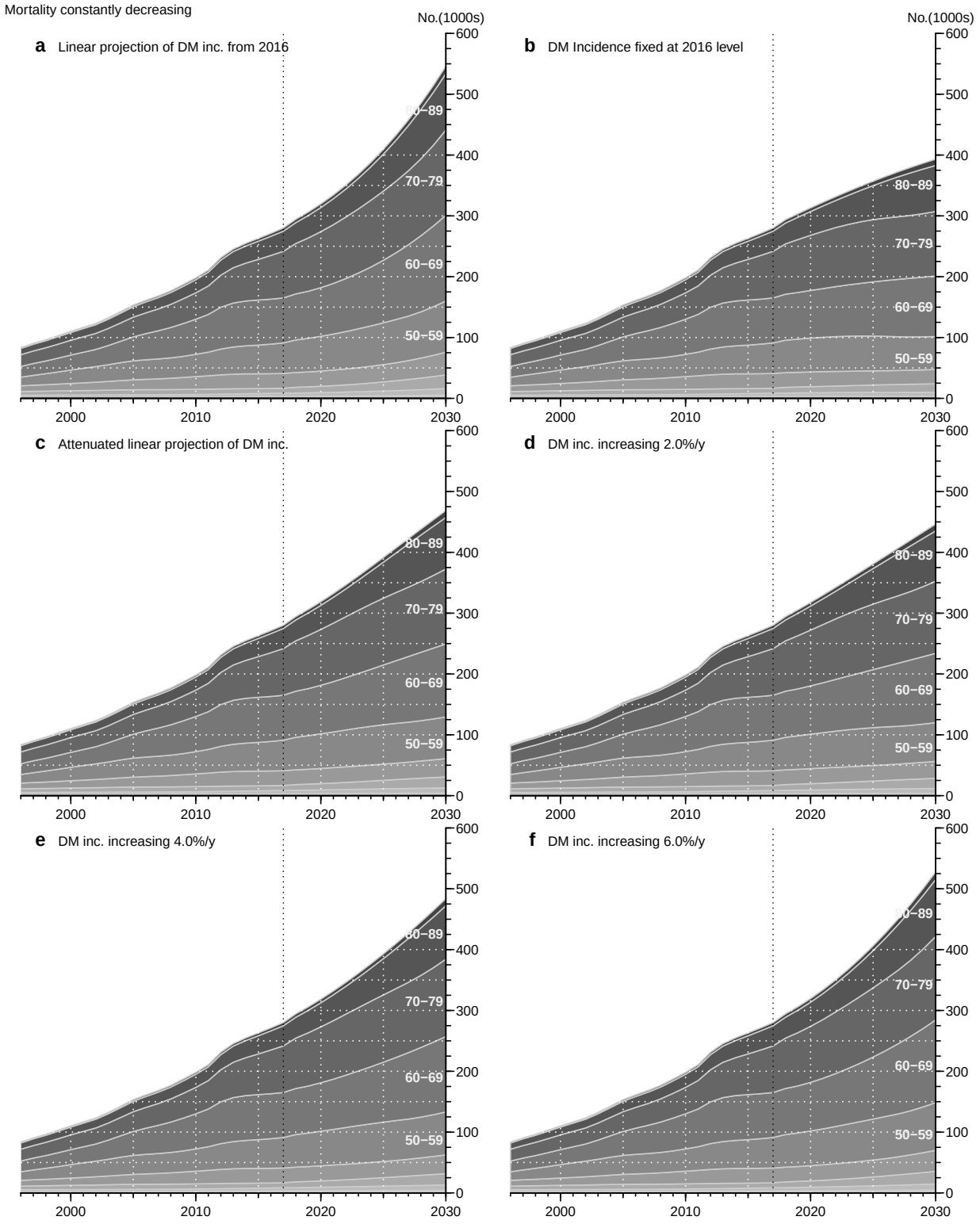

Figure ESM 10: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 with mortality rates predicted form the APC model. Numbers are combined for men and women, and subdivided by 10-year age-groups in different gray tones. The top right panel is the prediction on which we base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

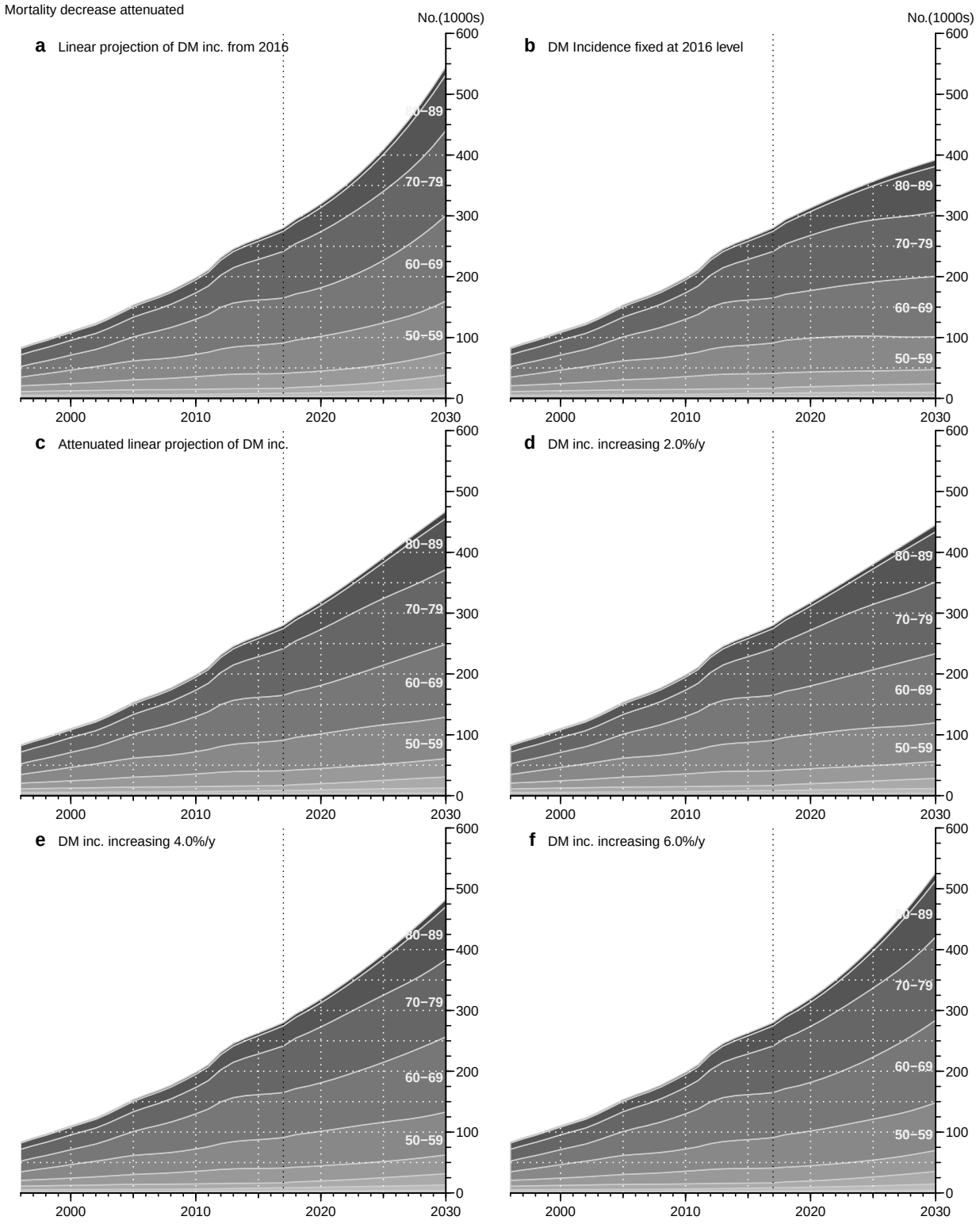

Figure ESM11: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 using attenuated mortality rates. Numbers are combined for men and women, and subdivided by 10-year age.groups in different gray tones. The middle right panel is the prediction on which we base our conclusions. The vertical dotted line indicates the end of data and start of prediction.*

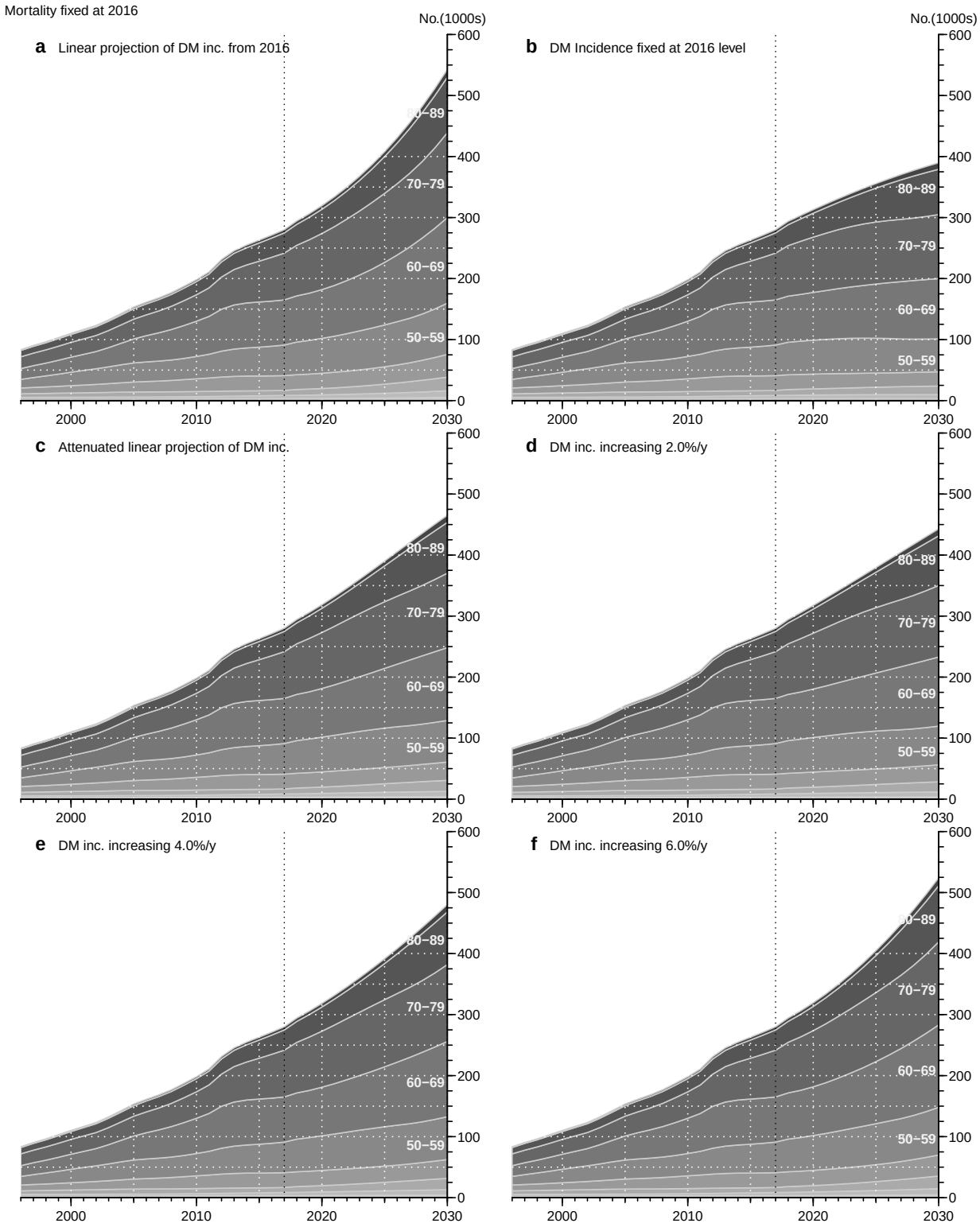

Figure ESM 12: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 using mortality rates fixed at the 2017 level. Numbers are combined for men and women, and subdivided by 10-year age.groups in different gray tones. The vertical dotted line indicates the end of data and start of prediction.*