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

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1 Material and methods

1.1 Probability model

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

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

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

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

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

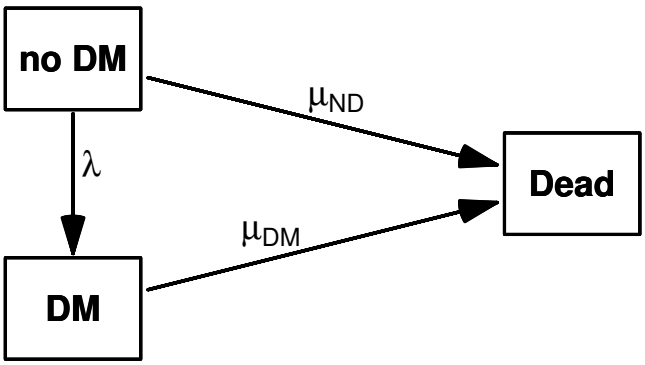

Figure ESM 1: *States and transition rates used: λ: Incidence rate, μ_{nD}: mortality rate in persons without diabetes, μ_{DM}: mortality rate in persons with diabetes. Prevalence of diabetes is the fraction in state "DM" relative to all in states "noDM" and "DM".*
Each rate is modeled separately for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

probabilities were used:

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

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

1.1.1 Projecting prevalences

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

1.2 Prevalence and rates 1996–2017

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

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

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

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

1.3 Demographic components

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

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

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

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

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

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

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

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

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

1.4 Projection of rates 2017–2040

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

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

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

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

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

1.5 Models for rate projection

1.5.1 Attenuation of predictions

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

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

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

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

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

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

1.5.2 Adding a drift to a prediction

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

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

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

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

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 )
```

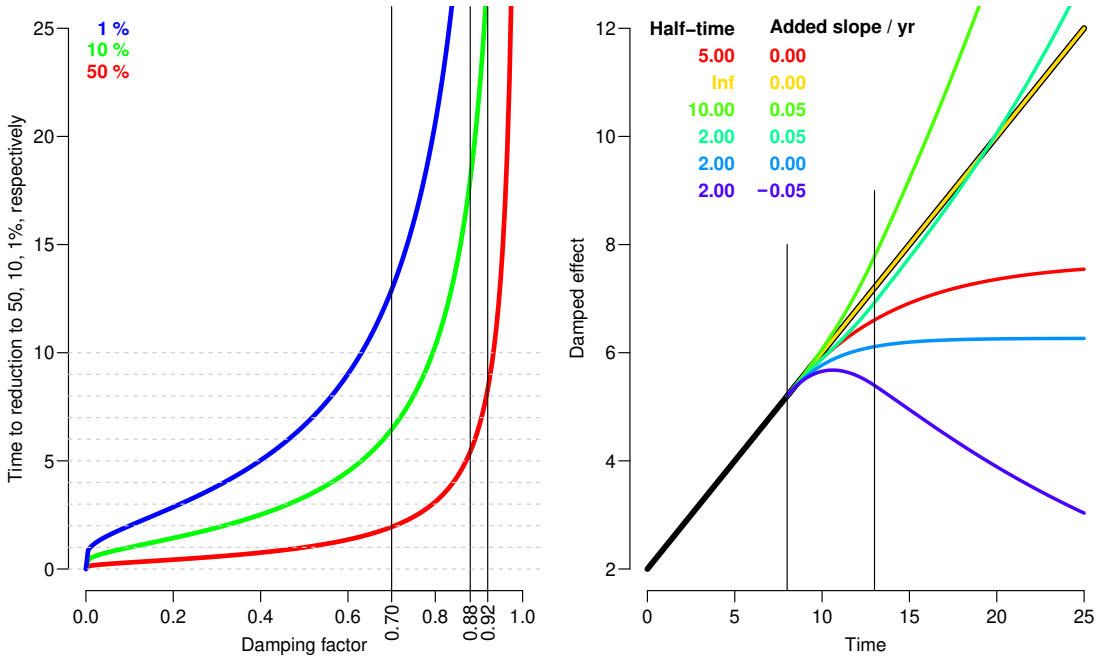

Figure ESM 2: *The left panel shows the time to reduction of the slope of a curve to 50, 10 and 1% of the original for different values of the damping factor. The right hand panel illustrates the* `damp` *function for attenuation of effects and addition of linear terms for various combinations of the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

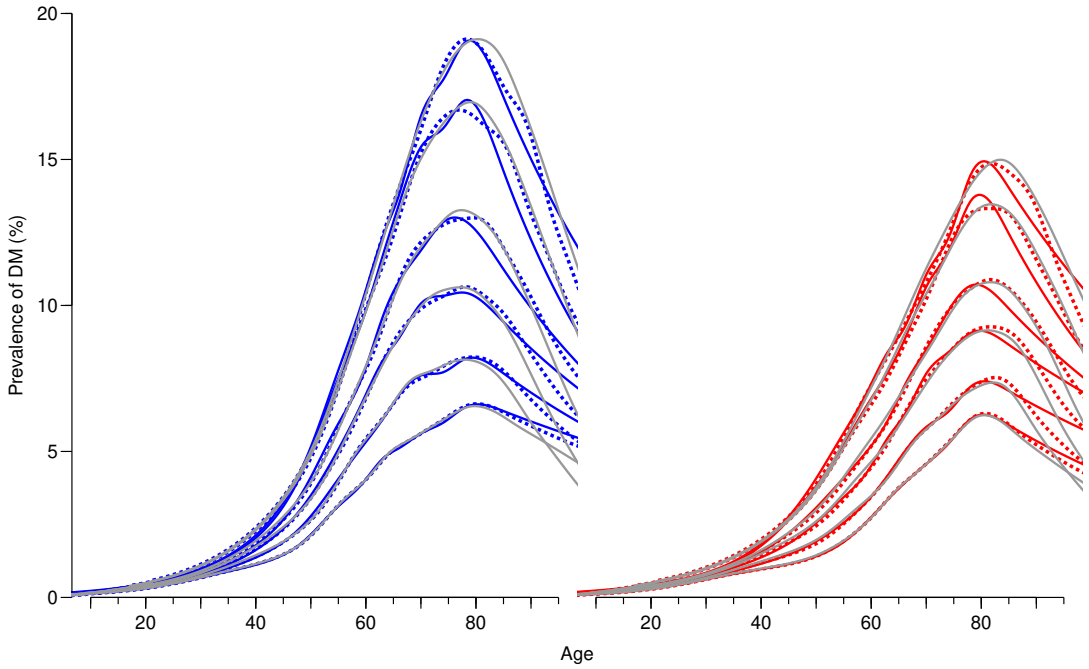

Figure ESM 3: *Observed (full lines) and predicted (broken lines) prevalence of DM in Denmark (from low to high) 1997, 2001,ldots,2017. The observed prevalences are smoothed using natural splines. The predicted prevalences are based on the prevalences as of 1995 and estimated rates from age-period-cohort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

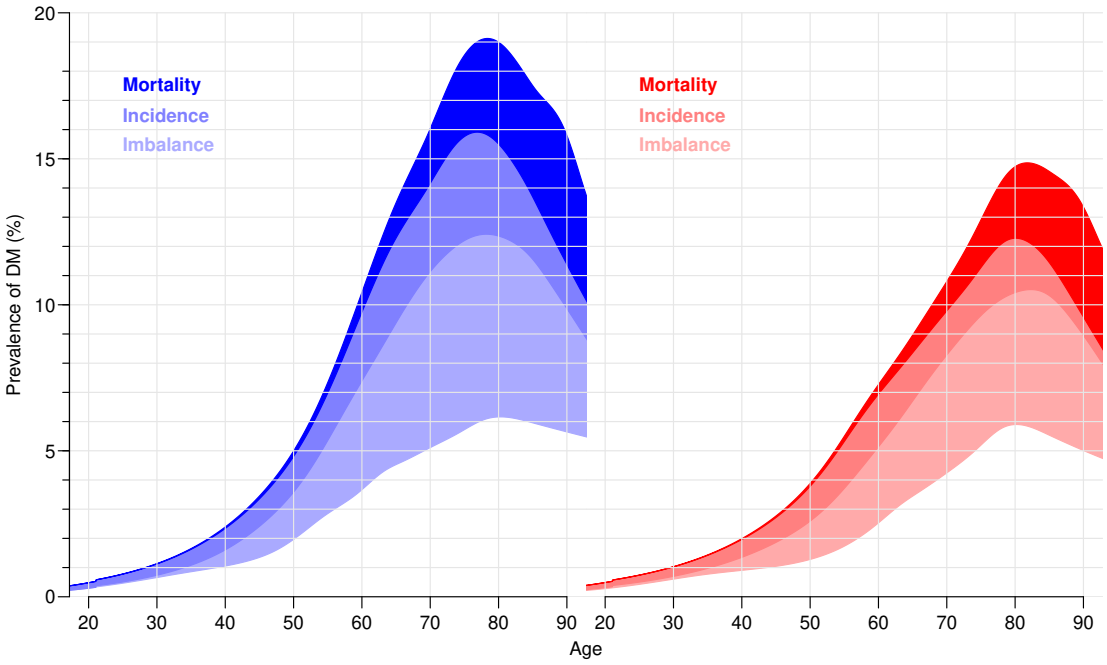

Figure ESM 4: *Age-specific prevalence as of 1 January 2017 subdivided by the components of the changes in diabetes prevalence in the period 1996–2016, based on prevalence in 1996 and models for incidence and mortality in the period. Men in blue, women in red. The white area at the bottom represents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

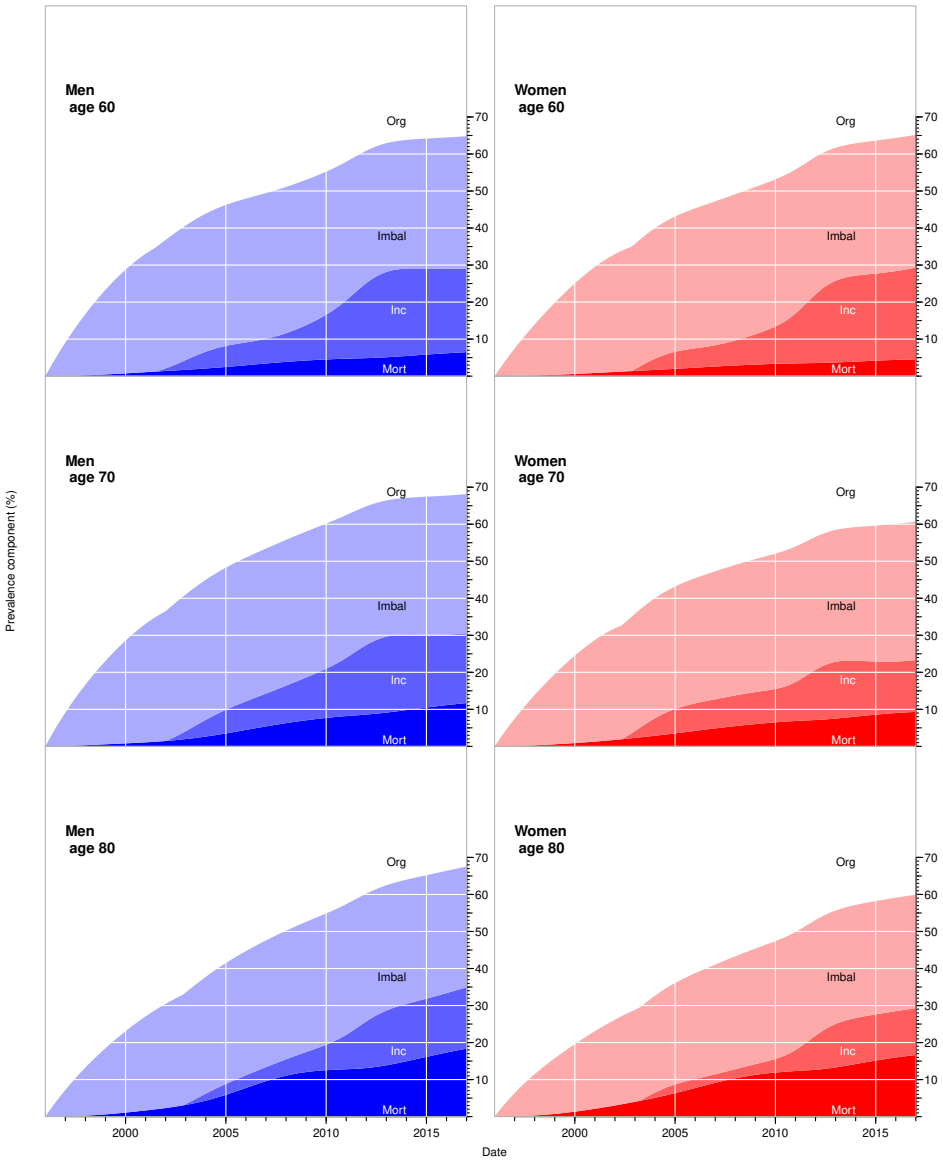

Figure ESM 5: *Fraction of the prevalent cases at different times attributable to a) declining mortality (bottom, full color), b) increasing incidence (middle, pale color) and c) incidence/mortality imbalance 1996 (top, weak color). The white areas above the curves correspond to the fraction of the cases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

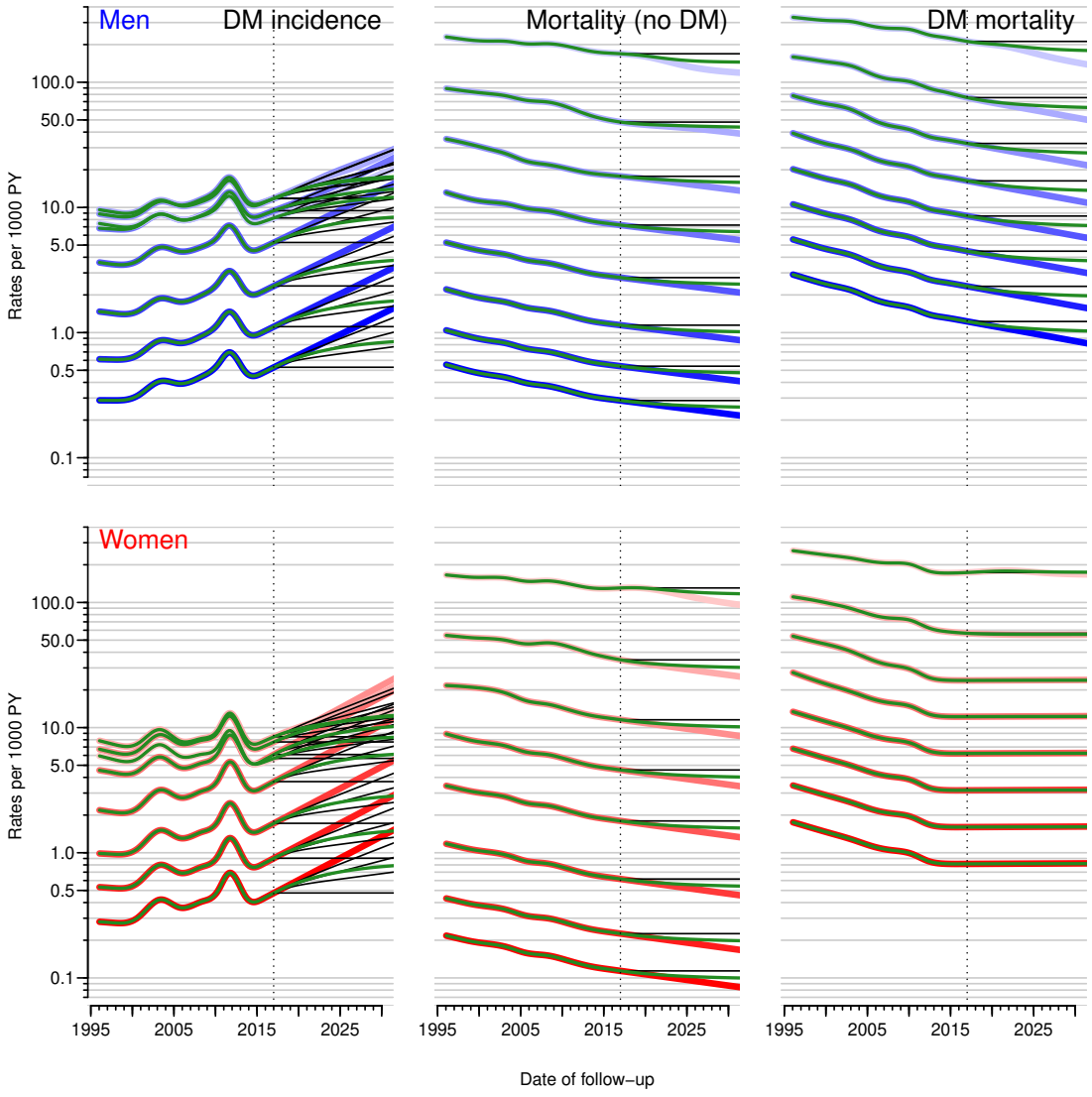

Figure ESM 6: *Observed and predicted incidence and mortality rates 1996–2030 for ages 20, 30,...,90. The naïve prediction based on natural spline models are shown in blue for men and red for women. The black predictions are rates fixed at the level of 2017-01-01. Green predictions are attenuated rates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

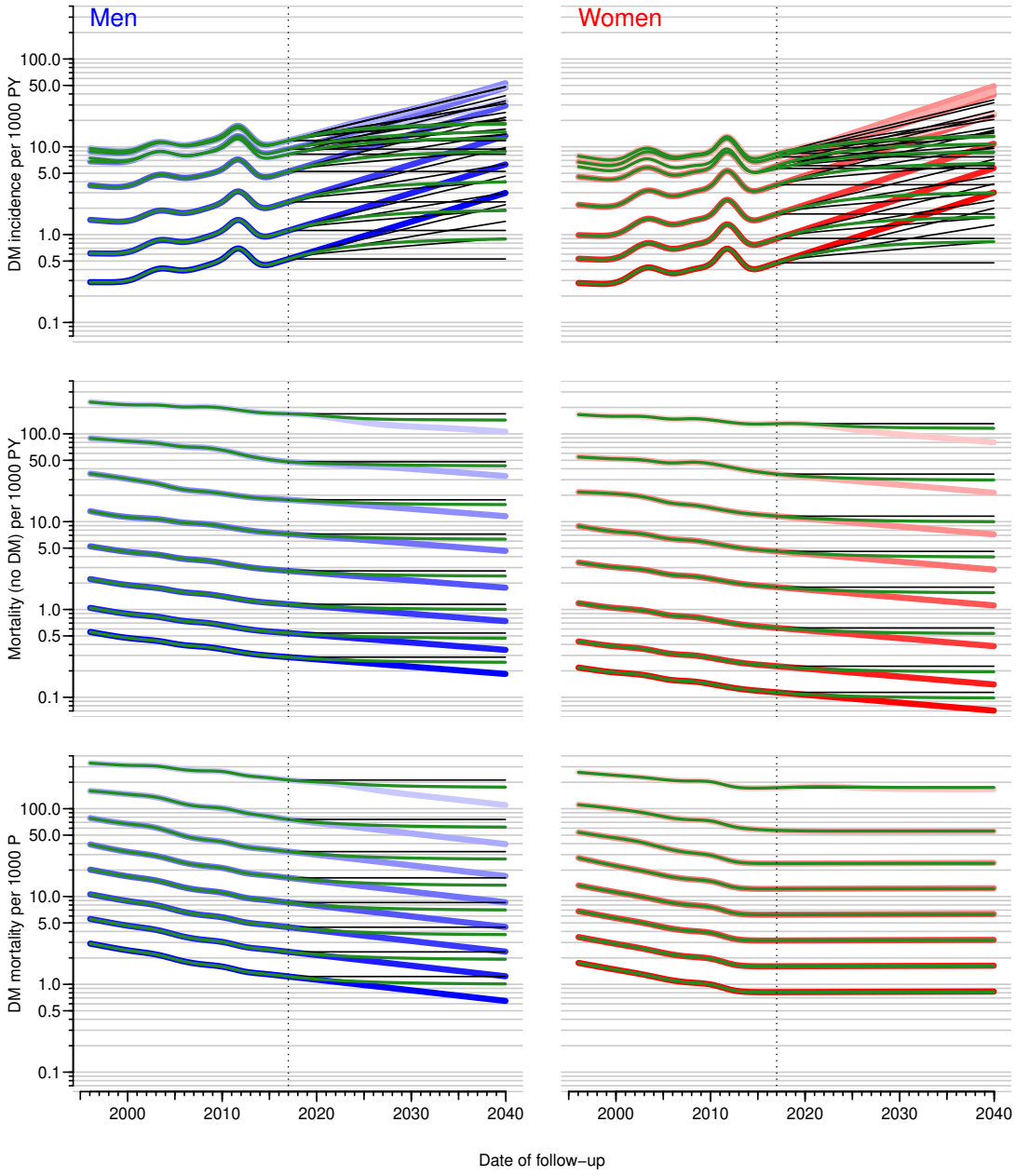

Figure ESM7: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2040 for ages 20, 30,. . . ,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

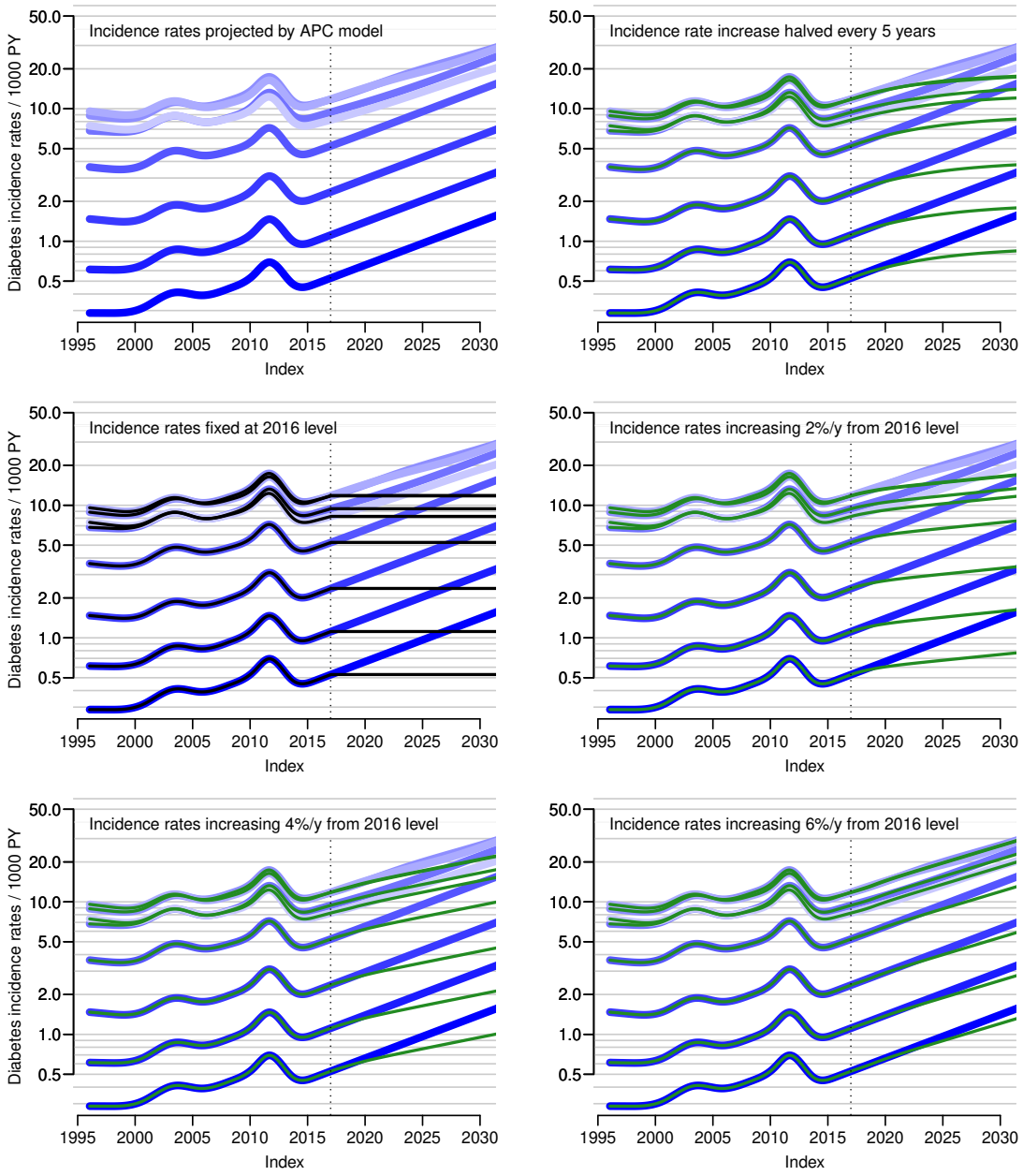

Figure ESM 8: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2030 for man at ages 20, 30,. . . ,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

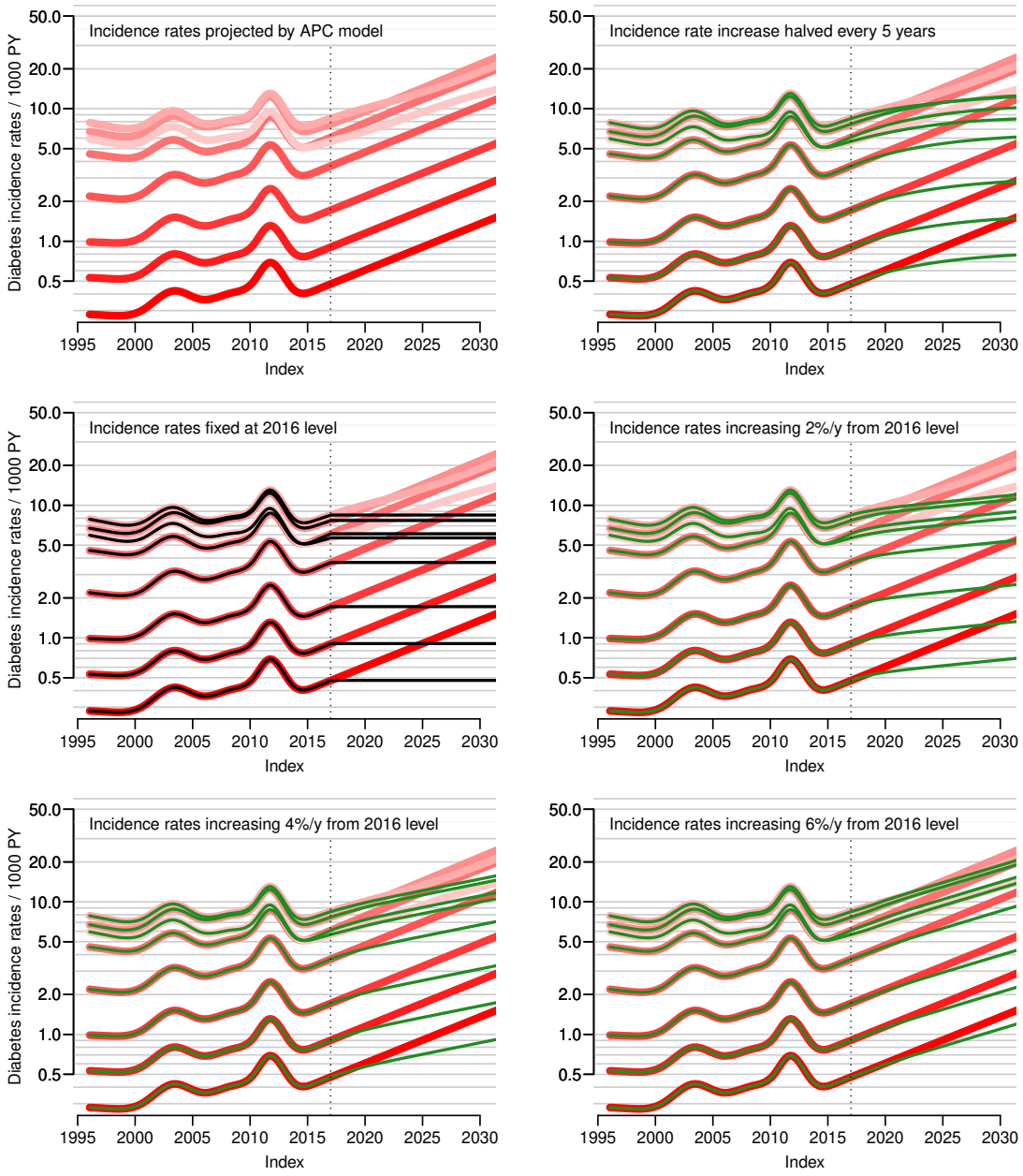

Figure ESM9: *Observed (till 2017) and predicted (from 2017) diabetes incidence rates 1996–2030 for women at ages 20, 30,...,90 (dark to bright colour). The vertical dotted line indicates the end of data and start of prediction.*

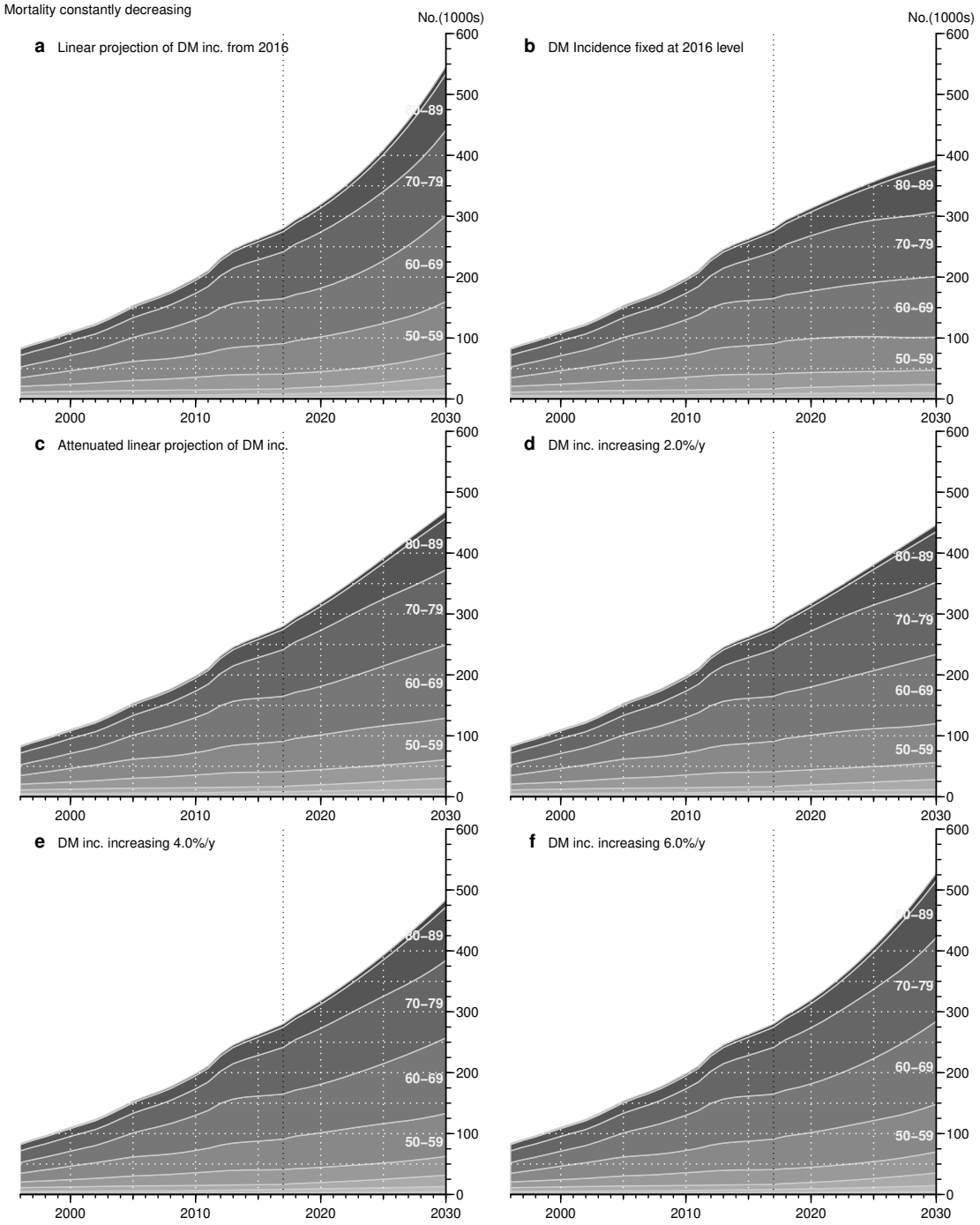

Figure ESM 10: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 with mortality rates predicted form the APC model. Numbers are combined for men and women, and subdivided by 10-year age-groups in different gray tones. The top right panel is the prediction on which we base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

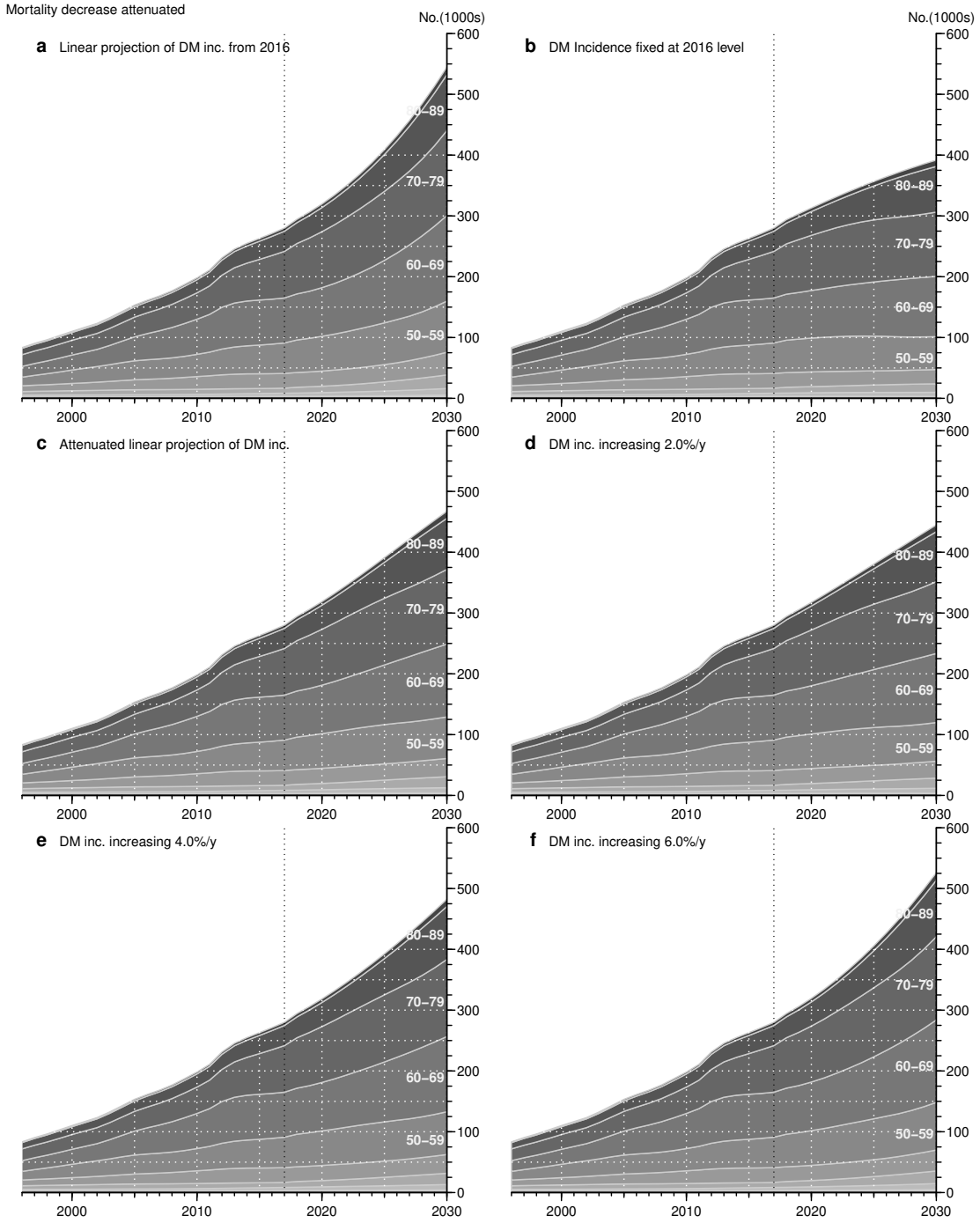

Figure ESM 11: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 using attenuated mortality rates. Numbers are combined for men and women, and subdivided by 10-year age.groups in different gray tones. The middle right panel is the prediction on which we base our conclusions. The vertical dotted line indicates the end of data and start of prediction.*

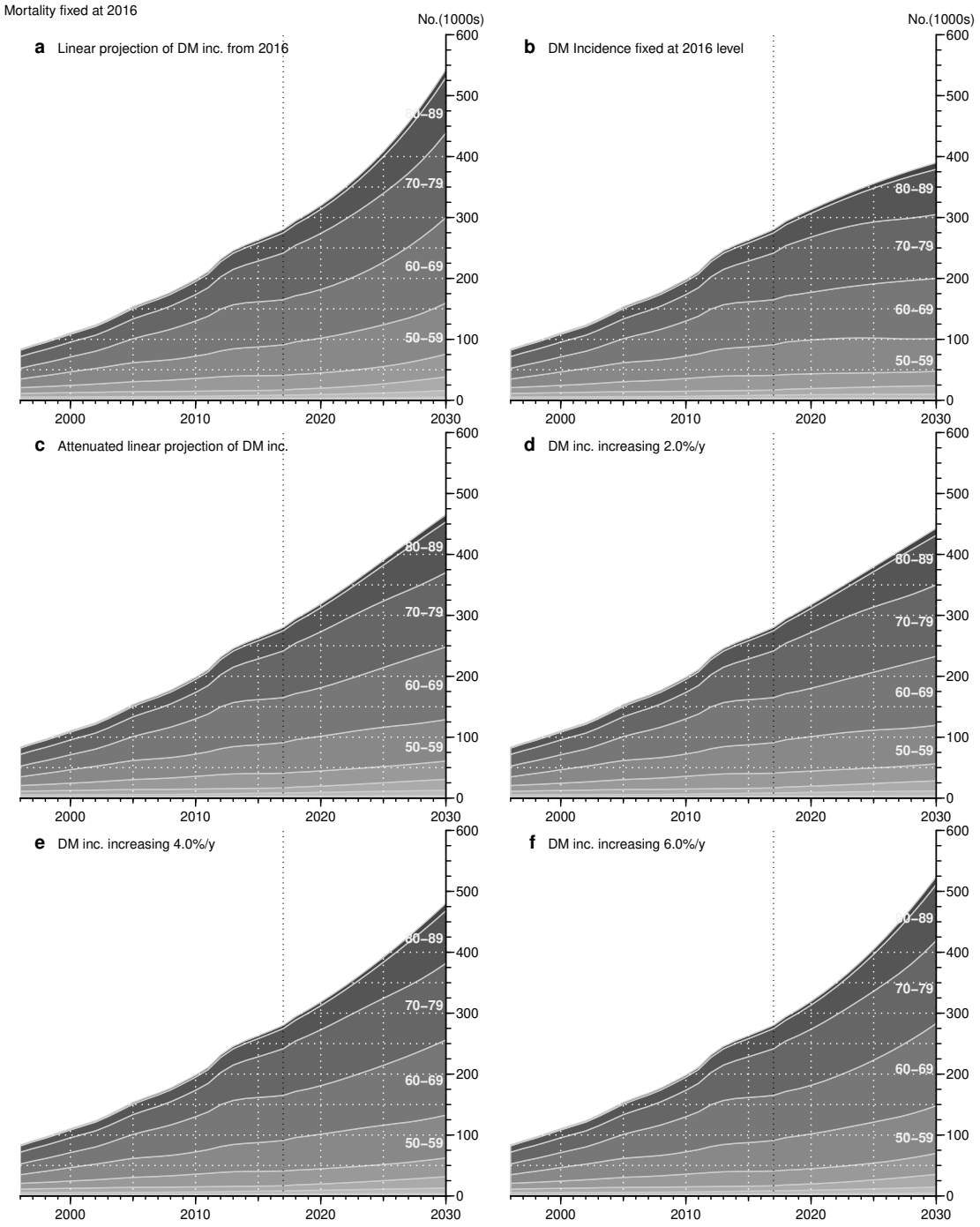

Figure ESM 12: *Observed (till 2017) and predicted (from 2017) no.of diabetes patients 1996–2030 using mortality rates fixed at the 2017 level. Numbers are combined for men and women, and subdivided by 10-year age.groups in different gray tones. The vertical dotted line indicates the end of data and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