Age- and time-dependent model of the prevalence of non-communicable diseases and application to dementia in Germany

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ABSTRACT

We derive a partial differential equation (PDE) that models the age-specific prevalence of a disease as a function of the incidence, remission and mortality rates. The main focus is on non-communicable diseases (NCDs), although the PDE is not restricted to NCDs. As an application of the PDE, the number of persons with dementia in Germany until the year 2050 is estimated based on German incidence data and official population projections. Uncertainty is treated by different scenarios about life expectancy, number of migrants, prevalence of the disease in migrants, and scenarios about the future incidence, and mortality of demented persons. Life expectancy and incidence of dementia have the strongest impact on the future number of persons with dementia. In nearly all scenarios, our estimated case numbers exceed former estimates. Furthermore, we use an example to show that the PDE method yields more accurate results than a common alternative approach.

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1. Introduction

Non-communicable diseases (NCDs) like cardiovascular disease, cancer, diabetes and dementia are severe health problems of the 21st century. All over the world, they already impose an enormous individual and societal burden that will even increase in the next decades (Marrero et al., 2012). Despite the importance of NCDs, mathematical models for the dynamics of NCDs are rarely examined. This is in contrast to infectious diseases with a variety of modeling approaches (e.g., Brauer et al. (2008), Brauer and Castillo-Chavez (2011), Diekmann and Heesterbeek (2000) and Keeling and Rohani (2008)). In this article we set up a new equation for describing the prevalence of NCDs. As an application, the equation is used to project the number of persons with dementia in Germany until 2050. Although there are estimates for Germany (Schulz and Doblhammer, 2012; Ziegler, 2010), the country with the most inhabitants in Europe, these estimates have methodological weaknesses. The article by Schulz and Doblhammer (2012) is based on scenarios about the prevalence, which neglects the fact that the prevalence is a result of a complex interplay of incidence and mortality rates of people with and without dementia. The estimates in Ziegler (2010) essentially have three drawbacks. First, the calculation relies on third-party software, which does not take into account that developing dementia and dying without dementia are competing risks (Putter et al., 2006). Thus, the numbers of Ziegler (2010) are likely to be inaccurate. Second, the estimates are outdated because the underlying official population projection has changed in the meantime. Third, the estimates do not take into account migration scenarios, which are part of the official population projections (Federal Statistical Office of Germany, 2009). Our calculation corrects for these weaknesses.

This article is organized as follows: In the next section we introduce the basic notation of the model and results from the literature. After this section, we generalize the equations allowing dependency on calendar time and migration. The central result of this article is an age-structured model of the prevalence of a disease based on a partial differential equation (PDE). As an application of the PDE, the official population projection is used to estimate the number of persons with dementia in Germany until 2050. Then, our method is compared to a common discrete time approach. Finally, the results are discussed.

2. Illness–death model

With a view to basic epidemiological parameters such as incidence, prevalence and mortality of a disease, it has been proven useful to consider simple illness–death models as shown in Fig. 1 (Keiding et al., 1990). Depending on the context, sometimes these are referred to as state models or compartment models. Here we consider three states: Normal or non-diseased with number of people denoted as $S$ (susceptible), the diseased state with number $C$ (cases) and the death state.

The transition rates between the states henceforth are denoted with the symbols as in Fig. 1: incidence $i$, remission $r$ and mortality rates $m_0$ and $m_1$. In general, the rates depend on calendar time.
and Lopez (1996) is:

\[ \text{The three states. A similar system to the one presented in Murray and Lopez, 1994, 1996). They used a system of ordinary differential equations (ODEs) to describe the transitions between the three states. A similar system to the one presented in Murray and Lopez (1996) is:} \]

\[
\begin{align*}
\frac{dS}{da} &= -\langle i + m_0 \rangle \cdot S + r \cdot C \\
\frac{dC}{da} &= \langle i \rangle \cdot S - (m_1 + r) \cdot C. 
\end{align*}
\]

By this system the changes in the numbers of the non-diseased and diseased persons aged \( a \) related to the rates as in Fig. 1. The age variable \( a \) describes the temporal progression. Let \( N(a) := S(a) + C(a) \) denote the total number of persons alive in the population at age \( a \). For \( a \geq 0 \) with \( N(a) > 0 \) define the age-

\[
\begin{align*}
p(a) &:= \frac{C(a)}{C(a) + S(a)}. 
\end{align*}
\]

Then, from Eq. (1) it follows that

\[
\begin{align*}
\frac{dN}{da} &= \frac{dS}{da} + \frac{dC}{da} \\
&= -m_0 \cdot S - m_1 \cdot C \\
&= -N \cdot \langle (1 - p) \cdot m_0 + p \cdot m_1 \rangle. 
\end{align*}
\]

The term \( m := \langle 1 - p \rangle \cdot m_0 + p \cdot m_1 \) is the overall mortality in the population. Hence, it holds that \( \frac{dN}{da} = -m \cdot N \), which is the defining equation of a stationary population (Preston and Coale, 1982). Although the model of a stationary population is widely used in demography, real populations rarely are stationary. Moreover, it would be better if Eq. (1) could be expressed in terms of the age-specific prevalence (2) instead of \( S \) and \( C \), which indeed can be achieved. In Brinks et al. (2013) it has been shown that system (1) can be transformed into the following one-dimensional ODE of Riccati type:

\[
\begin{align*}
\frac{dp}{da} &= (1 - p) \cdot (\langle i \rangle - p \cdot (m_1 - m_0)) - r \cdot p. 
\end{align*}
\]

3. Generalized equation of disease dynamics

In this section Eq. (3) is generalized. The rates \( i, r, m_0 \) and \( m_1 \) therefore depend on age \( a \) and calendar time \( t \). However, \( r \) and \( m_1 \) are assumed to be independent from the disease duration \( d \). As the population projections of the German Federal Statistical Office include scenarios about migration, we also include migration into the model. Let the numbers of the non-diseased \( S(t, a) \) and disease persons \( C(t, a) \) aged \( a \) at time \( t \) be non-negative and partially differentiable. Define \( N(t, a) := S(t, a) + C(t, a) \). Additionally, let \( \sigma(t, a) \) and \( \gamma(t, a) \) denote those proportions of \( N(t, a) \), such that \( \sigma(t, a) \cdot N(t, a) \) and \( \gamma(t, a) \cdot N(t, a) \) are the net migration rates of non-diseased and diseased persons aged \( a \) at time \( t \), respectively:

\[
\begin{align*}
\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \sigma &= \sigma \cdot (\langle S + C \rangle - \langle i + m_0 \rangle \cdot S + r \cdot C) \\
\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \gamma &= \gamma \cdot (\langle S + C \rangle + i \cdot S - (m_1 + r) \cdot C). 
\end{align*}
\]

After introducing the age-specific prevalence \( p(t, a) \),

\[
p(t, a) := \frac{C(t, a)}{C(t, a) + S(t, a)},
\]

for \( (t, a) \in D := \{ (t, a) \in [0, \infty) \} \cdot C(t, a) > 0 \), \( S(t, a) > 0 \), patients \( C(t, a) + S(t, a) > 0 \) the system (4) can be transformed into an equation similar to (3):

\[
\begin{align*}
\frac{\partial}{\partial t} + \frac{\partial}{\partial a} p &= (1 - p) \cdot \langle i - p(m_1 - m_0) \rangle - p \cdot r + \mu,
\end{align*}
\]

where \( \mu := \gamma (1 - p) - p r \) describes the impact of migration.

Obviously, if the incidence and mortality rates do not depend on the calendar time \( t \) then Eq. (5) with \( \mu = 0 \) implies Eq. (3). Hence, Eq. (5) is a generalization of Eq. (3).

The migration term \( \mu \) will be analyzed further now. The rates \( \sigma \) and \( \gamma \) are composed of persons entering (immigration) and leaving the population (emigration). Thus, we split \( \sigma \) and \( \gamma \) accordingly:

\[
\begin{align*}
\sigma &= \sigma_+ - \sigma_- \\
\gamma &= \gamma_+ - \gamma_-, 
\end{align*}
\]

where the subscripts refer to immigration (+) and emigration (−). Since \( \sigma_+ / \gamma_+ \geq 0 \), the rates \( \varphi_+ := \gamma_+ + \sigma_+ \) and \( \varphi_- := \gamma_- + \sigma_- \) are non-negative. For \( \varphi_+(t, a) > 0 \) define \( \varphi^+_m(t, a) := \varphi_+(t, a) / \varphi_-(t, a) \) the prevalence of the disease in the immigrants and for \( \varphi_-(t, a) > 0 \) define \( \varphi^-_m(t, a) := \varphi_-(t, a) / \varphi_+(t, a) \) the prevalence in the emigrants. The superscript \( m \) indicates that the prevalence refers to the migrants.

With these notations, it holds that

\[
\begin{align*}
\varphi_+(t, a) \cdot \left( \frac{\varphi^+_m(t, a) - \varphi_-(t, a)}{\varphi^-_m(t, a)} \right), \\
&\text{for } \varphi_-(t, a) = 0, \varphi_+(t, a) > 0; \\
\mu(t, a) &= \varphi_+(t, a) \cdot \left( \frac{\varphi^+_m(t, a) - \varphi_-(t, a)}{\varphi^-_m(t, a)} \right), \\
&\text{for } \varphi_-(t, a) > 0, \varphi_+(t, a) = 0; \\
&\text{for } \varphi_-(t, a) = \varphi_+(t, a) = 0. 
\end{align*}
\]

With the assumption that the prevalence of the disease in those aged \( a \) at time \( t \) who emigrate is the same as in those who emigrate, say \( \varphi^+_m(t, a) \), it holds that

\[
\mu(t, a) = \varphi \cdot (\varphi^+_m(t, a) - \varphi_-(t, a)) \cdot .
\]

From this, we get the obvious fact that if the disease prevalence \( \varphi^+_m \) in the migrants is the same as that of the residents, \( \varphi^+_m \equiv \varphi \), the change in prevalence \( \frac{d}{dt} \varphi \) does not depend on migration.
versa: we choose to model the mortality rates with the assumptions $L_0$, $L_1$, and $L_2$ of the Federal Statistical Office. Thus, we assume that the incidence $i$ of dementia is independent from calendar time $t$. Second, we change the incidence according to two scenarios: (A) From 2015 to 2025 the incidence rate of all age groups gradually decreases by 20% and remains at that level until 2050; (B) From 2015 to 2025 the incidence rate of all age groups gradually increases by 20% and remains at that level until 2050.

Although there are signs of the incidence of dementia decreasing with $t$ in Sweden (Quj et al., 2013) and The Netherlands (Schrijvers et al., 2012), the observed trends are not significant. The Dutch study observes a decrease of 25% over 10 years, which is similar to our scenario (A).

The overall mortality $m = (1 - p) \cdot m_0 + p \cdot m_1$ is prescribed by the assumptions $L_0$, $L_1$, and $L_2$ of the Federal Statistical Office. Thus, we choose to model the mortality rates $m_0$ and $m_1$ in terms of the relative mortality $R$ of persons with dementia compared to those without $R(t, a) = m(t, a)/m(t, a)$. We take the values of an epidemiological study from the UK (Rait et al., 2010). Compared to other surveys about mortality of persons with dementia, the study of Rait et al. examines a comparable population (Brodaty et al., 2013). Unfortunately, Rait et al. do not report mortality stratified by sex.

In two additional scenarios we calculate the impact of gradually decreasing $R$ in all age-groups by 10% and 20% from 2015 to 2025. From 2025 the relative mortality is assumed to remain at the decreased level until 2050.

4.3. Calculation

The solution of the PDE (5) is obtained by the methods of characteristics (Polyanin et al., 2002). As initial conditions, the age-specific prevalence of dementia in Germany in 2002 and the assumption that the prevalence of dementia is zero at ages below 60, have been used (Bickel, 2000; Ziegler and Dobilhammer, 2009). After solving the PDE for $p(t, a)$, the projected age distribution $N(t, a)$ (population pyramid) of the Federal Statistical Office is used to calculate the number of persons with dementia aged $a$ at $t$ by $C(t, a) = N(t, a) \cdot p(t, a)$. The total number of cases at $t$ is obtained by summation over $a$. All those persons aged 59 in year $t - 1$ newly enter the model in year $t$ by $N(t, 60)$. Since there are gender differences in the age distribution, in mortality and in the incidence rates, all calculations have been done for males and females separately.

4.4. Results

Fig. 2 shows the number of male (left) and female (right) persons with dementia over calendar time in the different scenarios of the Federal Statistical Office. In this calculation the prevalence of the migrants is assumed to be the same as in the residents ($p^{(m)}_t = p^{(m)} = p$). From Fig. 2 it can be seen that life expectancy ($L_0$, $L_1$, $L_2$) has a stronger impact on the case numbers than the migration scenarios. Table 2 shows the number of persons with dementia in Germany depending on the different scenarios of the Federal Statistical Office. The difference between the assumptions about the net migration ($W_1$, $W_2$) is almost negligible.

To study the impact of the prevalence in migrants, Figs. 3 and 4 show the most extreme cases ($p^{(m)}_t = (0, 0)$ and ($p^{(m)}_t = (1, 0)$ for the scenarios $L_0W_1$, $L_1W_2$, and $L_2W_2$. The upper and lower dashed lines are the $(p^{(m)}_t, p^{(m)}_t) = (1, 0)$ and $(p^{(m)}_t, p^{(m)}_t) = (0, 1)$ scenarios, respectively. The solid lines are the associated base cases $p^{(m)}_t = p$. The case numbers of all the other combinations of $p^{(m)}_t \in [0, 1)$ are located in the narrow corridor between these extreme cases.

Finally, the results of the epidemiological scenarios are reported. Figs. 5 and 6 show the impact of the changes in incidence and mortality (dashed lines) compared to no change (solid lines).

Table 3 shows the case numbers in the epidemiological scenarios. The scenarios without changes in the incidence or mortality rates is presented for better comparison (cf. Table 2).
Fig. 2. Number of persons with dementia until 2050 in the different scenarios: males (left) and females (right). See Table 1 for the assumptions in the scenarios.

Fig. 3. Number of male persons with dementia until 2050 in the different scenarios (L0W1, L1W2, L2W2) and the most extreme \( p^{(i)}_{\delta/} \) combinations. See Table 1 for the assumptions in the scenarios.

Fig. 4. Number of female persons with dementia until 2050 in the different scenarios (L0W1, L1W2, L2W2) and the most extreme \( p^{(i)}_{\delta/} \) combinations. See Table 1 for the assumptions in the scenarios.

Table 3

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2030</td>
<td>2050</td>
<td>2010</td>
</tr>
<tr>
<td>L0W1</td>
<td>480</td>
<td>767</td>
<td>1016</td>
<td>1054</td>
</tr>
<tr>
<td></td>
<td>( i - 20% )</td>
<td>480</td>
<td>631</td>
<td>823</td>
</tr>
<tr>
<td></td>
<td>( i + 20% )</td>
<td>480</td>
<td>898</td>
<td>1202</td>
</tr>
<tr>
<td></td>
<td>( R - 10% )</td>
<td>480</td>
<td>801</td>
<td>1114</td>
</tr>
<tr>
<td></td>
<td>( R - 20% )</td>
<td>480</td>
<td>839</td>
<td>1202</td>
</tr>
<tr>
<td>L1W2</td>
<td>483</td>
<td>876</td>
<td>1353</td>
<td>1072</td>
</tr>
<tr>
<td></td>
<td>( i - 20% )</td>
<td>483</td>
<td>724</td>
<td>1103</td>
</tr>
<tr>
<td></td>
<td>( i + 20% )</td>
<td>483</td>
<td>1023</td>
<td>1593</td>
</tr>
<tr>
<td></td>
<td>( R - 10% )</td>
<td>483</td>
<td>912</td>
<td>1404</td>
</tr>
<tr>
<td></td>
<td>( R - 20% )</td>
<td>483</td>
<td>950</td>
<td>1460</td>
</tr>
<tr>
<td>L2W2</td>
<td>485</td>
<td>987</td>
<td>1700</td>
<td>1078</td>
</tr>
<tr>
<td></td>
<td>( i - 20% )</td>
<td>485</td>
<td>818</td>
<td>1391</td>
</tr>
<tr>
<td></td>
<td>( i + 20% )</td>
<td>485</td>
<td>1149</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>( R - 10% )</td>
<td>485</td>
<td>1023</td>
<td>1752</td>
</tr>
<tr>
<td></td>
<td>( R - 20% )</td>
<td>485</td>
<td>1063</td>
<td>1809</td>
</tr>
</tbody>
</table>

L0, L1, L2: life expectancy in males: 82.0, 85.0, 87.7; in females: 87.2, 89.2, 91.2. W1, W2: net migration 100,000 or 200,000 per year.

5. Comparison with a method using discrete time increments

In this section we use an example to show that the application of Eqs. (3) and (5) leads to more accurate results than methods with discrete time steps, which are widely used, for example, in demography.

For simplicity we assume that there is no migration and no remission. Furthermore, let the rates just depend on the age \( a \). Thus, we are in the situation described in Eq. (1) with \( r = 0 \). The analogon of Eq. (1) expressed in terms of discrete time increments \( \delta > 0 \) is

\[
S(a + \delta) = S(a) - (i(a) + m_0(a)) \cdot S(a) \cdot \delta \\
C(a + \delta) = C(a) + i(a) \cdot S(a) \cdot \delta - m_1(a) \cdot C(a) \cdot \delta.
\]  

(6)

Formulations of this kind may be found in demographic multistate models (see, e.g., Preston et al. (2001)). Typical choices for the time increments are \( \delta = 1 \) or \( \delta = 5 \) (years).

For our example set \( i(a) = 6.5 \cdot 10^{-4} \cdot (a - 60) \), \( m_0(a) = \exp(-10.5 + 0.095 \cdot a) \), and \( m_1(a) = m_0(a) \), where the notation \( x_+ \) means the positive part of \( x \), i.e., \( x_+ = \max(x, 0) \).
Fig. 5. Number of persons with dementia until 2050 in the different demographic scenarios (L0W1, L1W2, L2W2) and the hypothetical changes in the incidence: males (left) and females (right). See Table 1 for the assumptions in the scenarios.

Fig. 6. Number of persons with dementia until 2050 in the different demographic scenarios and the hypothetical changes in the mortality: males (left) and females (right). See Table 1 for the assumptions in the scenarios.

Due to $m_0 = m_1$, the ODE (3) becomes linear, and the solution $p(a)$ for $a \geq 60$ can be expressed as

$$p(a) = 1 - \exp \left( -\int_{60}^{a} i(\tau) \, d\tau \right) = 1 - \exp \left( -3.25 \cdot 10^{-4} \cdot (a - 60)^2 \right).$$

(7)

Having the analytical solution at hand, we can compare (a) the numerical solution of Eq. (3) and (b) the discrete time approach with the prevalence in Eq. (7). To calculate the age-specific prevalence by the ODE, we chose the Runge–Kutta method of fourth order with constant step size of 1 year (Dahlquist and Björck, 1974). In the case of the discrete time method, we start with $S(60) = 1$ and $C(60) = 0$ and successively apply Eq. (6) for different choices of $\delta$ until we reach $a = 90$. Then, the values $p(a) = \frac{C(a)}{S(a) + C(a)}$, $a = 60, \ldots, 90$, are calculated.

Fig. 7 shows the results of the different approaches. The analytical solution given by Eq. (7) and the numerical solution of the ODE (3) (black line) are graphically indistinguishable. Furthermore, we observe that the difference between the analytical solution and the discrete time method increases as the time increments $\delta$ increase.

In a quantitative comparison at $a = 90$, we see that $\delta = 1, 2.5, 5$ lead to relative differences of 10.2%, 31.1% and 113% compared to the exact prevalence given by Eq. (7). The relative difference between the numerical solution of the ODE and the exact solution at $a = 90$ is less than $10^{-8}$. Hence, we may conclude that numerically solving Eq. (3) is superior in terms of accuracy to any of the discrete time approaches.
6. Discussion

In this work we developed a new equation linking the incidence, remission, and mortality rates with the prevalence of a chronic disease. In contrast to former works, the assumptions of stationary populations, independence from calendar time and zero net migration have been released. The new equation has a wide range of applicability in epidemiological, health care and health economic contexts. For example, the impact of primary prevention (i.e. lowering the incidence by a certain amount) on the prevalence can be calculated. This can be valuable, when one has to choose from several prevention strategies. Moreover, given the mortality rates, the equation allows the derivation of the incidence from a series of prevalence data in cases when cohort studies for surveying the incidence are not accessible. Since cohort studies mostly are difficult and expensive to conduct, this is often the case, especially in the developing countries. In the article Brinks et al. (2013) applications of Eq. (5) in the case of the incidence i being independent from calendar time t has been proven to yield accurate results in validation tasks.

As an application of the equation, we projected the numbers of persons with dementia in Germany until 2050. Since the prevalence of dementia in immigrants and emigrants is not known, we studied both extreme cases (all immigrants and no emigrants are diseased and vice versa). It turned out that the impact of migration is small compared to the overall trend of increasing numbers of persons with dementia. This holds true for both, the assumptions about the net migration (W1, W2) rates of the German Federal Statistical Office (Fig. 2), and the scenarios about the prevalence of dementia in migrants (Figs. 3 and 4). The reason for this small impact lies in the relatively low numbers of migrants to and from Germany. For example, in the life expectancy scenarios L1, the total numbers of persons aged 60+ in 2050 are 28.9 million and 29.6 million in the W1 and W2 migration scenarios, respectively. This is a difference of about 2.4%. In the L2 scenario, the corresponding numbers are 30.8 and 31.5 million, a difference of 2.3%. Although the impact is small in our application, in other situations this may be different. The resident population might be smaller or migration might take place on a larger magnitude. Our new equation is applicable in these settings as well.

Compared to the migration scenarios, the impact of the life expectancy scenarios (L0, L1, L2) of the official population forecast is considerably larger. In 2050, the estimated numbers in the scenarios with the lowest (L0) and greatest life expectancy (L2) differ by a factor of about 1.7 in males and 1.4 in females. Thus, uncertainty introduced by the life expectancy has a tremendous influence on the future case numbers. One reason is that life expectancy has a big impact on the future number of persons aged 60+. For example, for the migration scenario W1, in 2050 there are 26.8, 28.9 and 30.8 million persons aged 60+ in L0, L1 and L2, respectively. Compared to L0, this is a plus of 7.8% and 14.5% for L1 and L2.

The Federal Statistical Office assumes that scenario L1 is the most probable (Federal Statistical Office of Germany, 2009). In this scenario, the number of persons with dementia increases from about 1.5 million in 2010 to more than 3.6 million in 2050. The enormous increase of the number of persons with dementia for the next decades has been predicted by others as well. About a decade ago, Bickel forecasted about 2.05 million cases in 2050 (Bickel, 2001), and a recent article estimates up to 3 million persons with dementia in Germany in 2050 (Schulz and Dobzheimer, 2012). It has to be noted, that all our estimates involving the official life expectancy scenarios L1 and L2 reach or even exceed the number of 3 million demented persons in 2050. This holds also true for the scenario with the decreased incidence. Hence, our calculation yields exceptionally high case numbers. However, the former prognoses are based on applying the past prevalence to the future age distribution. They do not involve a model about the prevalence based on the interplay between the incidence and the mortalities of the diseased and non-diseased persons.

If we look for the reasons for the trend and the number of about 3.6 million diseased persons in 2050 predicted here, we find two factors: First, the number of males and females aged 60+ increases from 10.0 and 12.5 million in 2010 to 13.8 and 15.8 million in 2050, respectively (Federal Statistical Office of Germany, 2009). This is a plus of 3.8 million (~40%) in males and 3.3 million (~30%) in females. Second, if we look at the prevalence of dementia, we may notice an increase from 2010 to 2050 in both sexes. In 2010 the prevalence in the age-group 60+ is 4.8% and 8.5% in men and women, respectively. These numbers change to 10.0% and 14.9%. Since the incidence rate and the relative mortality in Eq. (5) do not change with calendar time, the increase is caused by the trend in the overall mortality.

It is unlikely that the incidence and the relative mortality will remain unchanged for the next decades. Since little is known about the causes of dementia, we examined two scenarios about the incidence rate. Compared to all other factors studied in this work, changes in the incidence have the strongest impact. On the one hand, the predicted number of 3.6 million persons with dementia in 2050 in the scenario L1W2 lowers to 3.0 million in the associated reduced incidence scenario. On the other hand, in the corresponding increased incidence scenario, the number of patients with dementia reaches about 4.3 million.

Due to better care of patients with dementia, the relative mortality probably will decrease more strongly than the overall mortality. A similar effect has been observed in diabetes (Carstensen et al., 2008). As is intuitively expected, in the two scenarios with decreasing relative mortality the numbers of cases increase. In the L1W2 the number of cases in 2050 rise to 3.7 and 3.9 million if the relative mortality is reduced by 10% and 20%, respectively.

This work has essentially four limitations. First, Eq. (5) needs the remission rate r and mortality rate m d of the diseased to be independent from the duration d of the disease. In real diseases independence from duration is only an approximation. For many infectious diseases, immune response is dependent on the time since onset of the disease. In NCDs the duration since onset of the disease plays a big role as well. Rait et al. found that the relative mortality (averaged over all patients) in the first year after diagnosis of dementia is 3.76, in the subsequent years only 2.4–2.6 (Rait et al., 2010). Keiding sketches a theoretical way of considering this kind of duration dependency (Keiding, 1991). However, then the mortality m d(t, a, d) as function of the covariates t, a and d has to be known in explicit terms, which to our best knowledge is not yet the case for dementia (see also Brodaty et al. (2013)). Due to the importance of dementia, further research is needed in that respect.

Second, although the new equation is not limited to the case μi ≥ 0, in practical applications information about the health of immigrants and emigrants is seldom obtainable. However, in the dementia example, the impact of migration on the estimated overall number of persons with dementia is weak. The reason lies in the fact that migration is low in those age classes when dementia is relevant.

Third, Eq. (5) only considers prevalence in migrants at the moment of emigration or immigration. Of course, large scale immigration is likely to change the incidence of the disease in the population, because immigrants’ health adapts to the new environment. There are examples where immigrants from the developing countries increase incidence of diabetes and related complications when adopting westernized lifestyle (Misra and Ganda, 2007). The opposite may also be true. In Canada, for example, immigrants continue to have a lower relative risk of chronic conditions compared to the native-born, even many years after immigration (McDonald and Kennedy, 2003).
The fourth limitation lies in the general problems in making predictions. While the time trend in the overall mortality may be foreseeable (by extrapolating the trend of the past), trends in the incidence of and mortality from dementia are not known. A change in both directions seems possible. The incidence may increase due to higher exposure to risk factors, it may decrease due to medical progress or healthier life-style. However, there are hints that the age-specific incidence is relatively stable, even across countries (Qiu et al., 2009). The situation may change, if a breakthrough in medication can be achieved. In animal models, progress in making dementia partly curable has been reported recently (Cramer et al., 2012). A discussion of how likely and when those achievements can be transferred to humans is beyond the scope of this article.

With respect to the mortality of the diseases, changes may occur with medical progress and quality of care. In other NCDs, for example in diabetes (Carstensen et al., 2008), the relative mortality decreases with calendar time, which reflects progress in medical care. Quality of care is affected by several factors, e.g., funding of the health care system or shortage in caregivers. Both factors are hardly foreseeable.

By comparing the results of our method with another approach using discrete time increments, we have seen that, depending on the size of the increments, considerable deviations from the exact solution may occur. Although some readers might regard the on the size of the increments, considerable deviations from the exact solution may occur. Although some readers might regard the

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## Supplementary data

Supplementary material related to this article can be found online at [http://dx.doi.org/10.1016/j.tpb.2013.11.006](http://dx.doi.org/10.1016/j.tpb.2013.11.006)

## References


