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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.*

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

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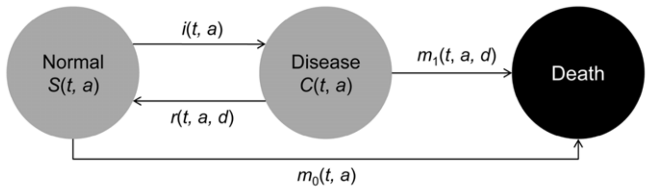

Fig. 1. Illness–death model.

t, age a and sometimes also on the duration d of the disease. For many diseases, age is a risk factor, which means that the rates depend on a. In addition, we include a dependence on the calendar time t to account for the progress in hygiene and medical care. For further references to compartment models, see for example Keiding (1991) or the text books (Kalbfleisch and Prentice, 2002; Aalen et al., 2008).

Murray and Lopez have considered a compartment model with rates being independent from calendar time t and duration d (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:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}a} &= -(i+m_0)\cdot S + r\cdot C \\ \frac{\mathrm{d}C}{\mathrm{d}a} &= i\cdot S - (m_1 + r)\cdot C. \end{aligned} \tag{1}$$

By this system the changes in the numbers of the non-diseased and diseased persons aged a are related to the rates as in Fig. 1. *The age variable a describes the temporal progression.* It can be shown that Eq. (1) implies the population being stationary. 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-specific prevalence

$$p(a) := \frac{C(a)}{C(a)+S(a)}. \tag{2}$$

Then, from Eq. (1) it follows that

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}a} &= \frac{\mathrm{d}S}{\mathrm{d}a} + \frac{\mathrm{d}C}{\mathrm{d}a} \\ &= -m_0\cdot S - m_1\cdot C \\ &= -N\cdot\left[(1-p)\cdot m_0 + p\cdot m_1\right]. \end{aligned}$$

The term $m := (1-p)\cdot m_0 + p\cdot m_1$ 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:

$$\frac{\mathrm{d}p}{\mathrm{d}a} = (1-p)\cdot(i - p\cdot(m_1 - m_0)) - r\cdot p. \tag{3}$$

3. Generalized equation of disease dynamics

In this section Eq. (3) is generalized. The rates i, r, m_0 and m_1 henceforth 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 diseased 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:

$$\begin{aligned} \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) S &= \sigma\cdot(S+C) - (i+m_0)\cdot S + r\cdot C \\ \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) C &= \gamma\cdot(S+C) + i\cdot S - (m_1 + r)\cdot C. \end{aligned} \tag{4}$$

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

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

for $(t,a) \in D := \{(t,a) \in [0,\infty)^2 \mid C(t,a) \geq 0, S(t,a) \geq 0, C(t,a) + S(t,a) > 0\}$ the system (4) can be transformed into an equation similar to (3):

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) p = (1-p)\left[i - p(m_1 - m_0)\right] - rp + \mu, \tag{5}$$

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

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

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

$$\begin{aligned} \sigma &= \sigma_+ - \sigma_- \\ \gamma &= \gamma_+ - \gamma_-, \end{aligned}$$

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 $p_+^{(m)}(t,a) := \frac{\gamma_+(t,a)}{\varphi_+(t,a)}$ the prevalence of the disease in the immigrants and for $\varphi_-(t,a) > 0$ define $p_-^{(m)}(t,a) := \frac{\gamma_-(t,a)}{\varphi_-(t,a)}$ the prevalence in the emigrants. *The superscript (m) indicates that the prevalence refers to the migrants.* With these notations, it holds that

$$\mu(t,a) = \begin{cases} \varphi_+(t,a)\cdot\left(p_+^{(m)}(t,a) - p(t,a)\right) \\ \quad -\varphi_-(t,a)\cdot\left(p_-^{(m)}(t,a) - p(t,a)\right), \\ \quad \text{for } \varphi_-(t,a), \varphi_+(t,a) > 0; \\ \varphi_+(t,a)\cdot\left(p_+^{(m)}(t,a) - p(t,a)\right), \\ \quad \text{for } \varphi_-(t,a) = 0, \varphi_+(t,a) > 0; \\ -\varphi_-(t,a)\cdot\left(p_-^{(m)}(t,a) - p(t,a)\right), \\ \quad \text{for } \varphi_-(t,a) > 0, \varphi_+(t,a) = 0; \\ 0, \quad \text{for } \varphi_-(t,a) = \varphi_+(t,a) = 0. \end{cases}$$

With the assumption that the prevalence of the disease in those aged a at time t who immigrate is the same as in those who emigrate, say $p^{(m)}(t,a)$, it holds that

$$\mu(t,a) = \varphi\left(p^{(m)}(t,a) - p(t,a)\right).$$

From this, we get the obvious fact that if the disease prevalence $p^{(m)}$ in the migrants is the same as that of the residents, $p^{(m)} \equiv p$, the change in prevalence $(\frac{\partial}{\partial t} + \frac{\partial}{\partial a})p$ does not depend on migration.