Theoretical Population Biology xx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Theoretical Population Biology

journal homepage: www.elsevier.com/locate/tpb

Projections of health indicators for chronic disease under a semi-Markov assumption

Mathilde Wanneveich [a,*], Hélène Jacqmin-Gadda [a], Jean-François Dartigues [a,b], Pierre Joly [a]

[a] University of Bordeaux, ISPED, Inserm, U1219 - Bordeaux Population Health Research Center, F-33000 Bordeaux, France
[b] University Hospital, memory consultation, CMRR, Bordeaux, F-33076, France

ARTICLE INFO

Article history:
Received 30 June 2017
Available online xxxx

Keywords:
Multi-states model
semi-Markov
Projection
Dementia
Epidemiology

ABSTRACT

Chronic diseases are a growing public health problem due to the population aging. Their economic, social and demographic burden will worsen in years to come. Up to now, the method used to provide projections and assess the future disease burden makes a non-homogeneous Markov assumption in an illness–death model. Both age and calendar year have been taken into account in all parameter estimations, but the time spent with the disease was not considered.

This work develops the method with a semi-Markov assumption to model mortality among the diseased and considering the time spent with the disease. The method is applied to estimate several health indicators for dementia in France in 2030.

We find that mortality among the individuals with dementia depends on age, calendar year and disease duration, and it is greater for men than for women at all ages. The projections for 2030 suggest a 27% increase of the number of dementia cases.

The model proposed in this work has flexible assumptions that make it adaptable to provide projections for various diseases.

Contents

* Correspondence to: Université de Bordeaux, ISPED, Inserm U1219, 146 rue Léo Saignat, CS61292, F-33076 BORDEAUX Cedex, France.
E-mail addresses: Mathilde.Wanneveich@u-bordeaux.fr (M. Wanneveich), Helene.Jacqmin-Gadda@u-bordeaux.fr (H. Jacqmin-Gadda), Jean-Francois.Dartigues@u-bordeaux.fr (J.-F. Dartigues), Pierre.Joly@u-bordeaux.fr (P. Joly).

https://doi.org/10.1016/j.tpb.2017.11.006
0040-5809/

1. Introduction

Currently, the high prevalence of some chronic diseases is a serious public health problem (Brayne, 2007; Jin et al., 2015). Furthermore, population aging foreshadows the increase in their burden in the coming years. Dementia like Alzheimer's disease is one of those diseases (World Alzheimer Report, 2015). Indeed, some projections suggest that the prevalence (defined as the number of cases) of dementia will reach between 1.400 and 1.700 million cases in 2030 in France (rise of 50% or more in 20 years Joly et al., 2013; Jacqmin-Gadda et al., 2013), and Brookmeyer et al. (1998) project a 3.7 fold increase for the United States population between 1997 and 2047.

Up to now, multistate models based on Markov processes have been a well-established method for modeling incidence and mortality for dementia (Keinding, 1991; Joly et al., 2002), and macro-simulation is often used to provide prevalence projections (Brookmeyer et al., 1998; Hebert et al., 2003; Wanneveich et al., in press). By modeling the three transition probabilities between healthy state, disease and death, this method makes possible to account for changes over calendar year and age of disease incidence and/or mortality. However, for many chronic diseases, mortality is likely to rise also with disease duration. For example, with Parkinson's disease, the time spent with the disease increases significantly the mortality among diseased subjects (Elbaz et al., 2003). Even if recent studies have taken into account the duration of the disease in their model, like Brinks and Landwehr's (2014), they do not consider it to provide projections. Thus, the development of projection models that account for several time parameters (such as calendar year, age and time spent with the disease) is essential in order to consider the mortality trend over time depending on the state of health.

In this paper, we propose an alternative to the model developed by Joly et al. (2013) by introducing a semi-Markov approach to model the mortality among diseased subjects. We first describe the model, its assumptions and the method used to estimate the model parameters and provide projections of several health indicators. Then, we present an application to dementia through the use of the French cohort PAQUID of elderly subjects combined with national demographic data and we provide projections for 2030 in France. The method and results are discussed in the last section.

2. Methods

2.1. Illness–death model & semi-Markov assumption

The model illustrated in Fig. 1 is a three-state model, called the illness–death model, which allows to connect the incidence to the prevalence of chronic diseases through the calendar year, the age of subjects and the disease duration (Keinding, 1991).

This model distinguishes three transition intensities. Initially, all subjects are non-diseased (i.e. state "0"), then either they die (i.e. state "2") or they become diseased (i.e. in state "1") and finally they die. The transition from "non-diseased" to "diseased", α_{01}, is interpreted as the incidence rate; α_{02} and α_{12} represent the mortality among non-diseased and diseased subjects, respectively. The transition intensities α_{01}, α_{02} may depend on t the calendar year and a the age at time t, meaning that $t - a$ is the year of birth. However α_{12} may also depend on d, the time spent with the disease (time unit in year for a, d and t). Finally, $\alpha_2(t, a)$ denotes the overall mortality rate at time t and age a, corresponding to the weighted mean of the mortality rates among diseased and non-diseased subjects. Our work is focused on incurable chronic diseases (such as dementia, Parkinson, …), therefore we do not account for any transition from diseased to non-diseased.

2.2. Assumptions

First, we assume that the incidence is null before age a_0. If the disease incidence is known to be negligible before a given age, then $a_0 \neq 0$, in the other cases $a_0 = 0$. As input to the model, we define $\nu(t, a_0)$ the age-specific population size at time t and age a_0.

Concerning the mortalities, we always consider an excess mortality among diseased subjects as compared to the mortality among non-diseased subjects: $\alpha_{02} < \alpha_{12}$. Therefore, the overall mortality is also larger than the mortality among non-diseased subjects and, in this work, we distinguish them: $\alpha_{02} < \alpha_2 < \alpha_{12}$. This is necessary when the prevalence of the disease or the over-risk of death (meaning the additional risk of death caused by the disease) are high such as for dementia (Joly et al., 2013). However, for diseases characterized by very low prevalence or over-risk of death, it may be supposed that $\alpha_{02}(t, a) = \alpha_2(t, a)$, as an approximation to simplify the methodology.

Lastly, for mortality among diseased subjects, two models were envisaged, motivated by discussion with clinicians. Both models assume that the mortality among diseased subjects depends on age and calendar year, following the same trend as non-diseased subjects. The over-risk of death depending on the time spent with the disease was either additive (Eq. (1)) or multiplicative (Eq. (2)):

$$\alpha_{12}(t, a, d) = \alpha_{02}(t, a) + h(d) \quad (1)$$

$$\alpha_{12}(t, a, d) = \alpha_{02}(t, a)e^{(\beta \times d)} \quad (2)$$

where $h(d)$ is a spline function of disease duration d. The two models were compared on the cohort PAQUID using the LCV (Likelihood based Cross-Validation) criterion, developed by Commenges et al. (2007). The LCV is better for model (1) compared to model (2) both for men (3.4697 *versus* 3.520) and women (3.5326 *versus* 3.601), meaning that model (1) is more appropriate on these data.

2.3. Estimation process and health indicators for projections

2.3.1. Estimation of transition intensities

First of all, let us define the cumulative functions from the transition intensities of the IDM which are required in this section.

The cumulative transition intensity from non-diseased to diseased between ages a_1 and a (with $a_0 \leq a_1 \leq a$) is

$$A_{01}(t, a_1, a) = \int_{a_1}^{a} \alpha_{01}(t - a + u, u)du. \quad (3)$$

The cumulative over-risk of death for a diseased subject over the d first years of disease is

$$H(d) = \int_0^d h(u)du. \quad (4)$$

The cumulative transition intensity of death between ages a_1 and a is

$$A_2(t, a_1, a) = \int_{a_1}^{a} \alpha_2(t - a + u, u)du. \quad (5)$$