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Impact of intervention targeting risk factors on chronic disease burden

Mathilde Wanneveich,^{1,2} H el ene Jacqmin-Gadda,^{1,2}
Jean-Fran ois Dartigues^{1,2} and Pierre Joly^{1,2}

The aging of the population is accompanied by a sharp rise of chronic disease prevalences, such as dementia. These diseases generally cannot be prevented or cured and persist over time, with a progressive deterioration of health, requiring specific care. To reduce the burden of these diseases, it is appropriate to propose interventions targeting disease risk factors, but the association between most of these risk factors and mortality makes it difficult to anticipate the potential impact of such interventions. A method was previously proposed to estimate changes in disease prevalence following an intervention targeting subjects at a given age where the incidence of the disease is supposed to be null. Here, we propose a general framework to make projections for life expectancies with and without the disease, the age at onset, and the lifelong probability of the disease, and to evaluate the consequences of preventive interventions targeting risk factors on these various measures of disease burden. The methodology takes into account the mortality trend over calendar time and age in both healthy and diseased subjects, and the change in mortality due to the intervention. The method is applied to make projections for dementia in 2030 according to several scenarios of public health interventions.

Keywords Dementia, life expectancy, mortality, prevalence, projection

I Introduction

The rise of life expectancy lead to an increase of age-related chronic disease prevalences such as dementia. Dementia is a common disease in the elderly people, characterized by a decline of cognitive abilities, which leads to a loss of autonomy and premature death. Most often, patients need specialized medical care which has significant economic and human costs. The current demographic situation suggests that the number of demented subjects is going to proportionally

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increase with the growing elderly population.¹ It is thus important to predict the number of demented cases in the future in order to plan the resources needed for patient care. In 2010 in France, there were about one million demented subjects.² Without major changes (such as demographic or environmental), and considering age-specific dementia incidence as constant over calendar time, we estimated that the number of demented subjects in France in 2030 will be around 1.75 million.³ To try to reduce the dementia burden, some approaches of intervention on dementia through its risk factors have been studied.⁴ However, to decide what type of intervention would be appropriate, it is important to carefully assess the anticipated impact of the intervention.

Previous studies have focused only on prevalence projections and most often, they have not taken into account the difference between overall mortality and mortality of non-demented subjects. The few studies investigating the impact of an intervention on the projections of dementia prevalence did not consider the direct impact of the intervention on mortality. Brookmeyer et al.⁵ studied the effect of an intervention delaying the onset of dementia for one to two years and/or disease progression, by modifying the transition intensities. To model the intervention impacts, they multiplied the transition intensities by various relative risks and translated these relative risks into average delay in disease onset and progression, but without considering change in the competing causes of death. Barnes and Yaffe⁶ used the attributable risks (the percentage of cases attributable to a given factor) to calculate the number of cases that could be prevented by reducing the prevalence of cardiovascular risk factors in the population. These studies do not account for the fact that modifying risk factors for dementia would impact mortality of non-demented subjects since most dementia risk factors are also death risk factors. Then by modifying the effects of a risk factor, they should have modified its effects on dementia and on death. We consider interventions targeting dementia risk factors because those are currently the most realistic preventive policies that we can propose. Indeed there is no treatment to cure most types of dementia such as Alzheimer's disease, and the causes of these diseases are not well known, while, there is efficient treatment or prevention strategy for some risk factors such as hypertension.⁷

Recently, a study conducted by Jacqmin-Gadda et al.² provided dementia prevalence projections in 2030 without intervention and with an intervention introduced in 2010 for subjects aged 65 years and non-demented. They used a model which differentiates overall mortality and non-demented mortality. This is essential because the risk of death is much higher among demented compared to non-demented subjects,^{8,9} and the prevalence of dementia is very high (especially among the oldest).^{10,11} As a consequence, the mortality of non-demented subjects is lower than the overall mortality. Moreover, their model allows to take into account the impact of an intervention by considering the impact on both mortality and dementia incidence.³ So far, only prevalence projections were given to assess the impact of an intervention, but they do not allow a comprehensive evaluation of the intervention. For instance, an intervention reducing the frequency of a risk factor for dementia could lead to an increased number of cases and even an increased global prevalence rate, because of a reduction in mortality, while increasing life expectancies without the disease.

The main objective of this article is to develop a general methodology to forecast life expectancies in different health states as well as the mean age at disease onset and the lifelong probability of disease, using a multistate approach, accounting for the difference between general population mortality and the mortality of non-demented subjects, and considering the impact of a hypothetical intervention. The intervention targets a dementia risk factor on all subjects older than a given age from a given year, and it may have an impact on dementia and also on death risks for both demented and non-demented subjects. In Section 2, we describe the model used, the method to take into account the impact of an intervention, and we develop a methodology to

estimate the life expectancies and other health indicators in this context. In Section 3, we apply the method to provide projections for dementia in 2030 under several scenarios of intervention occurring in 2015.

2 Methods

2.1 “Illness-death” model

The model illustrated in Figure 1 is a three-state model called illness-death. In our application, these states are “non-demented,” “demented,” and “dead.”

This model distinguishes three transition intensities: initially all subjects are non-demented (state “0”), then, either they die directly (state “2”), or they become demented (state “1”) and then die (state “2”). Thus α_{01} is the transition from state “non-demented” to state “demented” which is interpreted as the dementia incidence rate, and α_{02} and α_{12} represent respectively the mortality among non-demented and demented subjects. Each arrow (describing a transition between two states) is one-sided since the death is an absorbing state, and dementia can not be cured. All these intensities depend on two times, t the calendar time, and b the year of birth, so $t - b$ is the age at time t . Also, as input of the model, we define $\nu(a_0, b)$ as the size of the population at risk to develop dementia at age a_0 and born in b . Finally, $\alpha_2(t, b)$ denotes the overall mortality rate at time t for subjects born in b .

Without loss of generality, we assume that incidence is null before age a_0 ; a_0 may be 0 for some diseases as soon as data are available to estimate age-specific incidence at all ages.

In addition, we use a flexible modeling of death risk among demented subjects, assuming it is proportional to the death risk of non-demented subjects with an age- and time-specific relative risk. So α_{12} depends on age and on calendar time.

$$\forall t - b > a_0, \alpha_{12}(t, b) = \alpha_{12}(t - b|t) = g(t - b|t)\alpha_{02}(t - b|t),$$

with $g(t - b|t)$ as the relative risk of death for demented versus non-demented at age $t - b$ and calendar time t . This is a non-homogeneous Markov model because all transition intensities depend on age.

2.2 Exposure variable

To consider the impact of an intervention targeting a risk factor for dementia, we introduce a binary covariate z : z that equals 1 if the subject is exposed to the risk factor and 0 if not. A proportional

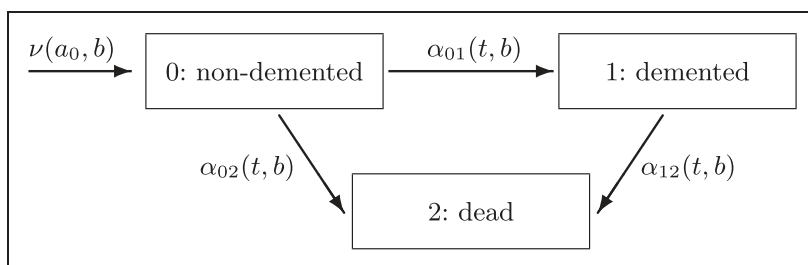


Figure 1. The illness-death model.

intensity model is assumed to take into account the risk factor's effects on the three transitions:

$$\alpha_{ij}(t-b|t, z) = \alpha_{ij}^0(t-b|t)(\theta_{ij})^z$$

where α_{ij}^0 is the baseline transition intensity between state i and state j , and θ_{ij} is the hazard ratio associated to z given by the literature. We will note $A_{ij}(x, t-b|t, z)$ as the cumulative transition intensities for the transition from i to j between x and $t-b$ years old:

$$A_{ij}(x, t-b|t, z) = \int_x^{t-b} \alpha_{ij}(u|t, z) du.$$

2.3 Intervention: Description and parameter definitions

The intervention takes place a given year τ , and its effects are maintained in time. The intervention may modify either the risk factor prevalence p , and/or the hazard ratios associated with the risk factor θ_{ij} . The hazard ratios and the risk factor prevalence are assumed to be known before the intervention. In contrast with Jacqmin-Gadda et al.,² who evaluated an intervention targeting only a_0 -year-old subjects (thus, only non-demented), we assume that the intervention targets all subjects older than a specified age at time τ . Younger subjects at time τ will be submitted to the intervention when they will reach this specified age. This, requires to separate subjects demented and non-demented at the intervention time τ . Indeed, for subjects exposed and demented at τ , only the death risk is impacted. For subjects exposed and non-demented, the risk of becoming demented is also modified. The risks of dementia and death for subjects unexposed are unchanged after the intervention.

Other parameters are introduced in the formulas: the prevalence $p(x)$ of the risk factor at age x is differentiated in $p_0(x)$ and $p_1(x)$, respectively, the prevalences for non-demented and demented at age x . The star denotes parameter values after the intervention. Thus, p^* is the modified prevalence of exposure after τ , and θ_{ij}^* are the modified hazard ratios after τ . Finally, $\omega(x)$ is the proportion of exposed subjects aged x years old who are still exposed after the intervention and the complementary $1 - \omega(x)$ is the proportion of exposed subjects who become unexposed after the intervention (see Figure 2), then $\omega(x) = \frac{p^*(x)}{p(x^-)}$. To simplify notation, we denote $\omega(x)$ as ω in the following, even if it depends on x .

Note that the unexposed group after intervention includes subjects who were never exposed and subjects who were exposed before the intervention but are no longer thereafter, as shown by $1 - p^*(x) = 1 - \omega p(x^-) = [1 - p(x^-)] + (1 - \omega)p(x^-)$, with $p(x^-)$ the prevalence of the risk factor at age x just before the intervention.

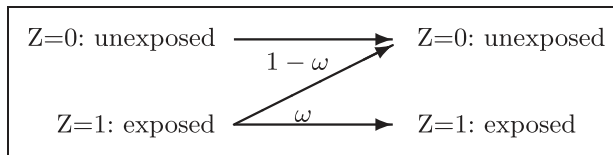


Figure 2. Exposition before intervention (on the left) versus after intervention (on the right).

2.4 Steps of the method for parameter estimations and projections

- Without intervention

Step (a) Estimations of parameters on cohort data.

We use cohort data to estimate $\alpha_{01}(t, b)$ and $g(t, b)$ by fitting a non-parametric illness death model with a penalized likelihood approach and spline approximation⁸ using the SmoothHazard R-package. This method handles semi-competing risks and interval censoring of age at dementia. Then, demographic national projections provide $\alpha_2(t, b)$ and $\nu(a_0, b)$. In addition, an approximation using a Gompertz–Makeham model is done to obtain continuous functions of age for $\alpha_2(t, b)$ for each birth cohort b .

Step (b) Estimations of the mortality among non-demented and demented subjects.

We solved a differential equation using a fourth-order Runge–Kutta method to estimate $\alpha_{12}(t, b)$ and $\alpha_{02}(t, b)$ from $\alpha_{01}(t, b)$, $g(t, b)$, and $\alpha_2(t, b)$ obtained at step (a) as described in the study by Joly et al.³

Step (c) Projections of several health indicators.

Knowing all the functions of interest after steps (a) and (b), several relevant health indicators are estimated for any time t , allowing an overview of the disease burden in the future (see Section 2.6).

- With intervention

The steps (a) and (b) are similar, and step (c) is replaced by steps (c₁) and (c₂). Step (c₁) allows the consideration of an intervention, and step (c₂) assesses the intervention impact on projections.

Step (c₁) Estimations of the baseline transition intensity among the unexposed subjects.

Estimating the baseline transition intensity requires the knowledge of the transition intensities α_{ij} in the global population and the hazard ratio θ_{ij} as well as the risk factor prevalence before the intervention. Then, a system of three equations linking marginal transition intensities (given by steps (a) and (b)) and exposure specific transition intensities is solved using the least square method and an approximation by cubic-spline functions (see details in the study by Joly et al.³).

Step (c₂) Projections of several health indicators after an intervention.

We developed all the formulas of the step (c) taking into account the intervention impact on subjects exposed to the risk factor (see Sections 2.5 and 2.6). Thus, disease projections are provided for any time t , and the intervention impact is assessed.

For steps (b) to (c₂), the program written in Fortran is available upon request from the authors.

2.5 Estimation of life expectancies

2.5.1 Life expectancies without intervention

Here, we aim to evaluate the impact of scenarios of intervention on life expectancies with and without the disease and other health indicators. We differentiate four life expectancies as Touraine et al.,¹² depending on the subject's dementia status at the age of interest. We first

present the life expectancies depending on the risk factor exposure by introducing the variable z in the formulas.

- *Life expectancy without dementia* at age $t - b$ is the remaining number of years that someone non-demented at age $t - b$ can expect to live without dementia:

$$LE_{00}(t - b|t, z) = \int_{t-b}^{\infty} P_{00}(t - b, u|t, z) du$$

with $P_{00}(t - b, u|t, z)$ being the probability for subjects born in b and alive at $t - b$ years old to be non-demented and alive at age u :

$$P_{00}(t - b, u|t, z) = e^{-A_{01}(t-b, u|t, z) - A_{02}(t-b, u|t, z)}$$

- *Life expectancy for demented subjects* is the remaining number of years of life for someone already demented at age $t - b$:

$$LE_{11}(t - b|t, z) = \int_{t-b}^{\infty} P_{11}(t - b, u|t, z) du$$

with $P_{11}(t - b, u|t, z)$ being the probability for subjects born in b , demented at $t - b$ to be alive at u :

$$P_{11}(t - b, u|t, z) = e^{-A_{12}(t-b, u|t, z)}$$

- *Life expectancy for non-demented subjects* at age $t - b$ is the total remaining number of years of life for someone non-demented at age $t - b$, irrespective of the evolution of his/her health (demented or non-demented):

$$LE_{0.}(t - b|t, z) = \int_{t-b}^{\infty} (P_{00}(t - b, u|t, z) + P_{01}(t - b, u|t, z)) du$$

with $P_{01}(t - b, u|t, z)$ being the probability for subjects born in b and non-demented at $t - b$ years old to be demented and alive at u :

$$P_{01}(t - b, u|t, z) = \int_{t-b}^u e^{-A_{01}(t-b, v|t, z) - A_{02}(t-b, v|t, z)} \alpha_{01}(v|t, z) e^{-A_{12}(v, u|t, z)} dv$$

The corresponding life expectancies for the whole population ($LE_{00}(t - b|t)$, $LE_{11}(t - b|t)$, and $LE_{0.}(t - b|t)$) are the means of the life expectancies for exposed and unexposed subjects weighted by the proportion of exposed and unexposed subjects at age $t - b$ and time t in the considered dementia state (formulas to estimate these proportions will be detailed in the context with intervention). Thereby, the next function concerns the global population including exposed and unexposed subjects.

- *Overall life expectancy* is the weighted mean of life expectancy for demented and for non-demented subjects at age $t - b$:

$$LE_{.}(t - b|t) = \pi_0(t - b|t)LE_{0.}(t - b|t) + (1 - \pi_0(t - b|t))LE_{11}(t - b|t)$$

where $\pi_0(t-b|t)$ is the proportion of non-demented subjects at age $t-b$ and time t among subjects alive:

$$\pi_0(t-b|t) = \frac{P_{00}(a_0, t-b|t)}{P_v(a_0, t-b|t)}$$

with $P_v(a_0, t-b|t)$ being the probability for subjects alive at a_0 years to be alive at age $t-b$ and time t , $P_v(a_0, t-b|t) = P_{00}(a_0, t-b|t) + P_{01}(a_0, t-b|t)$, where $P_{00}(a_0, t-b|t)$ and $P_{01}(a_0, t-b|t)$ are the probabilities without distinguishing the exposure status.

2.5.2 Postintervention life expectancies

Using the proportional intensity model and considering the new parameter values associated to the risk factors p^* and θ_{ij}^* , this section details the estimation of life expectancies at time t for age $t-b$ after the intervention. Each life expectancy is treated as the mean of life expectancies of exposed and unexposed subjects weighted by the prevalence of the risk factor at the age and time considered. As we explained before, the intervention targets all subjects older than a specified age, and for convenience, we assume the intervention targets subjects older than a_0 , the age from which the disease incidence is not null. Thus, we have to differentiate subjects older from subjects younger than a_0 at intervention.

– Subjects older than a_0 years at intervention.

- Postintervention life expectancy without dementia at age $t-b$:

$$LE_{00}(t-b|t, \tau, z) = p_0^*(t-b)LE_{00}(t-b|t, \tau, z=1) + (1-p_0^*(t-b))LE_{00}(t-b|t, \tau, z=0)$$

with $p_0^*(t-b)$ being the proportion after intervention of exposed subjects at age $t-b$ among non-demented subjects (see Appendix A.1).

- Postintervention life expectancy for demented subjects at age $t-b$:

$$LE_{11}(t-b|t, \tau, z) = p_1^*(t-b)LE_{11}(t-b|t, \tau, z=1) + (1-p_1^*(t-b))LE_{11}(t-b|t, \tau, z=0)$$

with $p_1^*(t-b)$ being the proportion after intervention of exposed subjects at age $t-b$ among demented subjects. This is the sum of $p_1^{*0}(t-b)$ the proportion of subjects exposed at $t-b$, non-demented at τ , and $p_1^{*1}(t-b)$ the proportion of subjects exposed at $t-b$ and demented at τ (see Appendix A.2).

- Postintervention life expectancy for non-demented subjects at age $t-b$:

$$LE_{0.}(t-b|t, \tau, z) = p_0^*(t-b)LE_{0.}(t-b|t, \tau, z=1) + (1-p_0^*(t-b))LE_{0.}(t-b|t, \tau, z=0)$$

- Postintervention overall life expectancy at age $t-b$:

$$LE_{..}(t-b|t, \tau, z) = \pi_0^*(t-b)LE_{0.}(t-b|t, \tau, z) + (1-\pi_0^*(t-b))LE_{11}(t-b|t, \tau, z)$$

with $\pi_0^*(t-b)$ being the proportion of subjects non-demented at age $t-b$ among subjects alive (see Appendix A.3).

– Subjects a_0 years old and younger at intervention.

By assumption, these subjects are not demented at intervention time. They will be impacted by the intervention when they reach a_0 years of age. Consequently, the probabilities P_{00} and P_{01} , used in the formulas, are simplified (see Appendix A.4).

2.6 Estimation of other health indicators

For a more comprehensive evaluation of the dementia burden, we propose to estimate other health indicators. This section presents their calculation in a context without intervention (with intervention the approach is similar by using the formulas of the previous section).

- Number of years spent with dementia for a subject healthy at age $t - b$:

This is the mean number of years a subject non-demented at age $t - b$ will spend with dementia before his/her death. It is the difference between the total life expectancy for a non-demented subject and his/her life expectancy without dementia:

$$T_{11}(t - b|t, z) = LE_0(t - b|t, z) - LE_{00}(t - b|t, z)$$

- *The life-long probability* represents the overall risk of developing dementia before death for a subject of age $t - b$, depending on the risk factor exposure:

$$F_{01}(t - b|t, z) = \int_{t-b}^{\infty} P_{00}(t - b, u|t, z)\alpha_{01}(u|t, z)du$$

- The average age at dementia onset¹³ knowing the exposure for a subject alive and non-demented at age a_0 and time t :

$$AV_{01}(a_0|t, z) = \frac{\int_{a_0}^{\infty} uP_{00}(a_0, u|t, z)\alpha_{01}(u|t, z)du}{F_{01}(a_0|t, z)}$$

The corresponding formulas for the whole population are obtained by the weighted mean of their exposure-specific counterparts.

- The prevalence of dementia between a_0 and 99 at time t .

This is the number of demented subject between a_0 (incidence null before) and 99 (insufficient information after 99 years) at time t :

$$Prev(a_0|t) = \sum_{z=0}^1 \sum_{i=0}^{99-a_0} v(a_0, t - 99 + i)P_{01}(a_0, 99 - i|t, z)$$

2.7 Computation of confidence intervals

A simulation-based approach which has already been applied in similar contexts^{14,15} is used to calculate confidence intervals for each health indicator. We compute confidence intervals accounting for the variability of the estimated parameters on our data set. Let us denote $\hat{\phi}$ the vector of the parameters estimates for the functions $\alpha_{01}(t, b)$ and $g(t, b)$, and $\hat{V}_{\hat{\phi}}$ the estimated covariance matrix of $\hat{\phi}$. We generate 200 vectors of parameters $\phi^{(1)}, \dots, \phi^{(200)}$ from the

multivariate normal distribution with expectation $\hat{\phi}$ and covariance matrix $\hat{V}_{\hat{\phi}}$. For each $\phi^{(k)}$, the transition intensities and health indicators are computed at time t .¹⁶ The 2.5th and the 97.5th empirical percentiles of these simulated samples estimate the lower and upper confidence bounds for 95% confidence intervals. This procedure is repeated for any t to obtain confidence intervals for each time-dependent health indicators.

3 Projections for dementia in France in 2030

3.1 Data

We used data from two sources to estimate the multistate model parameters. The first source was the French PAQUID cohort which was initiated in 1988 in order to study the aging population. The sample consists of 3675 subjects (2133 women and 1542 men) aged 65 years and older living in southwestern France, representative of the French population in term of age and gender.¹⁷ The subjects were screened for dementia at 1, 3, 5, 8, 10, 13, 15, 17, and 20 years after entry. Every visit, cognition was assessed with a battery of cognitive tests, and subjects screened as cognitively impaired were seen by neurologists who established the dementia diagnosis. Recent analyses, using 20 years of follow-up, identified 832 incident cases of dementia (247 men and 585 women), and 2937 deaths (1311 men and 1626 women), including 639 deaths after a dementia diagnosis (208 men and 431 women). Estimating the illness-death model on these data gave an estimate of dementia incidence and the relative risks of death for demented versus non-demented by age and gender. The estimation procedure of the non-homogeneous Markov model takes into account the interval-censoring of age at dementia.⁸

The French National Institute of Statistics, INSEE, provided French demographic projections,¹⁸ including the age- and sex-specific mortality for the overall French population, and the population at age 65 by gender for each calendar year. Before 2006, we used data from censuses and after this date, we used the central scenario about general French mortality projections proposed by INSEE, which assumes that the mortality trend follows the trend observed in France from 1988 to 2002. Representativeness of the PAQUID cohort is supported by the good fit between the age-specific death intensities estimated from the whole PAQUID sample and the INSEE mortality rates for the overall French population in 2000.³ As the estimates from the illness-death model are continuous functions of age, we fitted a Gompertz–Makeham model¹⁹ to the INSEE annual mortality rates to obtain a continuous function of age. This model fitted the age trend of mortality very well. Finally, the death risk for demented and non-demented subjects was computed by numeric resolution of a differential equation (fourth-order Runge–Kutta method).

3.2 Assumptions for this application

It is well known that dementia is rare before 65 years, and incidence rates before this age are not reliably estimated. Thus, we consider the incidence null before $a_0 = 65$ years in the application, but the method could be applied with lower a_0 if incidence estimates were available. We adapted the method to account for a change of incidence over calendar time, but we have no satisfactory hypotheses for dementia. Thus, we consider that incidence is homogeneous over calendar time and depends only on age. $\forall t - b > a_0, \alpha_{01}(t, b) = \alpha_{01}(t - b)$.

The relative risk of death for demented versus non-demented was estimated as a non-parametric function of age but was assumed constant with calendar time, ($g(t, b) = g(t - b)$). Thus, the hypothesized mortality trend with calendar time is similar among demented and non-demented, which is the most sensible assumption.

Finally, without any other realistic assumption, the ratio of risk factor prevalence, $\left(\omega(x) = \frac{p^*(x)}{p(x)}\right)$ before and after intervention is assumed constant with age.

3.3 Scenarios

We evaluated hypothetical scenarios of interventions targeting dementia risk factors. The intervention impacts either the risk factor prevalence or the hazard ratios of transition between states for exposed versus unexposed, or both. A typical example of a dementia risk factor is high blood pressure (HBP) at midlife (between 45 and 64 years old).²⁰ HBP is associated with cardiovascular mortality and, although still disputed,²¹ it is considered as a risk factor for dementia.^{20,22} Thus, an intervention targeting HBP could have an impact on mortality and on dementia incidence, and both must be taken into account when assessing the impact of this type of prevention campaign. Another well-known risk factor for dementia is apolipoprotein E (APOE4), which is the main genetic risk factor associated with Alzheimer's dementia and also with overall mortality.^{23,24}

For comparison, we use some of the scenarios proposed by Jacqmin-Gadda et al.,² where the intervention affected only subjects aged exactly 65 at τ , while we assume that all subjects above 65 at τ were immediately impacted. In both cases, subjects younger than 65 at τ undergo the intervention when they reach 65 years old. We estimate the impact on the whole population for an intervention in 2015 onward.

Scenarios 1 and 2 concern an intervention focusing on HBP, where the HBP prevalence rate at 65 years old is assumed to be $p_0(65) = 0.40$ (40% of the population alive and aged 65 years old is exposed to HBP before the intervention). For scenario 1, we assume that in the general context (i.e., without intervention) the effect of HBP is stronger on death ($\theta_{12} = \theta_{02} = 2$) than on dementia ($\theta_{01} = 1.5$). We distinguish subscenarios (a,b), depending on the impact of the intervention. In subscenario 1.a, the intervention reduces HBP prevalence at 65 years old by half ($p_0^*(65) = 0.2$), while in sub-scenario 1.b, HBP prevalence is unchanged, but according to literature on efficacy of antihypertensive drug, we consider that an antihypertensive drug could decrease the hazard ratio of dementia by 15% ($\theta_{01}^* = 1.27$),⁷ and the hazard ratio of death by 13% ($\theta_{12}^* = \theta_{02}^* = 1.74$) among hypertensive subjects.²⁵ For scenario 2, before the intervention, the effect of HBP is stronger for dementia risk ($\theta_{01} = 2$) than for death risk ($\theta_{12} = \theta_{02} = 1.5$). For this scenario, we evaluated the impact only for an intervention reducing the HBP prevalence: $p_0^*(65) = 0.2$ for sub-scenario 2.a; $p_0^*(65) = 0$ for sub-scenario 2.b.

Scenario 3 focuses on APOE4 with a hypothetical treatment diminishing the risk of dementia among exposed subjects. APOE4 prevalence at age 65 is $p_0(65) = 0.20$.²⁶ In this scenario, before the intervention the hazard ratio of dementia is twice as much as the hazard ratio of death ($\theta_{01} = 3$, and $\theta_{02} = \theta_{12} = 1.5$). The intervention reduces the hazard ratio of dementia by half ($\theta_{01}^* = 1.5$).

3.4 Results

Tables 1 and 2 provide projections for women in France of the dementia prevalence between 65 and 99 years, the average age at dementia onset AV_{01} in 2015 and in 2030, without intervention and for the five scenarios of intervention. Furthermore, it displays the life expectancies LE_{00} , $LE_{0.}$, LE_{11} , and $LE_{.}$, the lifelong probability of dementia F_{01} , and the mean number of years spent with dementia T_{11} for women aged 75 years old.

3.4.1 Projections without intervention

Without intervention and assuming no change in dementia incidence over time, an increase of 39.6 % of the number of demented women aged 65–99 years is expected between 2015 and 2030 due to

Table 1. Projections of dementia prevalence (in thousands of subjects) between 65 and 99 years, average age at dementia onset (AV_{01}), and lifelong probability of dementia (F_{01}) at age 75 for women in France, with 95% confidence intervals.

Scenario											Prev		AV_{01}	F_{01} (at age 75)
No.	$p_0(65)$	$p_0^*(65)$	ω	θ_{01}	θ_{01}^*	θ_{02}	θ_{02}^*	θ_{12}	θ_{12}^*	(N)	Percentage ^a			
Projections in 2015 without intervention											821	–	84.6	0.658
											[757;958]		[83.4;85.3]	[0.621;0.696]
Projections in 2030 without intervention											1146	–	85.3	0.703
											[1054;1348]		[84.2;85.9]	[0.666;0.740]
Projections in 2030 with intervention in 2015														
1.a	0.4	0.2	0.5	1.5	1.5	2	2	2	2	1410	+23.0	85.8	0.709	
										[1391;1735]		[84.5;86.3]	[0.672;0.742]	
1.b	0.4	0.4	1	1.5	1.27	2	1.74	2	1.74	1149	+0.3	85.6	0.697	
										[1094;1406]		[84.3;86.1]	[0.662;0.731]	
2.a	0.4	0.2	0.5	2	2	1.5	1.5	1.5	1.5	1297	+13.2	86.1	0.687	
										[1195;1474]		[84.8;86.6]	[0.657;0.717]	
2.b	0.4	0	0	2	2	1.5	1.5	1.5	1.5	1447	+26.3	86.8	0.671	
										[1342;1625]		[85.6;87.3]	[0.642;0.705]	
3	0.2	0.2	1	3	1.5	1.5	1.5	1.5	1.5	1050	–8.4	86.0	0.678	
										[977;1259]		[84.7;86.5]	[0.643;0.714]	

The values highlighted in bold reflect the parameter modifications after the intervention.

^aPercentage of change as compared with the predicted prevalence without intervention in 2030.

Table 2. Projections of life expectancies LE_{00} , LE_0 , LE_{11} , and $LE_{..}$ and the mean number of years spent with dementia T_{11} (for women without dementia) at age 75 for women in France, with 95% confidence intervals.

Scenario											LE_{00}	LE_0	LE_{11}	$LE_{..}$	T_{11}
No.	$p_0(65)$	$p_0^*(65)$	ω	θ_{01}	θ_{01}^*	θ_{02}	θ_{02}^*	θ_{12}	θ_{12}^*						
Projections in 2015 without intervention											11.97	15.79	8.57	15.52	3.82
											[11.72;12.26]	[15.71;16.00]	[7.39;10.07]	[15.50;15.58]	[3.45;4.28]
Projections in 2030 without intervention											12.44	17.04	10.41	16.77	4.60
											[12.19;12.72]	[16.97;17.25]	[9.17;11.73]	[16.74;16.83]	[4.25;5.06]
Projections in 2030 with intervention in 2015															
1.a	0.4	0.2	0.5	1.5	1.5	2	2	2	2	13.01	17.89	11.73	17.66	4.88	
										[12.61;13.25]	[17.79;18.07]	[10.56;12.73]	[17.60;17.70]	[4.54;5.46]	
1.b	0.4	0.4	1	1.5	1.27	2	1.74	2	1.74	12.78	17.41	11.22	17.19	4.63	
										[12.39;13.02]	[17.31;17.60]	[10.03;12.24]	[17.12;17.22]	[4.29;5.21]	
2.a	0.4	0.2	0.5	2	2	1.5	1.5	1.5	1.5	13.14	17.71	11.15	17.49	4.57	
										[12.79;13.34]	[17.59;17.87]	[9.95;12.19]	[17.42;17.51]	[4.25;5.08]	
2.b	0.4	0	0	2	2	1.5	1.5	1.5	1.5	13.82	18.36	12.02	19.11	4.54	
										[13.46;14.03]	[18.23;18.50]	[10.78;13.07]	[18.09;18.21]	[4.20;5.04]	
3	0.2	0.2	1	3	1.5	1.5	1.5	1.5	1.5	12.91	17.25	10.82	17.05	4.34	
										[12.53;13.13]	[17.13;17.43]	[9.61;11.87]	[16.98;17.09]	[4.00;4.90]	

The values highlighted in bold reflect the parameter modifications after the intervention.

the expected decrease in global mortality. Meanwhile, the age at dementia onset will be delayed by 0.7 years but the lifelong probability of dementia, for women aged 75 years old, will increase (Table 1). Furthermore, an increase of all life expectancies for women (with and without dementia) is observed between 2015 and 2030 (Table 2). The total life expectancy for a non-demented woman

aged 75 (LE_0) will increase by 1.25 years between 2015 and 2030, to reach 17.04 years in 2030, but the life expectancy without dementia (LE_{00}) will increase by only 0.47 years; the remaining additional 0.78 years will be spent living with dementia (T_{11}). In 2030, a non-demented woman aged 75 years will live on average 4.60 years with dementia before dying. The life expectancy for a demented woman aged 75 (LE_{11}) will increase by 1.84 years between 2015 and 2030. In 2030, a demented woman aged 75 years will be expected to live 10.41 years.

3.4.2 Projections with the five scenarios of intervention

Table 1 shows that the hypothesized scenarios of intervention targeting all the subjects aged 65 and older in 2015 can have a large impact on dementia prevalence in 2030. This is in contrast with the same scenarios targeting only subjects aged exactly 65 years as evaluated in Jacqmin-Gadda et al.² For scenarios 1.a, 2.a, and 2.b which reduced the risk factor prevalence in 2015, we observe a sharp rise in dementia prevalence by 23%, 13.2%, and 26.3% (respectively) as compared to projections without interventions. The increase in the number of demented subjects is larger when the targeted risk factor is more strongly associated with death than with dementia (scenario 1.a vs. 2.a). For scenario 1.b where the intervention decreased the hazard ratios associated with HBP by 13% and 15%, dementia prevalence is almost unchanged. Finally for scenario 3 that involved an intervention reducing the excess risk of dementia among APOE4 carriers only, the projections of dementia prevalence for 2030 could decrease by 8.4%. All scenarios delay the age at dementia onset, from 0.3 years for scenario 1.b to 1.5 years for scenario 2.b, the extreme scenario that assumes the eradication of a risk factor highly associated with dementia ($\theta_{01} = 2$) and moderately associated with death ($\theta_{02} = \theta_{12} = 1.5$).

Figure 3 displays the estimated lifelong probability of dementia for women aged 66–99 years in 2015 and in 2030, without intervention and with interventions, scenarios 1.a and 1.b, which are considered as the most realistic by now. These probabilities increase between 2015 and 2030 across all ages, but the interventions according to scenarios 1.a and 1.b would have little impact on these projections in 2030. However, Table 1 exhibits a small reduction in the lifelong probabilities of dementia for women aged 75 years under scenarios 2.a, 2.b, and 3.

As displayed in the Table 2, all scenarios lead to an increase of all life expectancies (with or without dementia), because they reduce mortality either directly (scenarios 1 and 2) or indirectly by decreasing dementia incidence (scenario 3). Obviously, the impact on life expectancies is larger when mortality is directly modified (scenario 1.b). By contrast, the mean number of years spent with dementia (T_{11}) significantly decreased only when the intervention reduced the incidence of dementia exclusively ($T_{11} = 4.34$ in scenario 3 vs. 4.60 without intervention).

Figure 4 displays the projections of life expectancies LE_{00} , LE_{11} , and LE_0 , and the number of years spent with dementia T_{11} , for women aged 66–99 years without interventions for the years 2015 and 2030, and with interventions according to scenarios 1.a and 1.b for 2030.

The intervention impact appears larger for the youngest subjects because the death risk becomes predominant for the oldest subjects, irrespective of context and thus, all the curves converge to the same value at 99 years. All life expectancies increase for the two scenarios of intervention compared to the projections for 2030 without intervention, but the difference is larger for the life expectancy of demented subjects (LE_{11}). The mean number of years spent with dementia (T_{11}) significantly changes only for scenario 1.a because this intervention strongly impacts mortality. More importantly, Figures 3 and 4 and Tables 1 and 2 clearly show that the five hypothetical scenarios of intervention designed according to the knowledge about risk factors of dementia would have less impact on all epidemiological measures of the burden of dementia (except age at onset) compared to the decrease in mortality expected between 2015 and 2030.

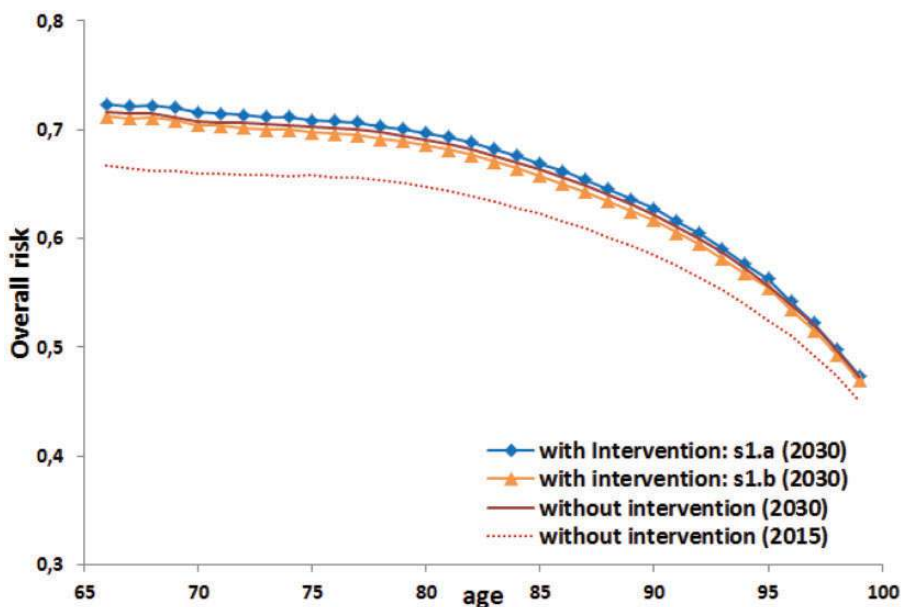


Figure 3. Evolution of the lifelong probability to develop dementia by age for women in 2015 and in 2030 without intervention and with intervention scenarios I.a and I.b.

Results for men displayed in the supplementary material are very similar except that their life expectancies, the average age of dementia onset, lifelong probability of dementia, and prevalence of dementia are always lower than those of women.

4 Discussion

The objective of this paper was to evaluate the impact of an intervention targeting chronic disease risk factors on the projections of life expectancies in different health states and other health indicators. The method assumes nonhomogeneous Markov illness-death model and proportional intensities models for the three transition intensities. This method takes into account subject age and calendar time for every transition intensity, and it distinguishes mortality among nondiseased subjects from overall mortality.

This method has many advantages. First, as in the study by Joly et al.,³ we carefully model mortality, distinguishing overall mortality from nondiseased mortality trends. This is essential for chronic disease with high mortality and high prevalence. In addition, the intervention impact is implemented in order to consider the impact of the risk factors on mortality (distinguishing diseased and nondiseased) and on disease incidence. Indeed, most often, a chronic disease risk factor is also a death risk factor, but most studies evaluating interventions do not take into account the effect on mortality. Second, this work enables a global view of an intervention by assessing its impact on several public health indicators: life expectancy in different health states, age at dementia onset, mean number of years spent with dementia, and the overall risk to develop dementia. For example, a rise in prevalence projections was found associated with a rise in life expectancy without the disease.

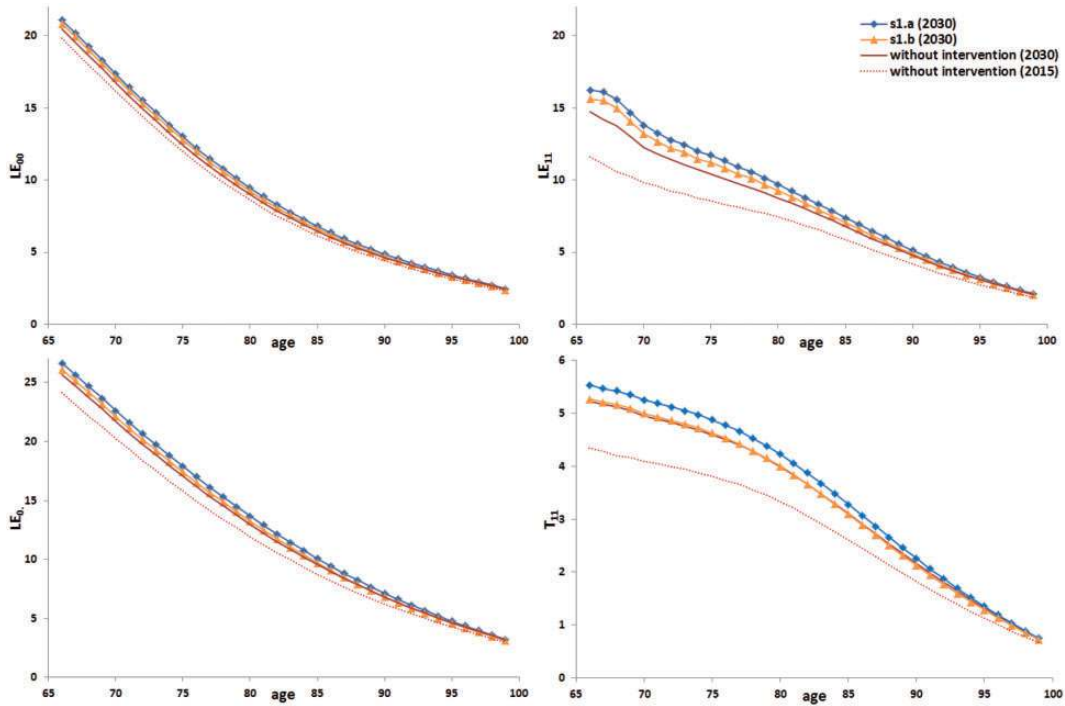


Figure 4. Projections of life expectancies and number of years spent with dementia for women by age, without intervention and with intervention scenarios I.a and I.b.

This is due to a decrease of both, the dementia incidence and the mortality among non-demented people. Consequently, the life expectancy without dementia raises, the population at risk to develop the disease increases and thus the prevalence too (more subjects develop dementia but older). Finally, compared to previous works,^{2,5,6} we implemented more realistic intervention scenarios targeting subjects of a large age range. Thus, the intervention affects the whole population at risk of developing the disease, which seems to be more appropriate and ethical. As a consequence, the proportion of exposed subjects that will become unexposed after the intervention computation is more complicated because the health state of each subject at the intervention time must be accounted for. However, the assumptions imposed for the application are flexible. Indeed, the proportion ω of exposed subjects that will become unexposed after the intervention and the mean change in the relative risk θ_{ij} after the intervention reflects the efficacy of the intervention but also the proportion of subjects really submitted and compliant to the intervention. Thus, this proportion is not necessarily 100%. Moreover, the method makes it possible to target a particular age group. The evaluated intervention may modify the prevalence and/or the hazard ratios associated to the risk factor, and these effects could depend on the age or year when the subject undergoes the intervention. We chose to evaluate quite simple and realistic scenarios because we do not have plausible assumptions and available information about more complex scenarios.

In this paper we applied the method to French data on dementia. Although many risk factors for dementia are suspected, only a few of them have been proven and their actual impacts are still

debated. Thus we focused on the APOE4 gene and HBP which are well-established risk factors for both dementia and death and which were already considered as possible target of intervention, with known prevalence in the elderly population.²⁷ HBP is assumed here as a time-independent exposure as only HBP at midlife was found associated with dementia.

To summarize, our findings suggest that the hypothetical interventions targeting APOE4 and HBP would have less impact on the burden of dementia across all indicators, than the decrease of mortality forecasted between 2015 and 2030. In addition, an intervention delaying the onset of dementia by two years as suggested in Brookmeyer et al.⁵ or by two and five years in Vickland et al.²⁸ seems very optimistic. Indeed, the largest estimated delay in our scenarios was 1.5 years in the most extreme scenario where a frequent risk factor (prevalence of 40%), which would double the risk of dementia and would increase the mortality by 50%, would be eradicated by the intervention. Given current knowledge about dementia risk factors, it is difficult to envisage more efficient scenarios. It is interesting to note that the estimates of the various health indicators have unequal precision. For prevalence, the confidence intervals are large, while they are small for life expectancies. That is partly due to the fact that the uncertainty is considered on dementia incidence $\alpha_{01}(t, b)$ and on the relative risk of death for demented versus non-demented $g(t, b)$, but not on the overall mortality $\alpha_2(t, b)$, which is obtained by projections provided by INSEE.

Some studies have suggested a declining trend in dementia incidence^{29,30} that could be explained by an improvement in educational level or better care of vascular risk factors over the previous years. However, these results are still inconsistent and may be blurred by changes in dementia diagnostic criteria. Thus we chose to make predictions under the assumption of constant incidence without intervention. Nevertheless, we adapted the method to account for a declining trend. Assuming a 1% decline each year since 2000, we found a 25% decrease in the prevalence in 2030 compared to the prevalence assuming constant incidence.

Up to now, the model has not taken into account the time spent with dementia. Therefore, two demented women aged 80 years are assumed to have the same life expectancy even if one woman has been demented for 10 years and the other for 1 year. In this regard, it could be interesting to relax the Markov assumption to allow dependence of mortality among demented subjects for the disease duration. In fact, we have previously shown that the Markov model fitted the PAQUID data better than the standard semi-Markov model.³¹ Nevertheless, a model allowing dependence of the mortality of demented subjects on both age and disease duration could be superior, but could also lead to estimation issues and complicate computations.

To conclude, we provide a general framework to evaluate the potential impact of scenarios of interventions targeting chronic disease risk factors on various public health indicators of the disease burden.

Declaration of conflicting interests

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Supplementary material

The supplementary material presents the results of this application for men.

References

1. Berr C, Akbaraly TN, Nourashemi F, et al. Epidémiologie des démences. *La Presse Médicale* 2007; **36**: 1430–1441.
2. Jacqmin-Gadda H, Alperovitch A, Montlathuc C, et al. 20-years prevalence projections for dementia and impact of preventive policy about risk factors. *Eur J Epidemiol* 2013; **28**: 493–502.
3. Joly P, Touraine C, Georget A, et al. Prevalence projections of chronic diseases and impact of public health intervention. *Biometrics* 2013; **69**: 109–117.
4. Polidori MC, Pientka L and Mecocci P. A review of the major vascular risk factors related to Alzheimer's disease. *J Alzheimer's Dis* 2012; **32**: 521–530.
5. Brookmeyer R, Johnson E, Ziegler-Graham K, et al. Forecasting the global burden of Alzheimer's disease. *Alzheimer's Dement* 2007; **3**: 186–191.
6. Barnes DE and Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011; **10**: 819–828.
7. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (hyvet-cog): a double-blind, placebo controlled trial. *Lancet Neurology* 2008; **7**: 683–689.
8. Joly P, Commenges D, Helmer C, et al. A penalized likelihood approach for an illness-death model with interval-censored data: application to age-specific incidence of dementia. *Biostatistics* 2002; **3**: 433–443.
9. Jagger C, Andersen K, Breteler MM, et al. Prognosis with dementia in Europe: a collaborative study of population-based cohorts. Neurologic diseases in the elderly research group. *Neurology* 2000; **54**: S16–S20.
10. Ramarosan H, Helmer C, Barberger-Gateau P, et al. Prevalence of dementia and Alzheimer's disease among subjects aged 75 years or over: updated results of the PAQUID cohort. *Rev Neurol* 2003; **159**: 405–411.
11. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2006; **366**: 2112–2117.
12. Touraine C, Helmer C and Joly P. Predictions in an illness-death model. *Stat Meth Med Res*. Epub ahead of print. 2013 May 22.
13. Brinks R, Landwehr S and Waldeyer R. Age of onset in chronic diseases: new method and application to dementia in Germany. *Popul Health Metr* 2013; **11**: 6.
14. van den Hout A and Matthews FE. Multi-state analysis of cognitive ability data: a piecewise-constant model and a Weibull model. *Stat Med* 2008; **27**: 5440–5455.
15. van den Hout A and Matthews FE. Estimating stroke-free and total life expectancy in the presence of non-ignorable missing values. *J R Stat Soc Ser A Stat Soc* 2010; **173**: 331–349.
16. Aalen OO, Farewell VT, de Angelis D, et al. A Markov model for HIV disease progression including the effect of HIV diagnosis and treatment: application to aids prediction in England and Wales. *Stat Med* 1997; **16**: 2191–2210.
17. Dartigues JF, Gagnon M, Michel P, et al. Le programme de recherche paquid sur l'épidémiologie de la démence. méthodologie et résultats initiaux. *Rev Neurol* 1991; **147**: 225–230.
18. Blanpain N and Chardon O. Projections de population 2007–2060 pour la France métropolitaine: méthode et principaux résultats. *Document de travail* 2010; F1008.
19. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos Trans R Soc* 1825; **115**: 513–583.
20. Tolppanen AM, Solomon A, Soininen H, et al. Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies. *J Alzheimer's Dis* 2012; **32**: 531–540.
21. Power MC, Weuve J, Gagne JJ, et al. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology* 2011; **22**: 646–659.
22. Duron E and Hanon O. Hypertension, cognitive decline and dementia. *Arch Cardiovasc Dis* 2008; **101**: 181–189.
23. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease Meta Analysis Consortium. *J Am Med Assoc* 1997; **278**: 1349–1356.
24. Genin E, Hannequin D, Wallon D, et al. APOE and Alzheimer disease: a major gene with semidominant inheritance. *Mol Psychiatry* 2011; **16**: 903–907.
25. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; **355**: 865–872.
26. Winnock M, Letenneur L, Jacqmin-Gadda H, et al. Longitudinal analysis of the effect of apolipoprotein E $\epsilon 4$ and education on cognitive performance in elderly subjects: the PAQUID study. *J Neurol Neurosurg Psychiatry* 2002; **72**: 794–797.
27. Tilvis RS, Kähönen-Väre MH, Jolkkonen J, et al. Predictors of cognitive decline and mortality of aged people over a 10-year period. *Dement Geriatr Cognit Disord* 2004; **59**: M268–M274.
28. Vickland V, McDonnell G, Wern J, et al. A computer model of dementia prevalence in Australia: foreseeing outcomes of delaying dementia onset, slowing disease progression, and eradicating dementia types. *Dement Geriatr Cognit Disord* 2010; **29**: 123–130.
29. Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic diseases in the elderly research group. *Neurology* 2000; **54**: S10–S15.
30. Rocca WA, Petersen RC, Knopman DS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimer's Dement* 2011; **7**: 80–93.
31. Commenges D, Joly P, Gégout-Petit A, et al. Choice between semi-parametric estimators of Markov and non-Markov multi-state models from generally coarsened observations. *Scand J Stat* 2007; **34**: 33–52.

Appendix

I Proportion after intervention of exposed subjects at age $t - b$ among non-demented subjects

$$p_0^*(t - b) = \frac{\omega p_0(a_0) P_{00}(a_0, \tau - b|t, \tau, z = 1) P_{00}(\tau - b, t - b|t, \tau, z = 1)}{P_{00}(a_0, t - b|t, \tau, z)}$$

$P_{00}(a_0, t - b|t, \tau, z)$ is the probability for subjects alive and non-demented at age a_0 to be still alive and non demented at age $t - b$ after an intervention:

$$\begin{aligned} P_{00}(a_0, t - b|t, \tau, z) &= \omega p_0(a_0) P_{00}(a_0, \tau - b|t, \tau, z = 1) P_{00}(\tau - b, t - b|t, \tau, z = 1) \\ &\quad + (1 - \omega) p_0(a_0) P_{00}(a_0, \tau - b|t, \tau, z = 1) P_{00}(\tau - b, t - b|t, \tau, z = 0) \\ &\quad + (1 - p_0(a_0)) P_{00}(a_0, t - b|t, \tau, z = 0) \end{aligned}$$

The first term is the probability to be exposed before and after an intervention and to remain alive and non-demented from age a_0 to $t - b$. The second term is the probability to be exposed before τ and unexposed thereafter and to remain alive and non-demented from age a_0 to $t - b$. The last term is the probability of being unexposed, alive and non-demented from age a_0 to $t - b$.

2 Proportion after intervention of exposed subjects at age $t - b$ among demented subjects

This is the sum of $p_1^{*0}(t - b)$ the proportion of subjects exposed at $t - b$, non-demented at τ , and $p_1^{*1}(t - b)$ the proportion of subjects exposed at $t - b$ and demented at τ :

$$p_1^*(t - b) = p_1^{*0}(t - b) + p_1^{*1}(t - b)$$

with
$$p_1^{*0}(t - b) = \frac{\omega p_0(a_0) P_{00}(a_0, \tau - b|t, \tau, z = 1) P_{01}(\tau - b, t - b|t, \tau, z = 1)}{P_{01}(a_0, t - b|t, \tau, z)}$$
 and
$$p_1^{*1}(t - b) = \frac{\omega p_0(a_0) P_{01}(a_0, \tau - b|t, \tau, z = 1) P_{11}(\tau - b, t - b|t, \tau, z = 1)}{P_{01}(a_0, t - b|t, \tau, z)}$$

$P_{01}(a_0, t - b|t, \tau, z)$ is the probability for non-demented and alive subjects at age a_0 to be demented and alive at age $t - b$ after intervention.

$$\begin{aligned} P_{01}(a_0, t - b|t, \tau, z) &= \omega p_0(a_0) P_{00}(a_0, \tau - b|t, \tau, z = 1) P_{01}(\tau - b, t - b|t, \tau, z = 1) \\ &\quad + \omega p_0(a_0) P_{01}(a_0, \tau - b|t, \tau, z = 1) P_{11}(\tau - b, t - b|t, \tau, z = 1) \\ &\quad + (1 - \omega) p_0(a_0) P_{00}(a_0, \tau - b|t, \tau, z = 1) P_{01}(\tau - b, t - b|t, \tau, z = 0) \\ &\quad + (1 - \omega) p_0(a_0) P_{01}(a_0, \tau - b|t, \tau, z = 1) P_{11}(\tau - b, t - b|t, \tau, z = 0) \\ &\quad + (1 - p_0(a_0)) P_{01}(a_0, t - b|t, \tau, z = 0) \end{aligned}$$

3 Proportion of subjects non-demented at age $t - b$ among subjects alive

$$\pi_0^*(t - b) = \frac{P_{00}(a_0, t - b|t, \tau, z)}{P_{00}(a_0, t - b|t, \tau, z) + P_{01}(a_0, t - b|t, \tau, z)}$$

4 Subjects a_0 years old and younger at intervention

By replacing $\tau - b$ by a_0 , which is the age when subjects will be submitted to the intervention, the previous probabilities P_{00} and P_{01} are simplified:

$$P_{00}(a_0, t - b|t, \tau, z) = \omega p_0(a_0)P_{00}(a_0, t - b|t, \tau, z = 1) + (1 - \omega p_0(a_0))P_{00}(a_0, t - b|t, \tau, z = 0)$$

$$P_{01}(a_0, t - b|t, \tau, z) = \omega p_0(a_0)P_{01}(a_0, t - b|t, \tau, z = 1) + (1 - \omega p_0(a_0))P_{01}(a_0, t - b|t, \tau, z = 0)$$