Sensitivity analysis of the multistate life table: An application to an illness-death model.

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Abstract

The object of this paper is to demonstrate sensitivity analysis of a multistate life table applied to an illness-death model and show its usefulness in studies on the compression or expansion of morbidity. The sensitivity of life expectancy to changes in the mortality rate and the related concept of entropy were introduced by Keyfitz in 1977. To analyze the sensitivity of healthy or disabled life expectancy to changes in underlying rates, one needs to differentiate the functions of the multistate life table, using matrix differentiation. Although the theory and techniques were developed years ago, this analysis is not often applied in demographic or epidemiological research. As the use of multistate models spreads and as modern software facilitates matrix algebra and differentiation, these sensitivity analyses can be an informative and powerful analysis tool. We will apply sensitivity analysis of a multistate illness-death model to the U.S. Health and Retirement Survey, showing its usefulness for prevention and intervention decisions.

Introduction

The fundamental question in sensitivity analysis is how an arbitrary change in the underlying parameters of a model changes a particular output variable of our interest. In demography, sensitivity analysis studies how a change in its underlying age- or time specific rates alters a particular output variable of the demographic model.

Many research questions study the structure and developments of demographic rates as such e.g. trends in age-specific fertility rates or the effect of risk factors on age-specific incidence or mortality rates. A summary measure of a set of age-specific rates and one of the most important demographic indicators is life expectancy. However, the linkage between life expectancy and the underlying demographic rates is not straightforward. The construction of the life table works through a system of age-structured rates and functions to derive life expectancy. The multistate life table is based on at least two sets of age-specific rates and the most important output variable is state-specific life expectancy. Sensitivity analysis needs differentiation of the functions building the life table. Because the multistate life table and its functions are defined in terms of matrices, its sensitivity analysis requires matrix differentiation. Although, the theory of multistate life table differentiation was developed years ago (Willekens,

Ekamper), it is seldomly used in the literature. New widely available software facilitates applications of sensitivity analysis using matrix differentiation.

A large literature exists on the impact of changing mortality rates on life expectancy (Pollard 1988), (Keyfitz and Caswell 2005),(Vaupel and Canudas-Romo 2003). In the recent debates about healthy life expectancy and expansion or compression of morbidity, it is more important to conduct sensitivity analysis of state-specific life expectancy, for example healthy life expectancy from a multistate illness-death model. Sensitivity of an illness-death model to changes in underlying rates can provide insights that are of great importance for prevention and intervention policies. Which rates contribute the most to healthy or disabled life expectancy and at what ages would an intervention be most effective? An informative measure of sensitivity is entropy, indicating the elasticity of state-specific life expectancy with respect to a uniform change in the underlying rates. State-specific entropies are comprehensive measures of sensitivity and are valuable in showing compression or expansion of morbidity because of changes in the rates.

Sensitivity analysis

Sensitivity analysis, also called perturbation or impact analysis, deals with the question how a marginal change in a model alters particular outcome variables that interest us. Sensitivity Analysis is common in physics and chemistry, in financial applications, risk analysis, ecology and many other areas where models are developed. In the field of population models, human, animal or plant populations, sensitivity analysis is often used to calculate the risk of extinction or overpopulation because of changes in vital rates.(Caswell 2000; Caswell 2007) In demography, sensitivity analysis is mostly used to analyse the uncertainty in the estimation of vital rates; one would like to know the impact of a change in one of the rates to the (forecasted) population size and structure.

There are basically two ways to conduct sensitivity analysis. The first is the numerical or simulation method, also called arithmetic or empirical approach, which is simply computing the function of interest under the changed and the original transition rates. (Keyfitz 1971; Laaksonen 1980; Ekamper and Keilman 1993). Also in health research the numerical approach is commonly used to assess sensitivity of a model (Nusselder, Looman et al. 2000; van Baal, Hoogenveen et al. 2006). This method

can be numerically tedious and it does not provide general insights in the mechanism of the model. We will use this numerical approach only to verify the results of the second approach, the analytical method, which we will use here. Although the theoretical and mathematical aspects were developed much earlier by Willekens ((Willekens 1977)), Arthur ((Arthur 1984)) and Ekamper ((Ekamper and Keilman 1993)), sensitivity analysis is used only rarely in demography. One of the reasons might be that the derivation of more complex demographic functions need matrix calculus. However, modern software like R, makes this type of analysis more accessible to a larger public.

A large literature exists on the impact of changing mortality rates on life expectancy (Pollard 1988), (Keyfitz and Caswell 2005),(Vaupel and Canudas-Romo 2003). The extend to which a change in mortality rate has an effect on life expectancy depends on the age-structure and hence on the shape of the survival function. This elasticity, depending on the concavity of the survival curve, was introduced by Keyfitz and is called the entropy of a life table or information (Keyfitz and Caswell 2005) chapter 4. When the entropy of a life table is close to 0, all mortality is concentrated at one single age. Entropy close to 1 indicates that mortality is about the same at all ages and a proportional change in the death rates translates into the same change in life expectancy.
The dynamics of a multistate illness-death model are not only driven by mortality rates, but also by incidence and recovery rates. Hill has derived formulas for the entropies of diseased and non-diseased life expectancy in relation to changes in incidence and mortality rates (Hill 1997). However, in this model the disease is irreversible and recovery is not possible. When including the possibility of reverse transitions like recovery, one needs to solve a system of equations, which is only possible with matrix algebra. A description of the multistate life table and subsequent life table functions can be found in Appendix 1. Analyzing the sensitivity of a multistate illness-death model expressed in matrices requires matrix differentiation.

Matrix differentiation

In the analytic approach of sensitivity analysis, general formulas are derived to express the impact of a particular change in terms of the output variable and these formulas are called sensitivity functions. As our multistate life tables are defined in terms of matrices, we need matrix differentiation techniques to perform sensitivity analysis. Matrix differentiation was defined by Neudecker as the procedure of

finding partial derivatives of the elements of a matrix function with respect to the elements of the argument matrix (Neudecker 1969). For details about the matrix differentiation techniques, we refer to Magnus and Neudecker (Magnus 1988) and the appendix of Willekens 1977 (Willekens 1977).

All calculations in this paper were done using R project for statistical programming. The life expectancy sensitivity function only uses simple matrix multiplication and the inverse of a matrix by the command *solve* or *inverse* in package matrixcalc. The R code to program the sensitivity function is given in appendix 2.

Sensitivity analysis of state-specific life expectancy

Willekens (1977) has derived the sensitivity functions for all lifetable functions applying matrix differentiation techniques. We will focus on the sensitivity of life expectancy, e(x), to a change in underlying transition rates **M**(x).

$$\frac{de(x)}{dM(x)} = -(e(x) - 0.5 * I) * (I - 0.5 * M(x))^{-1} * J * L(x) * l^{-1}(x)$$

J is a matrix indicating for which element of transition matrix **M**(x) one wants to calculate the sensitivity to a small change δ. The change δ can be expressed in absolute or in relative terms. When interested in the effects of an absolute change, hence an additive change, the result will be a sensitivity measure. If the change is proportional, the effect is measured as an elasticity. Let's first investigate the effects of an absolute change. Matrix J consists of zeros except for the element of interest and the diagonal element of that column (following (Ekamper and Keilman 1993)). For example, for the sensitivity to a change in rate μ_{12}(x) matrix **J** would be:

$$J = \begin{bmatrix} -\delta & 0 & 0 \\ \delta & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Because the off-diagonal transition rates in matrix **M**(x) are negative, a positive value in **J** indicates *decrease* in the original transition rate. As we are interested in the effect of a small change in transition rates, we will use 0.01 as δ in matrix **J**. The result of de(a)/dM(x) gives the changes in life expectancies per state at age a, $de_i(a)$, because of a small change in a rate at age x.

In a similar manor, the sensitivity function can be used to measure the effect of two or more simultaneous changes, for example, the impact of a decrease in all mortality rates by 0.01, from state 1 as well as from state 2. Matrix J would yield

$$J = \begin{bmatrix} -0.01 & 0 & 0 \\ 0 & -0.01 & 0 \\ 0.01 & 0.01 & 0 \end{bmatrix}$$

The numbers in the J matrix indicate an absolute change in the rate of interest. It is of course also possible to define the change as a percentage of the original rate and elements of J can be written as δ * μ(x). When expressing both the result and the change in relative terms of the initial life expectancy, $de_i(a)$ can be interpreted as an elasticity measure.

It can be interesting to analyse the impact of a change at a higher age x to life expectancy at an earlier age, say a. The sensitivity of life expectancy at a reference or starting age a, e(a), to a change in M(x) is

$$\frac{de(a)}{dM(x)} = -(e(x) - 0.5 * I) * (I - 0.5 * M(x))^{-1} * J * L(x) * l^{-1}(a) \qquad a \leq x$$

If a < x, a change at the higher age x, has a larger impact on life expectancy at that age, e(x), than on life expectancy at earlier age, e(a). In other words, a decrease in death rate at age 80 will increase e(80) more than e(55) for the simple reason that not all people aged 55 will actually survive to age 80. The relation between the two is given by the survivorship function l(x) ((Willekens 1977)equation 36) in the following way:

$$\frac{de(a)}{dM(x)} = \frac{de(x)}{dM(x)} * l(x) * l^{-1}(a)$$

Proportional change and sensitivity of a lifelong change

So far we have looked at absolute changes at one particular age and its impact on (state-specific) life expectancy. However, many risk factors or interventions have a proportional (or relative) rather than an additive effect on rates. The change matrix J for a proportional change of incidence rate $\mu_{12}(x)$ will yield

$$\mathrm{J}(x) = \begin{bmatrix} \partial * \mu_{11}(x) & 0 & 0 \\ -\partial * \mu_{12}(x) & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

From an epidemiological point of view it is more realistic that a certain intervention brings about a lifelong change, altering the rates (proportionally) from that age onwards. When expressing the change as a proportion of the original rates and the resulting effect on life expectancy as a proportion of the original life expectancy, the relation between the two is called elasticity. Note that elasticity is basically the same as sensitivity expressed in relative instead of absolute terms. To calculate the relative impact on life expectancy of a life long proportional change from age x onwards, one can simply add the elasticities of all ages

$$\frac{de(a)}{dM(x+)} = \sum_{x}^{\omega} \frac{de(a)}{dM(x)}$$

An advantage of elasticities is they are comparable for rates on different scales.

State-specific entropies

The relation between a proportional lifelong change in a rate and the resulting change in life expectancy is known in demography as entropy (Keyfitz and Caswell 2005). Hence, entropy is an elasticity measure giving information on the efficiency of an intervention changing the rates uniformly.

If a rate can be reduced over all ages by a certain intervention, the entropy reveals how efficient this intervention is in improving life expectancy. Even an impressive reduction of 50% of a rate may result in a poor increase of life expectancy when few people are at risk, the rate was initially low or few life years are to be saved. In demography, entropy is mainly used to express how a proportional change in the death rate translates into a change in total life expectancy. In case H=0, all deaths occur at one single age. At the other extreme, when H=1, death rates are the same over all ages and a proportional decrease in the rate will result in an equal increase in life expectancy.
Hill was the first to derive state-specific entropies of health and disease. He calculated how a reduction of 1% in the incidence of dementia would increase the number of person-years with and without dementia (Hill 1997). The main result was that a reduction in incidence rate is the most favorable intervention to compress the burden of dementia. One major limitation of Hill's method is that his model does not allow for recovery. Using the sensitivities from matrix differentiation, one can derive state-specific entropies of more complex Markov models including reverse transitions.

The entropy for state i can be written as

$$H_i = \frac{de_i(a)/dM(a^+)}{e_i(a)}/\delta$$

More precisely, the relative change in healthy life expectancy at age 55 because of a permanent proportional change δ in incidence rates from age 55 onwards is

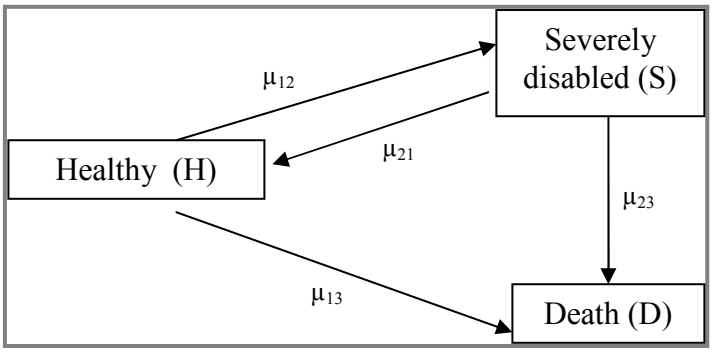
$$H_1 = \frac{de_1(55)/d\mu_{12}(55^+)}{e_1(55)}/\delta$$

State-specific entropies allow us to quantify the impact of permanent changes in the underlying rates.

Sensitivity analysis of healthy and disabled life expectancy: an application to the HRS data.

We estimated transition rates to and from ADL disability and to death based on the US Health and Retirement Survey (HRS), from 1992 to 2004, for men and women aged 55 and over. The illness-death model and state space is depicted in the following graph

Figure 1: Multistate illness-death model



The life table outcomes of our interest here are healthy, ADL disabled and total life expectancy at age 55. Applying the multistate life table to White non-Hispanic males from the HRS, healthy life expectancy, $e_1(55)$, disabled life expectancy, $e_2(55)$, and total life expectancy, $e_3(55) = e_1(55),+ e_2(55)$, yield

Healthy ex	Disabled ex	Total ex
14.03	8.81	22.85

The sensitivity of a small absolute change in the incidence rate at age 55, $\mu_{12}(55)$ to state-specific life expectancy at that age is calculated by

$$\frac{de(55)}{dM(55)} = -(e(55) - 0.5 * I) * (I - 0.5 * M(55))^{-1} * J * L(55) * l^{-1}(55)$$

using

$$J = \begin{bmatrix} -0.01 & 0 & 0 \\ 0.01 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

yields $de_i(55)$ for males of

Healthy ex	Disabled ex	Total ex
0.123	-0.092	0.031

Meaning that an absolute decrease in incidence rate at age 55 of 0.01 will increase healthy life expectancy at age 55 by 0.12 and will decrease disabled life expectancy by 0.09.
The impact of a change in incidence at a higher age, say age 80, is obviously much smaller.

$$\frac{de(55)}{dM(80)} = -(e(80) - 0.5 * I) * (I - 0.5 * M(80))^{-1} * J * L(80) * l^{-1}(55)$$

Results in $de_i(55)$ after a change of M(80)

Healthy ex	Disabled ex	Total ex
0.0062	-0.0043	0.0019

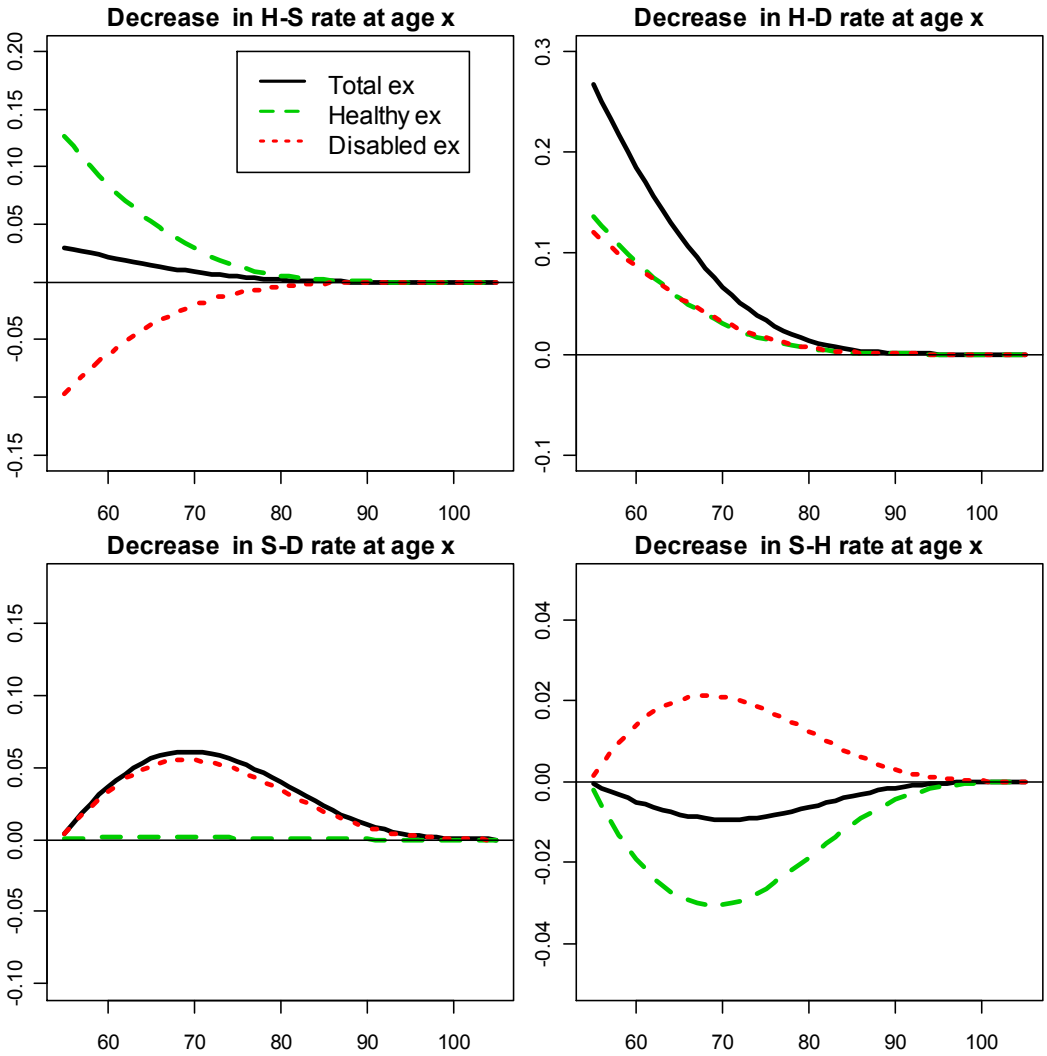
We verified the results by means of the numerical approach, decreasing the incidence rate at age 80 manually and recalculating the life expectancies at age 55:

	Healthy ex	Disabled ex	Total ex
life expectancy after a change in M(80)	14.039	8.808	22.847
$de_i(55)$ after a change in M(80)	0.0063	-0.0043	0.0020

The results are practically the same as from the analytical differentiation.

The next graphs show the sensitivities on life expectancies at age 55 of absolute changes in rates at different ages for males based on the analytic matrix differentiation method.

Figure 2: Sensitivity of state-specific life expectancy at age 55 to a change in rate at age x



The research question that can be answered by this type of sensitivity analyses is at what age an intervention is most effective in terms of prolonging healthy or total life expectancy. The graphs above show that decreasing incidence rate and death rate from healthy state is most efficient at young ages: the sooner the intervention, the better. However, for the death rate from disabled state and for the recovery rate there is a clear optimal age for an intervention to be most efficient, both around age 68 for US men. The age at which most effect can be reached depends on the number of persons exposed to the risks, the initial rates at that age and the life years to be saved.

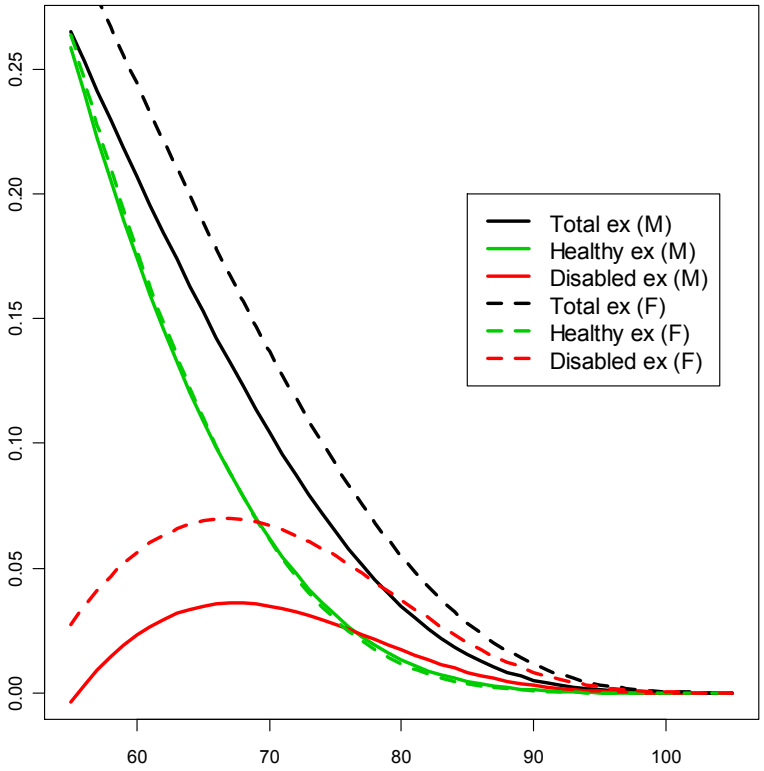
A simultaneous change: decelerating ageing

Let us show an example of changes to two or more rates at the same time. Imagine for example that a therapy would be discovered that would slow down the biological process of ageing, meaning that rates to disability and mortality rates from healthy and disabled state would all come down by let's say 1%. J would yield

$$J = \begin{bmatrix} -0.02 & 0 & 0 \\ 0.01 & -0.01 & 0 \\ 0.01 & 0.01 & 0 \end{bmatrix}$$

The state-specific life expectancy sensitivity function shows at what age this would have the largest effect for men and women.

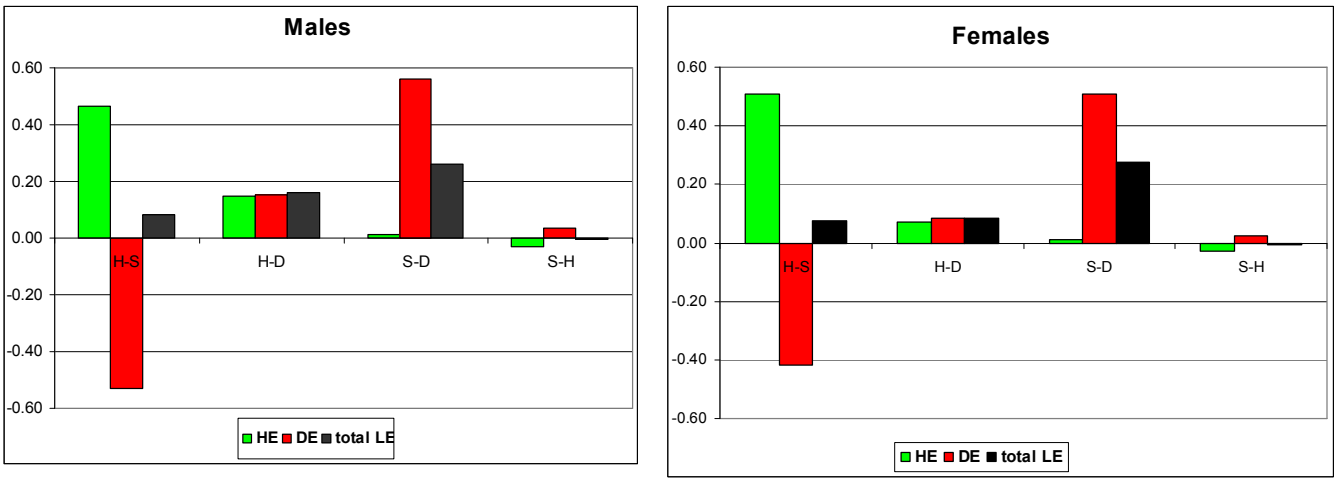
Figure 3: Changes in state-specific life expectancy for men and women as a result of decelerated ageing



The figure demonstrates that slowing down the pace of ageing earlier in life is the more beneficial in terms of gains in total and healthy life expectancy. Gains in disabled life expectancy however increase up to age 70, before coming down. Apparently the prevented incidences of disability do not outweigh the number of disabled that were saved from dying at these ages. This is especially true for women: decelerated ageing brings about equal gains in healthy life expectancy for men and women and all years that women gain more than men are gains in disabled life expectancy.

Entropies of health and disability

When we express the permanent change δ in terms of a relative change in the rate and the resulting change in life expectancy in relative terms of the initial life expectancy, the entropy H_i can be interpreted as elasticity. For example, the entropy of healthy life expectancy with respect to the incidence rate tells us by what percentage healthy life expectancy would increase if the incidence rate declines by δ percent.
An illustration of state-specific entropies by rate from the HRS is given in the next figure.



A reduction in death rate from healthy state (H-D) of 1 % from age 55 onwards will increase healthy and disabled life expectancy at age 55 both by 0.15%. The entropies demonstrate that if the aim is to extend healthy life expectancy, the most efficient way to achieve this is to reduce incidence rate, H-S (entropy is 0.46); a decline in death rate from disable state (S-D) or an increase in recovery rate (S-H)

have hardly any effect on healthy life expectancy. Reducing incidence rates have more impact on disabled life for females than for males, while a reduction in death rates give more gains for males.

Summary and discussion

This study demonstrates sensitivity analysis of a multistate life table and tries to show its usefulness for research on compression or expansion of morbidity. It builds on existing research on entropy of the survival curve, multistate life table functions and matrix differentiation. The linkage between a change in one of the rates and the resulting change in life expectancy is not straightforward, but depends on the initial level of the rate, the number of persons at risk and life years to be saved. The sensitivity functions of the state-specific life expectancy tell us for which rate and at what age an intervention would be most effective to gain (healthy) life years.

Epidemiological research often examines the relative change in a rate because of an intervention or riskfactor from a particular age onwards. The proportional hazards ratio expresses the relative risk, uniform over all ages. Sensitivity analysis of a life table bridges proportional hazard ratio analysis with demographic life table analyses by expressing the relative change in a rate to the relative change in resulting life expectancy as elasticity. These state-specific elasticities, or entropies, easily and intuitively show the effectiveness of healthcare interventions to save healthy or disabled life years.

Our multistate life table analysis rests on the assumption that disability dynamics follow a first-order Markov process, meaning that duration of disability does not influence the transition rates to recover of die. Furthermore, because of singularity of some matrices, we used the linear approach to derive the multistate life table functions. The linear approach assumes that the events are uniformly distributed over the interval. This approximation is adequate when transition rates are small or the interval is short. As incidence and mortality rates become rather large at higher ages, one needs to be cautious using the linear approximation when intervals are larger.

Like all differentiation methods, the sensitivity functions derived by matrix differentiation only hold as long as the changes under study are small. When the values in matrix J, indicating the changes, grow

larger, the resulting gains or losses in life expectancy from the analytical method will diverge from the real effects on life expectancy. To some extend this is equally true for the numerical approach as large changes in one particular rate will probably alter the entire system. One can easily test the accuracy of the analytical method by means of the empirical method.

Although multistate models in health research are considered superior to several other epidemiological models like the multiple-decrement life table or Sullivan's method (Barendregt, Bonneux et al. 1994), multistate models are not applied as wide-spread as one might expect or would wish for. One of the reasons could be the need for longitudinal data of at least two waves to estimate transition rates. Another possible explanation for researchers' reluctance might be the unfamiliarity with matrix algebra. Sensitivity analysis of multistate models using matrix differentiation has received very little attention in the literature, probably because of that same reason. This paper tries to demonstrate the usefulness of sensitivity analysis in multistate illness-death models and shows simple applications that could serve researchers and policymakers in studies and debate about compression and expansion of morbidity.

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Appendix 1: The multistate life table

The multistate life table is an extension of the simple life table, introducing more than two states. As opposed to other more simple transition models, like the multiple decrement life table, the multistate life table enables us to understand transitions to non-absorbing states.(Manton and Stallard 1988) The literature distinguishes status- and population based life tables ((Bongaarts, Burch et al. 1987) p 136-145). We will use the status-based method, meaning that life table measures depend on the state occupied at the reference age. For ages at which all individuals are in the same state, status-based and population-based measures are identical. Although some epidemiological models use the duration of a disease of impairment to predict mortality or disability processes, we will estimate transition rates only based on age and hence our model can be described as a time-inhomogeneous Markov process with a finite number of states.(Manton and Stallard 1988)

Population models using matrices are often classified as stage- or age classified matrix models (Caswell 2001).We will use a stage classified matrix model that changes over age. For every single age, transition rates to and from the different stages or states are estimated from observed transitions. All multistate lifetable functions are derived from these age-specific transition rates (Willekens 1977). Let **M**(x) denote the matrix of annual transition rates at age x

$$\mathrm{M}(x) = \begin{bmatrix} \mu_{12}(x) + \mu_{13}(x) & -\mu_{21}(x) & 0 \\ -\mu_{12}(x) & \mu_{21}(x) + \mu_{23}(x) & 0 \\ -\mu_{13}(x) & -\mu_{23}(x) & 0 \end{bmatrix}$$

Let **P**(x) be the matrix of age-specific transition probabilities with $p_{ii}(x)$ being the probability that a person will survive and remain in the current state at exact age x. The probabilities matrix can be derived from the transition rates matrix **M**(x). To be consistent with the differentiation method, we will use linear approximation to estimate the probabilities. Because the age intervals are small (1 year), the linear model gives a good approximation of the exponential approach.[1]

[1] Total life expectancy at age 55 for males was 22.84547 years with the linear and 22.84318 years with the exponential model.

$$P(x) = \left[I + 0.5 * M(x)\right]^{-1} * \left[I - 0.5 * M(x)\right]$$

Where I is the identity matrix containing ones on the diagonal and zeros elsewhere.

The probability that a person starting out in state k will be in state i ate age x is given by ${}_kl_i(x)$.

Following the Markov property we assume that the state at age x only depends on the state at age x-1 and l(x) can be calculated as

$$l(x) = P(x-1) * l(x-1)$$

Where l(0) is set at an arbitrary constant, called the radix, such as 100000.

Another useful life table function is the number of person-years lived in state i between age x and x+1, by the people who started out in state k. When using linear interpolation, **L**(x) can be written as

$$L(x) = 0.5 * \left[I + P(x)\right] * l(x)$$

Where ${}_1L_2(x)$ is the number of personyears lived in state 2 by persons starting out in state 1.

Perhaps the most important life table function, life expectancy e(x), can be obtained by aggregating L(x) over all ages beyond age x up to the maximum age ω.

$$e(x) = \left[\sum_{x}^{\omega} L(x)\right] * l^{-1}(x)$$

Element ${}_ie_k(x)$ expresses the expected number of years lived in state k beyond age x by an individual aged x, who is currently in state i.

Appendix 2: R code for life table functions, sensitivity functions and state-specific entropies.

```
# Function to calculate life table functions based on rates matrix M
dim <- 3
ltAges <- 55:105
LT.func <- function (M){
        I <- array(data=0,dim=c(dim,dim,length(ltAges)))
        A <- array(data=0,dim=c(dim,dim,length(ltAges)))
        B <- array(data=0,dim=c(dim,dim,length(ltAges)))
        P <- array(data=0,dim=c(dim,dim,length(ltAges)))
        I<-diag(rep(1,dim))     #Identity matrix
                for (i in 1:length(ltAges)){
                        A[,,i] <-solve(I + 0.5*M[,,i])
                        B[,,i] <- (I - 0.5*M[,,i])
                        P[,,i] <-A[,,i] %*% B[,,i]
                }
        radix <- 100000

        l <- array(data=0,dim=c(dim,dim,length(ltAges)))
        l[,,1]<- diag(rep(1,dim))
                for (i in 2:length(ltAges)){
                        l[,,i] <- (P[,,i-1]%*%l[,,i-1])
                }
        l <- l*radix

        I <- array(data=0,dim=c(dim,dim,length(ltAges)))
        L.X <- array(data=0,dim=c(dim,dim,length(ltAges)))
        I<-diag(rep(1,dim))
                        for (i in 1:length(ltAges)){
                        L.X[,,i] <-  0.5 * (I+P[,,i])
                }

        L.0 <- array(data=0,dim=c(dim,dim,length(ltAges)))
                for (i in 1:length(ltAges)){
                        L.0[,,i] <- L.X[,,i]%*%l[,,i]
                }

        e.x <- array(data=0,dim=c(dim,dim,length(ltAges)))
        T.x <- array(data=0,dim=c(dim,dim,length(ltAges)))
                 for (i in 1:length(ltAges)){
                        T.x[,,i] <- apply(L.0[,,i:length(ltAges)],1:2,sum)
                        e.x[,,i] <- T.x[,,i]%*%solve(l[,,i])
                 }
return(list(l,L.X,L.0,e.x))}
```

```
# Function J.change returns the J-matrix indicating the relative change of the rate of interest.
J.rel <- array(0,dim=c(3,3,length(ltAges)))

J.change <-     function(J.col,J.row,M, change){
                        for (i in 1:length(ltAges)){
                                J.rel[J.row,J.col,i] <- (change)*M[J.row,J.col,i]
                                J.rel[J.col,J.col,i] <- -(change)*M[J.row,J.col,i]
                        }
                 return(J.rel)}

# example of J indicating a decrease in H2Drate
Change <- 0.01
J <- J.change(3,1,M,change)

# Function to calculate the sensitivity of state-specific life expectancy with respect to a change in the
# rates,  indicated in Matrix J.
func.sens <-    function(J,a, l, L.0, M, e.x){
                dif.he <- rep(NA,length(ltAges))
                dif.de <- rep(NA,length(ltAges))
                dif.le <- rep(NA,length(ltAges))
                        for (x in 1:length(Ages)){
                                LL <- L.0[,,x]%*% solve(l[,,a])
                                kk<- solve(I-0.5*M[,,x]) %*% J[,,x]%*% LL
                                dif.ex <- -(e.x[,,x]-0.5*I)%*% kk
                                dif.he[x]<-dif.ex[1,1]
                                dif.de[x]<-dif.ex[2,1]
                                dif.le[x] <- dif.ex[3,1]
                        }
                return(cbind(dif.he,dif.de,dif.le))}

# Function to calculate state-specific entropy for males (1) and females (2) separately.
entropy <-      function(J.col, J.row, sex,change){
                        ifelse(sex==1,
                                {dif <- (data.frame(func.sens(J.change(J.col,J.row,M.m,change),
                                a,l.m,L.0.m,M.m,e.x.m)))
                                d.ex.rel <- apply( dif,2,sum)/e.x.m[,1,1]
                                entr <- -d.ex.rel/change} ,
                                {dif <- (data.frame(func.sens(J.change(J.col,J.row,M.f,change),
                                a,l.f,L.0.f,M.f,e.x.f)))
                                 d.ex.rel <- apply( dif,2,sum)/e.x.f[,1,1]
                                entr <- -d.ex.rel/change} )
                return(entr)}
```