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Discrete-Time Multistate Models:  
Extensions to Markov Chains  
with Rewards**

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# Statistical Inference for Discrete-Time Multistate Models: Extensions to Markov Chains with Rewards

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## Abstract

Markov Chains with rewards (MCWR) have been shown to be a useful modelling extension to discrete-time multistate models (DTMS). In this paper, we substantially improve and extend the possibilities that MCWR holds for DTMS. We make several contributions. First, we develop a system of creating and naming different rewards schemes, so-called "standard rewards". While some of these schemes are of interest in their own right, several new possibilities emerge when dividing one rewards result by another, the result of which we call "composite rewards". In total, we can define at least ten new useful outcome statistics based on MCWR that have not yet been used in the literature. Secondly, we derive expressions for asymptotic covariance matrices that are applicable for any standard rewards definition. Thirdly, we show how joint covariance matrices of two or more rewards results can be obtained, which leads to expressions for covariance matrices of composite rewards. Lastly, expressions for point estimates and covariance matrices of partial age ranges are derived. We confirm correctness of results by comparisons to simulation-based results (point estimates) and by comparisons to bootstrap-based results (covariance matrices).

# 1 INTRODUCTION

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In the context of the increased popularity of discrete-time multistate models (DMTS), Markov Chains with rewards (MCWR), originally developed by Howard (1960), have recently been used to extend the set of outcome statistics that DTMS estimation provides. Schneider, Myrskylä, and van Raalte (2023) use MCWR to fine-tune transition timing. Caswell and van Daalen (2021) provide a mathematically succinct and comprehensive account of using MCWR for the purpose of calculating health expectancies and related statistics. Dudel and Myrskylä (2020) show how MCWR can be used to calculate the number of episodes (e.g., disease episodes) and their mean duration.

Despite these developments, MCWR in the context of DTMS is a technique that still contains a lot of unused potential. Since Schneider (2023b) has presented asymptotic formulas for regular DTMS estimation, the question arises whether similar formulas can be derived for MCWR. This would obviate the need for time-consuming bootstrap procedures to which all of the aforementioned papers have to resort for practical inference. Secondly, a systematic exploration of the kinds of statistics that MCWR can provide has not yet been undertaken. Among the contributions of this paper is a treatment of both of these points.

The systematic exploration of MCWR undertaken here is focused on outcome statistics that are independent of the research question, i.e., do not require any specific information that is only available for a particular research project. The "rewards" that are then available are counts, ages, and durations, all of which are essentially determined by the basic setup (age grid) of the model. We develop a system of rewards definitions that we call "standard rewards". An example is the entry count as developed by Dudel and Myrskylä (2020), or, as a variation thereof, the decomposition of entry counts by the corresponding exit counts. While some standard rewards, as these examples show, can have a useful interpretation, much more can be gained by combining results from different standard rewards calculations. We call outcome statistics that are based on the arithmetic joining of two or more standard rewards "composite rewards". For the scope of this paper, this is confined to dividing one rewards result by another. To give an example, dividing results from a standard rewards definition using transition ages by the results of a standard rewards definition that counts entries yields the outcome of "mean age at all entries". In total, we develop at least ten standard or composite rewards outcome measures that are new and that have a useful interpretation.

This article makes two additional contributions. It takes all of the results developed in Schneider (2023b) and extends them to MCWR. Specifically, this includes a) group comparisons of MCWR results via the construction of joint covariance matrices of two or more results; and b) partial age ranges. As a consequence, all results based on MCWR can be used in the same flexible ways as the results from Schneider (2023b).

## 2 PRELIMINARY REMARKS AND NOTATION

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### 2.1 REFERENCE PAPER

This article firmly builds on Schneider (2023b). Everything stated in the preliminary remarks section there equally applies to this article. The reader is strongly encouraged to first get familiar with the material of that article. Since it is so fundamental for following notation and derivations in the present article, it is referred to as the BASE paper. Sections, equations, and figures of that paper are prefixed by "B". For example, section B-4.1 points to section 4.1, equation (B-53) to equation (53), and Figure B-3 to Figure 3, all in Schneider (2023b).

## 2.2 NOTATION AND ABBREVIATIONS

All of the notation and abbreviations of the BASE paper are used in this paper too. The BASE paper abbreviates its two different types of results, life expectancy and mean age at first entry, as LEXP and MAFN, respectively. This paper abbreviates results based on the rewards methodology as REWD. There are many different types of REWD results. They are all given 4-6 letter lower case abbreviations and are enumerated in later sections. To make the text more legible, they are enclosed in single quotes.

This article defines the following mathematical symbols in addition to the ones used in the BASE paper:

Symbol	Meaning	Size
REWD-related		
$F_R, E_R, \dots$	All LEXP-related notation is reused and augmented or modified by an $R$ subscript	
$R_a^s, \tilde{R}_a^s, \tilde{r}_a^s$	$R_a^s$ contains rewards towards state $s$ at age $a$ ;	$\bar{s}_{+1} \times \bar{s}$
	$\tilde{R}_a^s$ is exclusive of rewards to the absorbing state;	$\bar{s} \times \bar{s}$
	$\tilde{r}_a^s$ are the rewards to the absorbing state	$1 \times \bar{s}$
$\bar{R}_a^s$	rewards towards state $s$ at age $a$ , elementwise multiplied by transition probabilities and summed	$1 \times \bar{s}$
$R^s$	contains all $\tilde{R}_a^s$ and $\tilde{r}_a^s$ , conformably arranged w.r.t. $P$	$\bar{s}\bar{a}_{-1} + 1 \times \bar{s}\bar{a}_{-1} + 1$

Covariance matrices for:

(the expression in column "Size" applies to both matrix rows and matrix columns)

$V^{FR}, V^{ER}, \dots$	as matrices $V^F-V^e$ , but for rewards-based results	<i>varies</i>
$V^{full}$	In the context of LEXP: combined covariance matrix for conditional state expectancies, conditional expectancies, state expectancies, and the overall life expectancy; and analogously for REWD results	$\bar{s}^2 + 2\bar{s} + 1$

Matrices used in the transformation of one covariance matrix into another (delta method)

$G^{FR}$	$\tilde{V}^{tr} \rightarrow V^{FR}$	$\bar{s}^2\bar{a}_{-1} \times \bar{s}^2\bar{a}_{-2}$
$G^{full}$	REWD: $V^{ER} \rightarrow V^{full}$	$\bar{s}^2 + 2\bar{s} + 1 \times \bar{s}^2$

Matrices that hold information for two or more results

$\dot{V}^{FX}$	joint covariance matrix of the elements of any two matrices out of $F_1, F_R, F_{BA}$	<i>varies</i>
$\dot{V}^{comb}$	joint covariance matrix of the elements of any two matrices out of $E, E_R, U^{aw}$	<i>varies</i>

Symbol	Meaning	Size
$\check{V}^{full}$	joint covariance matrix of the elements of any two matrices out of $E^{full}, E_R^{full}, I^{full}$	<i>varies</i>
$\check{G}^{FX}$	$\check{V}^{tr} \rightarrow \check{V}^{FX}$	<i>varies</i>
$\check{G}^{full}$	$\check{V}^{comb} \rightarrow \check{V}^{full}$	<i>varies</i>
$V^{cps}$	covariance matrix for composite rewards result	$\bar{s}_{+1}^2 \times \bar{s}_{+1}^2$
$G^{cps}$	REWD: $\check{V}^{full} \rightarrow V^{cps}$	$\bar{s}_{+1}^2 \times 2\bar{s}_{+1}^2$

### 2.3 EXAMPLE DATA SET AND APPLICATION, BOOTSTRAP, AND REPLICATION CODE

This paper uses the same data set on cognitive impairment, the same multistate regression model, and the same bootstrap procedure as the BASE paper; see section B-2.5 for a description. In particular, the cognitive impairment multistate example from the BASE paper will be used here too. This model features three transient states (no, mild, and severe impairment), one absorbing state (death), and single-year ages ranging from 50 to 110. To ease exposition in early sections of this paper, the model is reduced to two transient states only (no impairment and any impairment) and to age intervals of length 10. Counting only transient states, we will refer to these two different model setups as the 2-state model and the 3-state model. A constant for the entirety of the paper is that there is always a single absorbing state. As in the BASE paper, a fixed initial proportion of states (88% without impairment, 10% mildly impaired, 2% severely impaired) that applies to the overall sample is also used for subgroups. This is inconsequential for the comparison of asymptotic CIs against bootstrap CIs.

A joint replication script that covers both papers is publicly available at <https://osf.io/nxeaf>. All calculations were performed using the Stata package "dtms" (Schneider, 2023a) in Stata 18.

### 2.4 CAVEATS

All of the caveats mentioned in the BASE paper also apply to this paper. Among them is the confinement of formulas to models with a single absorbing state. While this is of no relevance for the outcome statistics of the BASE paper, it does matter for some of the new rewards definitions. For example, the reward that is called 'stab' (state at absorption) could be defined in broader terms if more than one absorbing state were incorporated into the formulas. This shortcoming cannot be circumvented easily by redefining some absorbing states as transient states. However, the generalization of formulas to more than one absorbing state is straightforward once the concepts of the current paper are understood.

## 3 MARKOV CHAINS WITH REWARDS

### 3.1 AN ILLUSTRATIVE EXAMPLE

The idea behind the rewards method is to link probabilities of reaching certain states (as contained in the fundamental matrix), conditional on the initial state, with transition probabilities out of that state, where each of these out-transitions is assigned a reward. We will base our introduction on the idea of Dudel and Myrskylä (2020) to use MCWR to estimate the number of disease episodes and recoveries. Consider an illness-death model with recovery that has two transient

states, which we label as "no impairment" and "impaired", and one absorbing state, death; with state encodings 1, 2, and 3, respectively. Assume that the model contains ages  $\mathbf{z} = [50, 60, \dots, 100]$ . The BASE paper defines a matrix  $\hat{\mathbf{P}}$  which collects transition probabilities in a table-like format. That matrix, filled with example numbers for the model currently discussed, is

		$\mathbf{p}_{11}$	$\mathbf{p}_{12}$	$\mathbf{p}_{13}$	$\mathbf{p}_{21}$	$\mathbf{p}_{22}$	$\mathbf{p}_{23}$
		--	--	--	--	--	--
$\hat{\mathbf{P}} =$	<b>50</b>	.	.	.	.	.	.
	<b>60</b>	0.95	0.04	0.01	0.35	0.61	0.04
	<b>70</b>	0.93	0.06	0.01	0.25	0.68	0.06
	<b>80</b>	0.86	0.10	0.04	0.15	0.74	0.12
	<b>90</b>	0.67	0.18	0.16	0.06	0.69	0.25
	<b>100</b>	.	.	1	.	.	1

where orange labels indicate the meaning of columns and rows. The subscripts of the transition probabilities are in  $ji$ -format. A dot in the matrix indicates that the matrix element is never used in any calculations. A corresponding rewards definition that counts disease episodes (state 2) is

		$\mathbf{r}_{11}^2$	$\mathbf{r}_{12}^2$	$\mathbf{r}_{13}^2$	$\mathbf{r}_{21}^2$	$\mathbf{r}_{22}^2$	$\mathbf{r}_{23}^2$
		--	--	--	--	--	--
$\hat{\mathbf{R}}^2 =$	<b>50</b>	.	.	.	.	.	.
	<b>60</b>	0	1	0	0	0	0
	<b>70</b>	0	1	0	0	0	0
	<b>80</b>	0	1	0	0	0	0
	<b>90</b>	0	1	0	0	0	0
	<b>100</b>	.	.	0	.	.	0

The ones in the column labeled  $\mathbf{r}_{12}^2$  count whenever the disease state is entered: For the transition  $1 \rightarrow 2$  (subscripts), a reward of 1 is assigned to state 2 (superscript). MCWR calculations use the information in  $\hat{\mathbf{P}}$  and  $\hat{\mathbf{R}}^2$  to calculate the number of episodes. We can define a similar rewards matrix that counts the number of recoveries: For the transition  $2 \rightarrow 1$ , a reward of 1 is assigned to state 1.

		$\mathbf{r}_{11}^1$	$\mathbf{r}_{12}^1$	$\mathbf{r}_{13}^1$	$\mathbf{r}_{21}^1$	$\mathbf{r}_{22}^1$	$\mathbf{r}_{23}^1$
		--	--	--	--	--	--
$\hat{\mathbf{R}}^1 =$	<b>50</b>	.	.	.	.	.	.
	<b>60</b>	0	0	0	1	0	0
	<b>70</b>	0	0	0	1	0	0
	<b>80</b>	0	0	0	1	0	0
	<b>90</b>	0	0	0	1	0	0
	<b>100</b>	.	.	0	.	.	0

Before we systematically explore the outcome statistics that can be estimated with different definitions of the rewards matrices  $\hat{\mathbf{R}}^s$ , we state the formulas for the point estimates.

### 3.2 POINT ESTIMATES

Markov chains with rewards are an extension of regular Markov chains, so the following elaborations can be seen as an extension of the derivations for life expectancy. The MCWR extension of a Markov chain nests life expectancy calculations as a special case. MCWR formulas have been made fruitful and developed further for analyses in ecology and demography by Caswell (2011) and van Daalen and Caswell (2017).

Derivations are done in the stage-within-age ordering, where the full transition matrix  $\mathbf{P}$  is

$$\mathbf{P} = \begin{bmatrix} \mathbf{U} & \mathbf{0} & \mathbf{0} \\ \mathbf{p}_d & \mathbf{1} & \mathbf{1} \end{bmatrix} \quad (1)$$

where  $\mathbf{U}$  is as defined in (B-1) and  $\mathbf{p}_d$  contains the probabilities of dying (getting absorbed) for ages 2, ...,  $\bar{a}-1$

$$\mathbf{p}_d = [\mathbf{p}_{d,2} \quad \cdots \quad \mathbf{p}_{d,\bar{a}-1}] \quad (2)$$

and, in  $ij$ -notation (see section B-2.1.1),

$$\mathbf{p}_{d,a} = [p_{d1,a} \quad \cdots \quad p_{d\bar{s},a}] \quad (3)$$

The second block column of (1) corresponds to age  $\bar{a}$  at which subjects are assumed to get absorbed. The last block column is a single column and corresponds to the absorbing state. We define an age-specific submatrix of  $\mathbf{P}$

$$\check{\mathbf{P}}_a = \begin{bmatrix} \mathbf{U}_a \\ \mathbf{p}_{d,a} \end{bmatrix} \quad (4)$$

and a conformably partitioned rewards matrix

$$\mathbf{R}_a^s = \begin{bmatrix} \tilde{\mathbf{R}}_a^s \\ \tilde{\mathbf{r}}_a^s \end{bmatrix} \quad (5)$$

where  $\tilde{\mathbf{R}}_a^s$  rewards transitions among the transient states and  $\tilde{\mathbf{r}}_a^s$  rewards transitions to the absorbing state. Rewards are with respect to state  $s$  and at transition age  $a$ . Even though it is not directly relevant for the derivations in this section, it is worth noting that the definition of  $\mathbf{R}_a^s$  implies a matrix  $\mathbf{R}^s$  that includes information for all ages  $a$  and that mimics the structure of  $\mathbf{P}$ :

$$\mathbf{R}^s = \begin{bmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} & \mathbf{0} \\ \tilde{\mathbf{R}}_2^s & \mathbf{0} & \mathbf{0} & & \mathbf{0} & \mathbf{0} \\ 0 & \tilde{\mathbf{R}}_3^s & \mathbf{0} & & \mathbf{0} & \mathbf{0} \\ \vdots & & \ddots & \ddots & \vdots & \\ \mathbf{0} & \mathbf{0} & \cdots & \tilde{\mathbf{R}}_{\bar{a}-1}^s & \mathbf{0} & \mathbf{0} \\ \tilde{\mathbf{r}}_2^s & \tilde{\mathbf{r}}_3^s & \cdots & \tilde{\mathbf{r}}_{\bar{a}-1}^s & \tilde{\mathbf{r}}_{\bar{a}}^s & 0 \end{bmatrix} \quad (6)$$

Returning to our definition of age-specific matrices, the central concept of an elementwise assignment of rewards to transitions and the summation over all out-transitions of a state is embodied in the expression

$$\mathbf{1}_{\bar{s}} \cdot (\check{\mathbf{P}}_a \odot \mathbf{R}_a^s) = \bar{\mathbf{R}}_a^s \quad (7)$$

where we have introduced the symbol  $\bar{\mathbf{R}}_a^s$ . As usual, the bar accent indicates summation over the rows, so without it we have  $\mathbf{R}_a^s = \check{\mathbf{P}}_a \odot \mathbf{R}_a^s$ . The idea of linking probabilities of reaching states with rewards for out-transitions from those states is captured, in analogy to (B-25), by

$$\mathbf{F}_R^s = \left[ \bar{\mathbf{R}}_2^s \quad \bar{\mathbf{R}}_3^s \mathbf{U}_2 \quad \cdots \quad \bar{\mathbf{R}}_{\bar{a}}^s \prod_{a=\bar{a}-1}^2 \mathbf{U}_a \right] = [\mathbf{f}_2 \quad \mathbf{f}_3 \quad \cdots \quad \mathbf{f}_{\bar{a}-1} \quad \mathbf{f}_{\bar{a}}] \quad (8)$$

where we have introduced  $\mathbf{f}_a$  as a shorthand for the matrix products of the first term in brackets. Note that (8) is a row vector since the  $\bar{\mathbf{R}}_a^s$  are row vectors. Stacking over all  $\bar{s}$  states, we have

$$\mathbf{F}_R = \begin{bmatrix} \mathbf{F}_R^1 \\ \vdots \\ \mathbf{F}_R^{\bar{s}} \end{bmatrix} \quad (9)$$

Summing up the block columns corresponding to each age then yields the point estimates, for which we use the symbol  $\mathbf{E}_R$  to emphasize the analogy to (B-18):

$$\mathbf{E}_R = \mathbf{F}_R (\mathbf{1}'_{\bar{a}-1} \otimes \mathbf{I}_{\bar{s}}) \quad (10)$$

The conditional, state, and overall linear combinations and the composition of all results within a single matrix are then done as in (B-19)-(B-23). In particular, we have

$$\mathbf{e}_R^{full} = \begin{bmatrix} \text{vec } \mathbf{E}_R \\ \mathbf{e}_R^{cond} \\ \mathbf{e}_R^{state} \\ e_R \end{bmatrix} \quad (11)$$

which is best presented by rearranging the elements as

$$\mathbf{E}_R^{full} = \begin{bmatrix} \mathbf{E}_R & \mathbf{e}_R^{state} \\ \mathbf{e}_R^{cond'} & e_R \end{bmatrix} \quad (12)$$

For the example model and numbers given in section 3.1, matrix (12) is, displayed as a properly labeled table,

		initial state		
		no imp.	any imp.	total
reward to:	no imp.	0.03	0.59	0.10
	any imp.	0.32	0.15	0.30
	total	0.35	0.74	0.40

The results of rewards calculations have the same structure as life expectancy: In the last row and last column of (12) contain the sum (rows) and weighted sum (columns) of the preceding rows and columns, respectively (compare B-22).

For our illness-death example, this means that  $\mathbf{E}_R$  is a  $2 \times 2$  matrix, with columns indicating the initial state and rows indicating the state that is rewarded. For example, the row 2, column 1 element of  $\mathbf{E}_R$  shows the number of disease episodes for subjects that were initially healthy. Summing columns over the rows yields total rewards conditional on initial state; a weighted sum of rows over columns yields overall state rewards; and a combination of these operations gives the grand total. In our case, this grand total of 0.4 is to be interpreted as the expected number of times that a subject randomly picked from the initial population changes to a different transient state during its lifetime.

### 3.3 A SYSTEM OF REWARDS DEFINITIONS: STANDARD REWARDS

#### 3.3.1 Formal Definition

A number of meaningful rewards can be estimated by filling rewards matrices with non-stochastic information that pertains to the model setup. Essentially, this relates to transition ages, time durations, or counts.

The system of rewards definitions we propose is captured by 4–6-character rewards names that pin down 4 different pieces of information. These names are composed of

$$\underbrace{\{n|x|u|t|f\}}_{\text{selection part}} + \underbrace{\{cnt|tbt|atr|amp|att\}}_{\text{value part}} \underbrace{[+ \#]}_{\substack{\text{state detail} \\ \text{number}}} \underbrace{[+ \{i|p|n\}]}_{\text{sign part}} \quad (13)$$

where terms in curly braces separated by a vertical line represent alternatives and terms in brackets are optional. The selection part of a standard reward selects the columns of a rewards matrix  $\mathbf{R}$ , the value part fills in the values, the state detail number optionally requests state detail, and the sign part determines the sign. We call rewards definitions that follow this scheme *standard rewards*.

The individual abbreviations in (13) mean the following:

#### Selection part

- n (rewards) entries
- x (rewards) exits
- u (rewards) unchanged
- t total (the union of n, x, u)
- f full matrix (all columns)

'n' and 'x' are to be viewed as 'rewards entries' and 'rewards exits'. For example,  $r_{12}^2$  is a 'rewards entry' because state 2 is both entered and rewarded; while  $r_{12}^1$  is not, and neither is  $r_{22}^1$ . 'u' refers to transitions without change of state, again in the "rewards sense" that the rewards number must match the *ji*-part ( $r_{11}^1$  and  $r_{22}^2$  qualify, but  $r_{22}^1$  and  $r_{11}^2$  do not). Columns not matched by the selection part specification are filled with zeroes.

#### Value part

- cnt count (ones)
- tbt time bound to transition
- atr age (at) transition
- amp age (at) mid-point (within entry-interval and/or exit-interval of the transition)
- att age times time

'cnt' just fills in ones, negative ones in the case of the standard reward 'xcnt', and a mixture of positive and negative ones for 'ncnt#' and 'xcnt#'. 'cnt' is the only value part specification that has no reference to time. All other specifications depend on transition timing (for example, mid-period). 'atr' fills in the age at transition, which does not differ across non-zero columns. The other specifications need lengthier explanations, which are postponed to the next subsection.

#### State (detail) number

- # state number

A state detail number in standard rewards refers to state  $s$  of the model. A state detail number is only allowed for selection parts 'n' and 'x', whose definitions are then modified: When '#' is specified, only the entries (exits) of the state # are selected. For the other states, the exits (entries) to state # are selected. To give two examples, 'ncnt#' counts the entries for state # and provides detail about the states that subjects came from. 'xcnt#' counts the exits from state # and provides detail about the states into which subjects go. Both 'ncnt#' and 'xcnt#' fill in positive and negative ones. Negative ones are always used for counts of state exits (see the section on the sign part below). If the value part is not 'cnt', positive numbers are used everywhere.

An important convention is introduced at this point. Whenever a state detail number is present, the formulas for the point estimates are modified in that the totals row of  $E_R^{full}$  (equation (12)), which normally holds  $E_R$  summed over the rows, now simply repeats the row of  $E_R$  that corresponds to the state whose detail is requested. This is because the default operation of summing over the rows would identically result in a row of zeroes, which would be unsuitable for the usage of these standard rewards as denominators in the construction of composite rewards. Composite rewards will be explained in section 3.4.

Sign part

i	inverted
p	all positive
n	all negative

By default, numbers are taken to be positive numbers, with the following exceptions: 'x' in combination with 'cnt' (the rewards exit count) uses negative numbers; and 'xcnt#' and 'ncnt#', where # is the state detail number, use a mixture of positive and negative numbers. Adding an explicit sign part to the standard rewards name changes the default usage of signs.

Additional formal expressions for the above as well as example matrices are provided in appendix section 8.2.

### 3.3.2 Explanation of Non-Trivial Value Parts

The three values parts 'tbt', 'amp', and 'att' of (13) have not yet been explained because they require lengthier elaboration, which we turn to now. They are mainly used for the calculation of composite rewards, which are treated further below in section 3.4. Example rewards matrices shown in this section are based on two transient states. Appendix section 8.2.2 shows additional example rewards matrices based on three transient states.

#### 3.3.2.1 Time-Bound-to-Transition

The value part 'tbt' records the time-bound-to-transition according to a certain transition timing, and its prime application is the standard reward 'tbt', which is illustrated in the following. Consider the model setup given in section 3.1. If we assume mid-period transitions, we have the situation as depicted in scheme MID-SPLIT, section B-2.1.4, Box B-1. It is helpful to consult that scheme if statements below are not clear. The corresponding rewards for the example model setup and assumption MID-SPLIT are:

		$r_{11}^1$	$r_{12}^1$	$r_{13}^1$	$r_{21}^1$	$r_{22}^1$	$r_{23}^1$	$r_{11}^2$	$r_{12}^2$	$r_{13}^2$	$r_{21}^2$	$r_{22}^2$	$r_{23}^2$
$\dot{R} = [\dot{R}^1 \quad \dot{R}^2] =$	<b>50</b>	.	.	.	.	.	.	.	.	.	.	.	.
	<b>60</b>	10	5	5	5	0	0	0	5	0	5	10	5
	<b>70</b>	10	5	5	5	0	0	0	5	0	5	10	5
	<b>80</b>	10	5	5	5	0	0	0	5	0	5	10	5
	<b>90</b>	10	5	5	5	0	0	0	5	0	5	10	5
	<b>100</b>	.	.	5	.	.	0	.	.	0	.	.	5

The row labels of that matrix record the prediction ages. Under assumption of mid-period transitions the first transition takes place between the first two prediction ages, at 55. When staying healthy, this transition is preceded by five healthy years and followed by five healthy years. The first element of the first column, labeled  $r_{11}^1$ , records the reward for the healthy state for that particular transition. It is equal to ten, the total reward of all time that is bound to that transition. Since the model has equally spaced age intervals, this value also applies to transitions at later ages (65, 75, ...). The reward for the impaired state of that transition,  $r_{21}^1$ , is zero, since no time preceding the transition nor the time after the transition is spent in the impaired state. Impairment incidences are always preceded by five years in the healthy state and followed by five years in the impairment state, so we have  $r_{12}^1 = r_{12}^2 = 5$ . Finally, when dying from the healthy state, we have  $r_{13}^1 = 5$ . The rewards for the impaired state are set up according to the same logic. The standard reward 'tbt' yields results that are identical to life expectancy calculations.

### 3.3.2.2 Age-(at)-Midpoint and Age-Times-Time

The value part 'amp', whose prime application is the standard reward 'tamp', under the mid-period transition assumption, has a rewards matrix of

		$r_{11}^1$	$r_{12}^1$	$r_{13}^1$	$r_{21}^1$	$r_{22}^1$	$r_{23}^1$	$r_{11}^2$	$r_{12}^2$	$r_{13}^2$	$r_{21}^2$	$r_{22}^2$	$r_{23}^2$
$\dot{R} = [\dot{R}^1 \quad \dot{R}^2] =$	<b>50</b>	.	.	.	.	.	.	.	.	.	.	.	.
	<b>60</b>	55	52.5	52.5	57.5	0	0	0	57.5	0	52.5	55	52.5
	<b>70</b>	65	62.5	62.5	67.5	0	0	0	67.5	0	62.5	65	62.5
	<b>80</b>	75	72.5	72.5	77.5	0	0	0	77.5	0	72.5	75	72.5
	<b>90</b>	85	82.5	82.5	87.5	0	0	0	87.5	0	82.5	85	82.5
	<b>100</b>	.	.	92.5	.	.	0	.	.	0	.	.	92.5

Consider the first row that contains numbers, with corresponds to the transition at 55. The time-bound-to-transition of the element in column  $r_{11}^1$  spans the time from 50 to 60, the mid-point of which is 55. The time-bound-to-transition of the elements in columns  $r_{12}^1$  and  $r_{13}^1$  span the time from 50 to 55, so the mid-points are 52.5, Finally, the time-bound-to-transition of the element in column  $r_{21}^1$  spans the time from 55 to 60, so the mid-point is 57.5. The rewards for the impaired state are set up according to the same logic.

'amp' does not have a use of its own, but is used only to calculate the value part age-times-time, 'att', which is the elementwise matrix product of the rewards matrices for 'amp' and 'tbt'. Its main use is for the calculation of the composite reward 'mais' (mean age in state), which is elementwise calculated as 'tatt' / 'tbt' (see below).

### 3.3.3 Alias Rewards

It is helpful to define separate names for standard rewards that have a particularly interesting interpretation, but a name that is difficult to remember. We make two such definitions here. First, the standard reward 'ncnt' counts the number of entries to states. A description that is more suitable for researchers is the "number of episodes", so we use the name 'epis'

as a synonym for 'ncnt'. Secondly, 'ncntAp', where 'A' must be substituted by  $\bar{s}_{+1}$ , the number of the absorbing state, is the standard rewards name for the entry detail for the absorbing state, with all counts converted to positive numbers. The entry detail for the absorbing state shows the origins of those transitions. A more useful description for the calculation is "state at absorption." Therefore, we use the name 'stab' as a synonym for 'ncntAp'. The two names 'epis' and 'stab' are referred to as *alias rewards*.

For the first alias reward, 'epis', a slight adjustment is suggested and followed in this paper: While the standard reward 'ncnt' does not count the initial state as an "episode", 'epis' does so. The resulting numbers can be obtained by simply adding an identity matrix to  $E_R$ , which also changes the column and row totals of  $E_R^{full}$  (see equations (10) and (12)).

### 3.4 COMPOSITE REWARDS

Many standard rewards are not meaningful by themselves, but gain their usefulness only in conjunction with a second standard reward. For example, consider the two standard rewards 'tbt' and 'ncnt'. The first one is the time-bound-to-transition, which is equivalent to life expectancy. The second one is the entry (episodes) count. When dividing the former elementwise by the latter, the result is the mean duration of episodes, abbreviated in this article as 'mdur'. Another example are the two standard rewards 'natrA' and 'ncntAp'. The former provides the state detail for age-at-transition numbers for entries to the absorbing state. The latter provides state detail for the entry count to the absorbing state. An elementwise division of the former by the latter yields the mean age at absorption, which we abbreviate by 'maab'.

The following table below lists several definitions of composite rewards. All of them consist of an elementwise division of a first set of standard rewards results by a second set of standard rewards results. The elementwise division is performed on two matrices, each calculated as in (10) or (12).

<b>Composite rewards name</b>	<b>Description</b>	<b>Calculation in terms of standard rewards</b>
mdur	mean duration of episodes	tbt / ncnt
maan	mean age, all entries	natr / ncnt
maax	mean age, all exits	xatr / xcnti
maan#	mean age, all entries, detail for state encoded #	natr# / ncnt#p
maax#	mean age, all exits, detail for state encoded #	xatr# / xcnt#p
maab	mean age at absorption	natrA / ncntAp (A=absorbing state)
mais	mean age in state	tatt / tbt

### 3.5 SUMMARY OF REWARDS-BASED OUTCOME MEASURES

The following table lists the outcome measures discussed in the previous sections that have a useful interpretation. It can be used as a reference table to look up abbreviations. In subsequent text, these abbreviations will not be explained again.

**Table 1: List of Rewards-Based Outcome Measures**

Standard rewards	
xcnt	exit count
ncnt#	entry count, detail for state #: breakdown w.r.t. exits to other states
xcnt#	exit count, detail for state #: breakdown w.r.t. entries from other states
Alias rewards	
epis	number of episodes
stab	state at absorption
Composite rewards	
mdur	mean duration of episodes
maan	mean age, all entries
maax	mean age, all exits
maan#	mean age, all entries, detail for state encoded #
maax#	mean age, all exits, detail for state encoded #
maab	mean age at absorption
mais	mean age in state

In the introduction we claimed to have developed "at least ten" new useful outcome measures. Table 1 lists 12 different results, but the rewards 'epis' and 'mdur' had already been developed before (Dudel & Myrskylä, 2020), which reduces the count to ten. We say "at least ten", because the system of standard rewards and their usage for the construction of composite rewards may contain additional useful definitions. For example, in analogy to the composite rewards 'maan' and 'maax', one could define the composite reward 'maau' (mean age, all unchanged states), which has the mean age of all transitions where subjects stay in the same state. It can be calculated by dividing the standard reward 'uatr' by the standard reward 'ucnt'. We do not see an immediate use for this – but this may depend on the application. Hence the wording of "at least ten."

### 3.6 INTERPRETATION

The following elaborations use numbers from the 3-state cognitive impairment example to clarify interpretation of all rewards results listed in Table 1. Example numbers will be given in small tables that indicate the type of reward in the upper left corner. Each table is then followed by a short verbal explanation of selected numbers.

		initial state			
		no imp.	mild imp.	severe imp.	total
reward to:	xcnt				
	no imp.	-1.929	-1.717	-1.201	-1.894
	mild imp.	-1.610	-2.483	-1.687	-1.699
	severe imp.	-0.336	-0.388	-1.276	-0.360
	total	-3.875	-4.588	-4.164	-3.952

*Interpretation:* Those initially severely impaired on average leave their current state (change state) 4.164 times, and are moving 1.201 times to the unimpaired state, 1.6871 times to state mild and 1.276 times to state severe. On average, a subject exits a state and moves to a different state 3.952 times, which includes transitions to the absorbing state. Note that exits are by default displayed using negative numbers. Note also that the total number 3.952 corresponds to the total number for the alias reward 'epis'. We will remark on that when we look at that reward further below.

		initial state			
		no imp.	mild imp.	severe imp.	total
reward to:	ncnt1				
	no imp.	0.929	1.717	1.201	1.014
	mild imp.	-0.924	-1.707	-1.136	-1.007
	severe imp.	-0.005	-0.009	-0.065	-0.007
	total	0.929	1.717	1.201	1.014

*Interpretation:* Those initially severely impaired enter (at any point during their lifetime) the no-impairment state 1.201 times. That number decomposes into 1.136 transitions from the mildly impaired state and 0.065 transitions from the severely impaired state. Note that the totals row simply repeats the row of the state for which detail was requested. If it contained the sum of the state rows it would contain zeroes. On average, a subject enters the no-impairment state 1.014 times. Initial states are not counted as state entries.

		initial state			
		no imp.	mild imp.	severe imp.	total
reward to:	xcnt1				
	no imp.	-1.929	-1.717	-1.201	-1.894
	mild imp.	1.454	1.287	0.896	1.426
	severe imp.	0.008	0.008	0.005	0.008
	total	-1.929	-1.717	-1.201	-1.894

*Interpretation:* Those initially severely impaired exit the no-impairment state 1.201 times. Of those 0.896 go to the mildly impaired state and 0.005 go to the severely impaired state. This is not a proper decomposition since the latter two numbers do not add to the first one: The remainder goes to the absorbing state (death). Note how the row 1, columns 2 and 3 numbers correspond to the numbers of the 'ncnt1' result above. Differences arise in column 'no imp.', where the

'xcnt1' number is 1.929, versus 0.929 for 'ncnt1'. It is higher by 1 because it includes the initial state, which is left with certainty at absorption. Add to that the 0.929 entries to state 1 which occur after the initial age, which also will lead to certain exits at absorption. The column one differences then lead to differences in the initial proportions weighted total (-1.894 v. 1.014).

		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	1.929	1.717	1.201	1.894
	mild imp.	1.610	2.483	1.687	1.699
	severe imp.	0.336	0.388	1.276	0.360
	total	3.875	4.588	4.164	3.952

*Interpretation:* Counting the initial state, those starting out non-impaired will have on average 1.929 visits to the non-impaired state. They will enter a transient state that is different from the current one on average 3.875 times, counting the initial state as a state entry. Those starting out severely impaired will on average have 1.201 visits to the non-impaired state. They will on average enter a transient state 4.164 times, counting the initial state as an entry to severe impairment. The average subject will enter a new transient state 3.952 times, again counting the initial state as a state entry.

Note that the numbers in the 'epis' table are the exact negatives of the ones in the 'xcnt' table. Three remarks need to be made about this: 1) The numbers are identical because each entry to a state must have a corresponding exit, at the latest when subjects enter the absorbing state. 2) 'epis', by convention, is based on, but not identical to, 'ncnt'. The former counts initial states as state entries (episodes), whereas the latter does not. The difference between the two, however, is fixed (does not depend on transition probabilities). 3) 'epis' (or 'ncnt') and 'xcnt' are redundant (contain the same information) only when estimated over the full age range. In section 5 results for partial age ranges are developed, and here 'epis' (or 'ncnt') differs from 'xcnt'.

		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	0.467	0.422	0.300	0.460
	mild imp.	0.358	0.394	0.280	0.360
	severe imp.	0.174	0.183	0.420	0.180
	total	1.000	1.000	1.000	1.000

*Interpretation:* On average, 46.0% of subjects die when being healthy, 36.0% when being mildly impaired, and 18.0% when being severely impaired. Conditionally on being severely impaired initially, these numbers change to 30.0%, 28.0%, and 42.0%, respectively.

<b>mdur</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	12.714	12.432	11.943	12.678
	mild imp.	2.381	1.980	2.216	2.319
	severe imp.	2.249	2.207	1.658	2.203
	total	7.514	5.911	4.851	7.272

*Interpretation:* Counting the initial state as an episode, the mean duration of no-impairment stays for those starting out unimpaired is 12.714 years. Those starting out mildly impaired on average stay in a particular state 5.911 years, taking the initial episode of mild impairment into account. On average, a subject stays in a particular state 7.272 years before moving to a different (transient or absorbing) state.

<b>maan</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	68.804	60.157	61.369	67.164
	mild imp.	70.862	71.031	63.965	70.732
	severe imp.	77.333	72.204	73.046	76.677
	total	70.953	65.954	63.772	70.191

*Interpretation:* The average age at which those who start out mildly impaired enter the no-impairment state is 60.157. This can be based on any (one or multiple) number of entries into the healthy state, and the entry may occur from the mild or severe impairment state. Note that the interpretation is not that the average age of transitions from mild to no impairment is 60.157. The average age at which those starting out in the severe impairment state change state is 63.772. The average age at which subjects enter an alive state is 70.191. None of this counts the initial age.

<b>maax</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	71.772	72.589	73.312	71.866
	mild imp.	73.243	64.540	66.181	71.830
	severe imp.	79.582	74.412	56.644	77.398
	total	73.060	68.388	65.316	72.354

*Interpretation:* The average age at which those who start out mildly impaired exit the no-impairment state is 72.589. This can be based on any (one or multiple) number of exits from the healthy state, and the exits may lead to any of the other (transient or absorbing) states. This is important: The interpretation is not that the average age of transitions from no impairment to mild impairment is 72.589. The average age at which those starting out in the severe impairment state

exit any state is 65.316. The average age at which subjects exit a transient state (to a transient or absorbing state) is 72.354. None of this counts the initial state and base age.

<b>maan1</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	68.804	60.157	61.369	67.164
	mild imp.	68.793	60.143	61.863	67.170
	severe imp.	70.700	62.696	52.717	66.296
	total	68.804	60.157	61.369	67.164

*Interpretation:* On average, a subject enters the no-impairment state at age 67.164. These entries are composed of exits from mild impairment that occur at age 67.170 and of exits from severe impairment occurring at age 66.296. The totals row just repeats the values for the state on which detail is provided.

<b>maax1</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	71.772	72.589	73.312	71.866
	mild imp.	70.266	71.117	71.874	70.363
	severe imp.	73.252	73.902	74.486	73.327
	total	71.772	72.589	73.312	71.866

*Interpretation:* On average, a subject exits the no-impairment state at age 71.866. These exits are composed of entries to mild impairment that occur at age 70.363, entries to severe impairment occurring at age 73.327, and deaths, whose mean age is not recorded in the table. The totals row just repeats the values for the state on which detail is provided.

<b>maab</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	76.430	77.055	77.588	76.502
	mild imp.	80.886	76.208	77.113	80.315
	severe imp.	82.697	79.216	60.338	81.299
	total	79.119	77.117	70.202	78.740

*Interpretation:* On average, a subject that dies in the non-impaired state is 76.502 years old; and 80.315 and 81.299 years when dying in the mild and severe impairment states, respectively. The average age at death is 78.740, the same number that one gets from LEXP calculations of the BASE paper.

<b>mais</b>		initial state			total
		no imp.	mild imp.	severe imp.	
reward to:	no imp.	65.134	66.006	67.051	65.235
	mild imp.	73.528	67.384	67.181	72.641
	severe imp.	78.838	74.112	58.216	77.226
	total	66.595	66.512	66.150	66.581

*Interpretation:* The average age of all time lived in the unimpaired state is 65.235; and 72.641 and 77.226 are the average ages of all time lived with mild and severe impairment, respectively. Averaging over all person-years lived, the average age is 66.581.

### 3.7 CONFIRMATION OF POINT ESTIMATES VIA SIMULATION

The derivations in section 3.2 and their interpretation given in section 3.5 can be checked for agreement with numbers obtained via the simulation of life histories. When based on simulated trajectories, the numbers for the different rewards-based concepts are obtained by very simple computations. For example, to obtain 'stab' numbers, one simply takes the state proportion of the period preceding death in the simulated trajectories. Likewise, 'mais' is simply calculated by taking the average age, taking only periods into account in which a subject's life history passes through a particular state. These computations have to be done separately by the state at base age, with subsequent (weighted) summing, but this is only a minor complication. While simulation cannot give a definitive answer about correctness of analytical results due to the randomness inherent in the procedure, it can provide an impression as to whether results seem consistent or rather point towards errors.

In order to make the comparison, we use the 3-state cognitive impairment multistate setup that is used in the BASE paper (see section B-2.5). The three transient states of the model are no impairment, mild impairment, and severe impairment.

Figure 1 shows the results of a comparison between analytically calculated rewards point estimates and the ones obtained via simulation of life histories. Three different simulations are employed, differing by the number of trajectories (1,000, 10,000, and 100,000).<sup>1</sup> Convergence of the results based on simulations towards the analytical result with increasing number of trajectories is then an indication of correctness of the analytical derivations and calculations.

Results are shown for the complete set of rewards listed in section 3.5 (graph rows) and for a subset of 4 of the 16 components of a rewards result (graph columns) for the example application. Since the magnitudes of results vary across rows and columns of the graph, one has to pick individual scales for each subgraph in order to achieve a useful visualization. For the purpose of harmonizing scales across subgraphs, Figure 2 copies the layout of Figure 1, but presents simulation numbers as relative differences with respect to the analytical numbers. The harmonized horizontal scales make a visual assessment of convergence easier. Moreover, the relative difference of analytical results with respect to themselves is always zero, so convergence emerges if the relative differences of simulation results converge to zero.

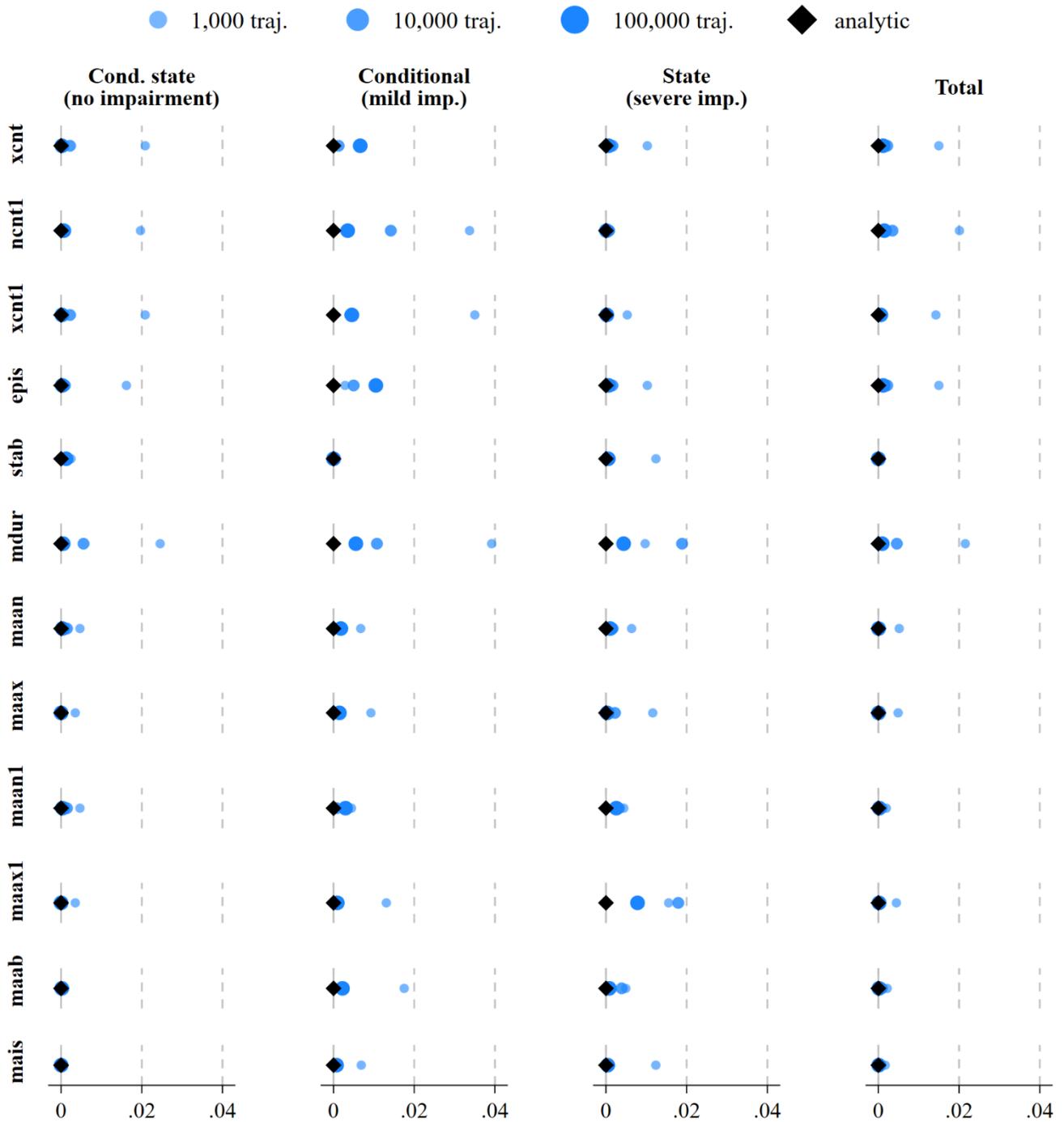
<sup>1</sup> The three simulated trajectory data sets are not independent: A simulated data set of a given size forms the first part of the next larger simulated data set. For example, the simulated data set of 1,000 trajectories forms the first part of the simulated data set of 10,000 trajectories.

**Figure 1: Convergence of Rewards Numbers Based on Simulations to Analytically Calculated Results**



Notes: Convergence of rewards point estimates based on simulations to analytically calculated results (black diamonds) by increasing number of simulated trajectories, ranging from 1,000 trajectories (small light blue circles) to 100,000 (big dark blue circles). Each row shows results for a single alias reward or a composite reward (see section 3.5 for a listing of abbreviations). The first column shows results for the no impairment state, conditional on no impairment at the base age. The second column shows results for (the sum of) all states, conditional on mild impairment at the base age. The third column shows results for the severe impairment state, with initial states weighted by population fractions. The fourth column shows the total, i.e., results for (the sum of) all states, with initial states weighted by population fractions.

Figure 2: Relative Difference of Analytically Calculated and Simulated Rewards Numbers



Notes: Convergence of rewards point estimates to analytically calculated results (black diamonds) by increasing number of simulated trajectories, ranging from 1,000 trajectories (small light blue circles) to 100,000 (big dark blue circles). Numbers depicted are relative differences of the simulation result and analytic result, calculated as  $|a - s| / (|s| + 1)$ , where  $a$  and  $s$  are the values for the analytic and simulated results, respectively. Otherwise the notes from Figure 1 apply.

Each of the 48 subgraphs of Figure 1 (or of Figure 2) suggests two comparisons that matter with respect to the question of convergence: whether the simulation with 10,000 trajectories is closer to the analytical result than the simulation with 1,000 trajectories; and similarly for the simulations with 100,000 and 10,000 trajectories. Out of the total number of 96 comparisons, 16 fail. There is a single subgraph that fails both comparisons ('epis' – conditional). This may be explained by the fact that the "Conditional (mild imp.)" column of graphs is based only on a small subset of trajectories (~8%), according to the initial proportion of mild impairment. The number of subgraphs that have a single failure is 14 (e.g., 'stab' – conditional state, 'mdur' - state). However, these unfavorable comparisons seem to be due to chance. For example, 'maax1' – total violates one comparison, but the visual inspection of the subgraph still suggests convergence of results. In addition, the overall level of relative differences is very small (i.e., simulated and analytical numbers are very close, in general). The overall picture that emerges from these graphs therefore is that simulation results generally converge towards analytical results, with exceptions that are plausibly due to chance.

### 3.8 COVARIANCE MATRICES FOR STANDARD REWARDS

A matrix derivative rule used in this section, in addition to the ones used in BASE, is, for generic matrices (see, e.g., Lütkepohl, 1996, p.185),

$$\frac{\partial \text{vec}(\mathbf{A} \odot \mathbf{X})}{\partial \text{vec}(\mathbf{X})'} = \frac{\partial \text{vec}(\mathbf{X} \odot \mathbf{A})}{\partial \text{vec}(\mathbf{X})'} = \text{diag}(\text{vec}(\mathbf{A}))$$

where  $\text{diag}(\cdot)$  constructs a diagonal matrix from its vector input.

We are seeking, for (8),

$$\frac{\partial \text{vec}(\mathbf{f}_i)}{\partial \text{vec}(\mathbf{U}_j)'}$$

which we can, again in analogy to section B-4.2, write as

$$\frac{\partial \text{vec}(\mathbf{f}_i)}{\partial \text{vec}(\mathbf{U}_j)'} = \frac{\partial \text{vec}(\bar{\mathbf{R}}_i^s * \prod_{a=i-1}^{j+1} \mathbf{U}_a * \mathbf{U}_j * \prod_{a=j-1}^2 \mathbf{U}_a)}{\partial \text{vec}(\mathbf{U}_j)'}$$

in order to facilitate application of the matrix differentiation rule (B-27). In the present context, the only case that needs a closer look is the one of  $i = j$ , because here the term  $\bar{\mathbf{R}}_i^s$  gets differentiated, so the goal becomes to obtain an expression for

$$\frac{\partial \text{vec}(\bar{\mathbf{R}}_a^s)}{\partial \text{vec}(\mathbf{U}_a)'}$$

We start by noting that

$$\frac{\partial \text{vec}(\bar{\mathbf{R}}_a^s)}{\partial \text{vec}(\mathbf{U}_a)'} = \frac{\partial \text{vec}(\mathbf{1}_{\bar{s}} \cdot (\check{\mathbf{P}}_a \odot \mathbf{R}_a^s))}{\partial \text{vec}(\mathbf{U}_a)'} = \frac{\partial \text{vec}(\mathbf{1}_{\bar{s}} \cdot (\check{\mathbf{P}}_a \odot \mathbf{R}_a^s))}{\partial \text{vec}(\check{\mathbf{P}}_a \odot \mathbf{R}_a^s)'} \times \frac{\partial \text{vec}(\check{\mathbf{P}}_a \odot \mathbf{R}_a^s)}{\partial \text{vec}(\mathbf{U}_a)'}$$

where the first term is  $\mathbf{I}_{\bar{s}} \otimes \mathbf{1}_{\bar{s}+1}$ . For the second term, recall that

$$\check{\mathbf{P}}_a \odot \mathbf{R}_a^s = \begin{bmatrix} \mathbf{U}_a \\ \mathbf{p}_{d,a} \end{bmatrix} \odot \begin{bmatrix} \bar{\mathbf{R}}_a^s \\ \bar{\mathbf{r}}_a^s \end{bmatrix} \quad (14)$$

It will helpful to work with the transpose of (14)

$$[\mathbf{U}'_a \odot \tilde{\mathbf{R}}_a^{s'} \quad \mathbf{p}'_{d,a} \odot \tilde{\mathbf{r}}_a^{s'}] \quad (15)$$

To arrive at this expression, we use the definition of the commutation matrix  $\mathbf{K}_{nm}$  (see section B-2.4) and its special property that  $\mathbf{K}_{nm} = \mathbf{K}_{mn}^{-1}$  to write

$$\frac{\partial \text{vec}(\check{\mathbf{P}}_a \odot \mathbf{R}_a^s)}{\partial \text{vec}(\mathbf{U}_a)'} = \frac{\partial \mathbf{K}_{\bar{s}\bar{s}+1} \text{vec}(\check{\mathbf{P}}'_a \odot \mathbf{R}_a^{s'})}{\partial \mathbf{K}_{\bar{s}\bar{s}} \text{vec}(\mathbf{U}'_a)'} = \mathbf{K}_{\bar{s}\bar{s}+1} \frac{\partial \text{vec}(\check{\mathbf{P}}'_a \odot \mathbf{R}_a^{s'})}{\partial \text{vec}(\mathbf{U}'_a)'} \mathbf{K}_{\bar{s}\bar{s}}$$

What remains to be developed are the derivatives of the two expressions in (15). The first one is

$$\frac{\partial \text{vec}(\mathbf{U}'_a \odot \tilde{\mathbf{R}}_a^{s'})}{\partial \text{vec}(\mathbf{U}'_a)'} = \text{diag}(\text{vec}(\tilde{\mathbf{R}}_a^{s'}))$$

and the second one is

$$\frac{\partial \text{vec}(\mathbf{p}'_{d,a} \odot \tilde{\mathbf{r}}_a^{s'})}{\partial \text{vec}(\mathbf{U}'_a)'} = \frac{\partial \text{vec}(\mathbf{p}'_{d,a} \odot \tilde{\mathbf{r}}_a^{s'})}{\partial \text{vec}(\mathbf{p}'_{d,a})'} * \frac{\partial \text{vec}(\mathbf{p}'_{d,a})}{\partial \text{vec}(\mathbf{U}'_a)'} \quad (16)$$

The probabilities of dying are one minus the probabilities of transitioning to any one of the transient states, so  $\mathbf{p}_{d,a}$  can be written in terms of the stochastic quantities as

$$\mathbf{p}_{d,a} = \mathbf{1}_{\bar{s}} - (\mathbf{1}_{\bar{s}} \cdot \mathbf{U}_a)$$

and its transpose as

$$\mathbf{p}'_{d,a} = \mathbf{1}'_{\bar{s}} - (\mathbf{U}'_a \cdot \mathbf{1}'_{\bar{s}})$$

Substituting this into the second term of (16) we get

$$\frac{\partial \text{vec}(\mathbf{p}'_{d,a} \odot \tilde{\mathbf{r}}_a^{s'})}{\partial \text{vec}(\mathbf{U}'_a)'} = \text{diag}(\tilde{\mathbf{r}}_a^{s'}) \times (-\mathbf{1}_{\bar{s}} \otimes \mathbf{I}_{\bar{s}}) = -(\mathbf{1}_{\bar{s}} \otimes \text{diag}(\tilde{\mathbf{r}}_a^{s'}))$$

Putting all the different parts together, our final result is

$$\frac{\partial \text{vec}(\bar{\mathbf{R}}_a^s)}{\partial \text{vec}(\mathbf{U}_a)'} = \frac{\partial \text{vec}(\mathbf{1}_{\bar{s}} \cdot (\check{\mathbf{P}}_a \odot \mathbf{R}_a^s))}{\partial \text{vec}(\mathbf{U}_a)'} = (\mathbf{I}_{\bar{s}} \otimes \mathbf{1}_{\bar{s}+1}) \mathbf{K}_{\bar{s}\bar{s}+1} \begin{bmatrix} \text{diag}(\text{vec}(\tilde{\mathbf{R}}_a^{s'})) \\ -(\mathbf{1}_{\bar{s}} \otimes \text{diag}(\tilde{\mathbf{r}}_a^{s'})) \end{bmatrix} \mathbf{K}_{\bar{s}\bar{s}} \quad (17)$$

With this result in hand, we can extend equation (B-28) to read

$$\mathbf{G}^{FR} = \quad (18)$$

	$\mathbf{U}_2$	$\mathbf{U}_3$	$\mathbf{U}_4$	...	$\mathbf{U}_{\bar{a}-1}$
$\bar{\mathbf{R}}_2^s$	$[\mathbf{I} \otimes \mathbf{1}] \frac{\partial \text{vec}(\bar{\mathbf{R}}_2^s)}{\partial \text{vec}(\mathbf{U}_2)'}$	$\mathbf{0}$	$\mathbf{0}$	...	$\mathbf{0}$
$\bar{\mathbf{R}}_3^s \mathbf{U}_2$	$\mathbf{I} \otimes \bar{\mathbf{R}}_3^s$	$[\mathbf{U}_2' \otimes \mathbf{1}] \frac{\partial \text{vec}(\bar{\mathbf{R}}_3^s)}{\partial \text{vec}(\mathbf{U}_3)'}$	$\mathbf{0}$		$\mathbf{0}$
$\bar{\mathbf{R}}_4^s \mathbf{U}_3 \mathbf{U}_2$	$\mathbf{I} \otimes \bar{\mathbf{R}}_4^s \mathbf{U}_3$	$\mathbf{U}_2' \otimes \bar{\mathbf{R}}_4^s$	$[(\mathbf{U}_3 \mathbf{U}_2)' \otimes \mathbf{1}] \frac{\partial \text{vec}(\bar{\mathbf{R}}_4^s)}{\partial \text{vec}(\mathbf{U}_4)'}$		$\mathbf{0}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
$\bar{\mathbf{R}}_{\bar{a}-1}^s \mathbf{U}_{\bar{a}-2} \dots \mathbf{U}_2$	$\mathbf{I} \otimes \bar{\mathbf{R}}_{\bar{a}-1}^s \dots \mathbf{U}_3$	$\mathbf{U}_2' \otimes \bar{\mathbf{R}}_{\bar{a}-1}^s \dots \mathbf{U}_4$	$(\mathbf{U}_3 \mathbf{U}_2)' \otimes \bar{\mathbf{R}}_{\bar{a}-1}^s \dots \mathbf{U}_5$	$\left[ (\mathbf{U}_{\bar{a}-2} \dots \mathbf{U}_2)' \otimes \mathbf{1} \right] \frac{\partial \text{vec}(\bar{\mathbf{R}}_{\bar{a}-1}^s)}{\partial \text{vec}(\mathbf{U}_{\bar{a}-1})}'$	$\mathbf{0}$
$\bar{\mathbf{R}}_a^s \mathbf{U}_{\bar{a}-1} \dots \mathbf{U}_2$	$\mathbf{I} \otimes \bar{\mathbf{R}}_a^s \dots \mathbf{U}_3$	$\mathbf{U}_2' \otimes \bar{\mathbf{R}}_a^s \dots \mathbf{U}_4$	$(\mathbf{U}_3 \mathbf{U}_2)' \otimes \bar{\mathbf{R}}_a^s \dots \mathbf{U}_5$	...	$(\mathbf{U}_{\bar{a}-2} \dots \mathbf{U}_2)' \otimes \bar{\mathbf{R}}_a^s$

A stacked and reordered version over all states

$$\mathbf{G}^{FR} = \mathcal{K}_{jia}^{iaj} \begin{bmatrix} \mathbf{G}_R^{F_1^1} \\ \vdots \\ \mathbf{G}_R^{F_{\bar{s}}} \end{bmatrix} \mathcal{K}_{jia}^{aji'} \quad (19)$$

can then be used to transform the covariance matrix of transition probabilities in

$$\mathbf{V}^{FR} = \mathbf{G}^{FR} \tilde{\mathbf{V}}^{tr} \mathbf{G}^{FR'} \quad (20)$$

Simple sums of matrix blocks over ages then yield

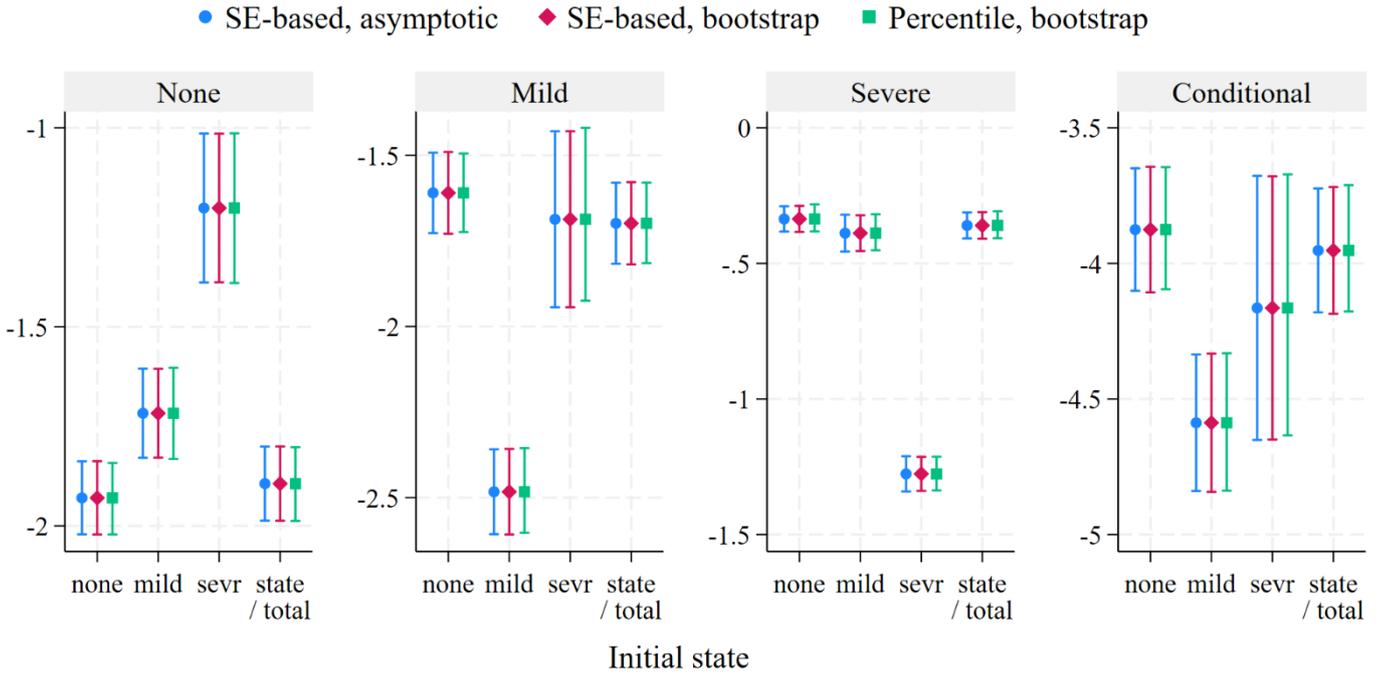
$$\mathbf{V}^{ER} = (\mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1}) \mathbf{V}^{FR} (\mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1})' \quad (21)$$

The expressions for the conditional, state, overall, and full linear combinations are in simple analogy to (B-31)-(B-35).

### 3.9 COMPARISON TO BOOTSTRAP RESULTS: STANDARD AND ALIAS REWARDS

Using results from the cognitive impairment example, Figure 3 compares 95% asymptotic and bootstrap confidence intervals (CIs; compare section B-4.3 and Figure B-1) of the standard reward 'xcnt'. There are only minute differences between them.

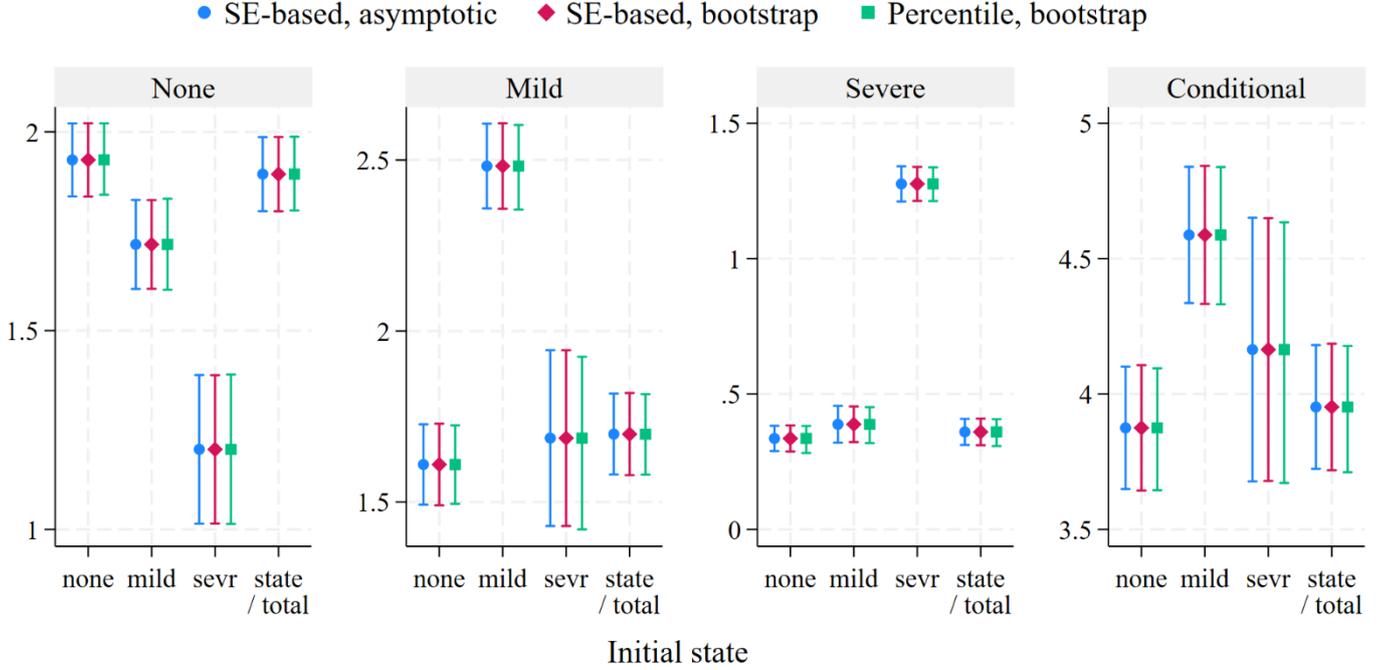
**Figure 3: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Standard Reward 'xcnt' (Exit Count)**



Notes: The numbers and confidence intervals pertain to the standard reward 'xcnt', which counts exits from states. Subgraphs 1-3 show the number of exits from a state, by initial state (categorical axis: none, mild, or severe) and weighted using initial state proportions. The rightmost subgraph shows the total number of exits from all states taken together (the sum total). The four plot triplets of each subgraph correspond to one row of matrix (12); that is, the order of the 16 plot triplets, from left to right over the full graph, i.e., across subgraph headings (outcome states) and subgraph categorical axes (initial states), in terms of equation (12), is  $\text{vec}(\mathbf{E}_R^{full'})$  (note the transpose). Blue dots and whiskers show 95% asymptotic confidence intervals based on the derivations in this article. Red diamonds and whiskers depict 95% confidence intervals based on the standard errors obtained from 500 bootstrap samples; and green squares and whiskers show 95% bootstrap percentile intervals. Each point estimate triplet uses a single value: the asymptotic one.

Figure 4 performs the same comparison, but with respect to the alias reward 'epis'. Again, asymptotic and bootstrap CIs are very close. Analogous visual comparisons that apply to the remaining standard and alias rewards of section 3.5 are relegated to appendix section 8.1. All of them show a close correspondence of asymptotic and bootstrap CIs.

**Figure 4: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results:**  
Alias Reward 'epis' (Number of Episodes)



Notes: The numbers and confidence intervals pertain to the alias reward 'epis', which counts the number of episodes of (entries into) states. Otherwise the notes from Figure 3 apply.

## 4 GROUP COMPARISONS

### 4.1 COMBINING STANDARD REWARDS

Derivations are in full analogy to the life expectancy ones in section B-6.2, using matrices  $\check{\mathbf{G}}^{FR}$ ,  $\check{\mathbf{V}}^{FR}$ ,  $\check{\mathbf{V}}^{ER}$  in place of their obvious counterparts, e.g.,

$$\check{\mathbf{V}}^{FR} = \check{\mathbf{G}}^{FR} \check{\mathbf{V}}^{tr} \check{\mathbf{G}}^{FR'} \quad (22)$$

$$\check{\mathbf{G}}^{FR} = \begin{bmatrix} \mathbf{G}_1^{FR} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_2^{FR} \end{bmatrix} \quad (23)$$

The only difference concerns the summation matrix in the calculation of  $\check{\mathbf{V}}^{ER}$ , which is obtained by

$$\check{\mathbf{V}}^{ER} = \begin{bmatrix} \mathbf{I}_{S^2} \otimes \mathbf{1}_{\bar{a}_{-1}} & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{\bar{S}^2} \otimes \mathbf{1}_{\bar{a}_{-1}} \end{bmatrix} \check{\mathbf{V}}^{FR} \begin{bmatrix} \mathbf{I}_{S^2} \otimes \mathbf{1}_{\bar{a}_{-1}} & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{\bar{S}^2} \otimes \mathbf{1}_{\bar{a}_{-1}} \end{bmatrix}' \quad (24)$$

## 4.2 COMBINING DIFFERENT TYPES OF RESULTS

Formulas from section B-6.4 apply unchanged when combining rewards results with LEXP or MAFN results. For example, combining REWD with MAFN is done by

$$\begin{aligned}\ddot{\mathbf{G}}^{FX} &= \begin{bmatrix} \mathbf{G}_1^{FR} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_2^{FBA} \end{bmatrix} \\ \dot{\mathbf{V}}^{FX} &= \ddot{\mathbf{G}}^{FX} \dot{\mathbf{V}}^{tr} \ddot{\mathbf{G}}^{FX'} \\ \dot{\mathbf{V}}^{comb} &= \begin{bmatrix} \mathbf{I}_{S^2} \otimes \mathbf{1}_{\bar{a}-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{\bar{a}-1} \otimes \mathbf{g}_2^{im} \end{bmatrix} \dot{\mathbf{V}}^{FX} \begin{bmatrix} \mathbf{I}_{S^2} \otimes \mathbf{1}_{\bar{a}-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{\bar{a}-1} \otimes \mathbf{g}_2^{im} \end{bmatrix}' \\ \ddot{\mathbf{G}}^{full} &= \begin{bmatrix} \mathbf{G}_1^{full} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_2^{full} \end{bmatrix} \\ \dot{\mathbf{V}}^{full} &= \ddot{\mathbf{G}}^{full} \dot{\mathbf{V}}^{comb} \ddot{\mathbf{G}}^{full}'\end{aligned}$$

where  $\dot{\mathbf{V}}^{comb}$  is the covariance matrix of combined/mixed result types. A subscript of 1 in this instance refers to an expression pertaining to rewards-based results and a subscript of 2 to an expression for mean age at first entry, but the procedure applies more generally to *any* mixture of results (LEXP, MAFN, or REWD).

## 4.3 N-GROUP COMPARISONS

For rewards too the formulas given in section B-6.1 to B-6.5 and above generalize to N-group comparisons in the obvious way. They apply to any mixture of results.

## 4.4 COVARIANCE MATRICES FOR COMPOSITE REWARDS

Composite rewards are calculated as the division of one set of results by another set of results, where each of the two results sets are standard rewards. For example, the composite reward 'maan' is calculated by dividing the standard reward 'natr' by the standard reward 'ncnt'. The point estimates for composite rewards are

$$\mathbf{E}_{cps}^{full} = \mathbf{E}_{R_1}^{full} \oslash \mathbf{E}_{R_2}^{full} \quad (25)$$

where  $\oslash$  denotes elementwise division. The formulas for calculating a joint covariance matrix of two different results have been laid out in section 4.2. When using them for the combination of standard rewards for the purpose of calculating a composite rewards result, the following simplifications are present:

- The two standard rewards are based on the same transition probabilities. Therefore, the combined covariance matrix of transition probabilities is just  $\dot{\mathbf{V}}^{tr} = \mathbf{1}_{2,2} \otimes \tilde{\mathbf{V}}^{tr}$ , where  $\tilde{\mathbf{V}}^{tr}$  is the covariance matrix of transition probabilities that the standard rewards have in common.
- The linear combination matrix  $\mathbf{G}^{full}$  is the same for both standard rewards:  $\mathbf{G}_1^{full} = \mathbf{G}_2^{full}$ .

Using these facts and equations from sections 4.1 and 4.2, the combined covariance matrix of the standard rewards is calculated as

$$\begin{aligned}
\ddot{\mathbf{G}}^{FR} &= \begin{bmatrix} \mathbf{G}_1^{FR} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_2^{FR} \end{bmatrix} \\
\ddot{\mathbf{V}}^{FR} &= \ddot{\mathbf{G}}^{FR} \ddot{\mathbf{V}}^{tr} \ddot{\mathbf{G}}^{FR'} \\
\ddot{\mathbf{V}}^{comb} &= \begin{bmatrix} \mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1} \end{bmatrix} \ddot{\mathbf{V}}^{FR} \begin{bmatrix} \mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1} \end{bmatrix}' \\
\ddot{\mathbf{G}}^{full} &= \begin{bmatrix} \mathbf{G}_1^{full} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_1^{full} \end{bmatrix} \\
\ddot{\mathbf{V}}^{full} &= \ddot{\mathbf{G}}^{full} \ddot{\mathbf{V}}^{comb} \ddot{\mathbf{G}}^{full'}
\end{aligned}$$

$\ddot{\mathbf{V}}^{full}$  is the joint covariance matrix of the two standard rewards:

$$\text{cov}(\text{vec}[\mathbf{E}_{R_1}^{full} \quad \mathbf{E}_{R_2}^{full}])$$

which we need to transform into the covariance matrix of the elementwise division

$$\text{cov}(\text{vec}(\mathbf{E}_{R_1}^{full} \oslash \mathbf{E}_{R_2}^{full}))$$

This again requires application of the delta method. The matrix derivative we need is

$$\frac{\partial \text{vec}(\mathbf{E}_{R_1}^{full} \oslash \mathbf{E}_{R_2}^{full})}{\partial \text{vec}[\mathbf{E}_{R_1}^{full} \quad \mathbf{E}_{R_2}^{full}]'}$$

Denoting temporarily by  $e_{1,i}$  and  $e_{1,j}$  the  $i$ -th and  $j$ -th element of  $\text{vec} \mathbf{E}_{R_1}^{full}$ , respectively, and in an analogous fashion for  $\text{vec} \mathbf{E}_{R_2}^{full}$ , we have

$$\begin{aligned}
\frac{\partial \left( \frac{e_1}{e_2} \right)_i}{\partial e_{1,j}} &= \frac{1}{e_{2,i}} \quad \text{if } i = j, \text{ and } 0 \text{ otherwise} \\
\frac{\partial \left( \frac{e_1}{e_2} \right)_i}{\partial e_{2,j}} &= -\frac{e_{1,i}}{e_{2,i}^2} \quad \text{if } i = j, \text{ and } 0 \text{ otherwise}
\end{aligned}$$

which, in matrix notation, is

$$\mathbf{G}^{cps} = \frac{\partial \text{vec}(\mathbf{E}_{R_1}^{full} \oslash \mathbf{E}_{R_2}^{full})}{\partial \text{vec}[\mathbf{E}_{R_1}^{full} \quad \mathbf{E}_{R_2}^{full}]'} = \left[ \text{diag}(\text{vec} \mathbf{E}_{R_2}^{full})^{-1} \quad - \text{diag}(\text{vec} \mathbf{E}_{R_1}^{full}) \odot \text{diag}(\text{vec} \mathbf{E}_{R_2}^{full})^{-2} \right] \quad (26)$$

The covariance matrix of the composite rewards result is then

$$\mathbf{V}^{cps} = \mathbf{G}^{cps} \ddot{\mathbf{V}}^{full} \mathbf{G}^{cps'} \quad (27)$$

Composite rewards can, in turn, be combined with (any number of) other composite rewards, and/or with (any number of) other results. This can be achieved by expanding (B-54) and (B-55) and the formulas of section 4.2 to include all desired non-composite results. Say that, for a particular calculation, a combined covariance matrix for  $K_{non}$  purely non-composite results and  $K_{cps}$  composite results is desired. In order to obtain the joint covariance matrix of the final

$K = K_{non} + K_{cps}$  results, in a first step the joint covariance matrix of the total of  $K_{non} + 2K_{cps}$  non-composite results must be calculated, and then be transformed using

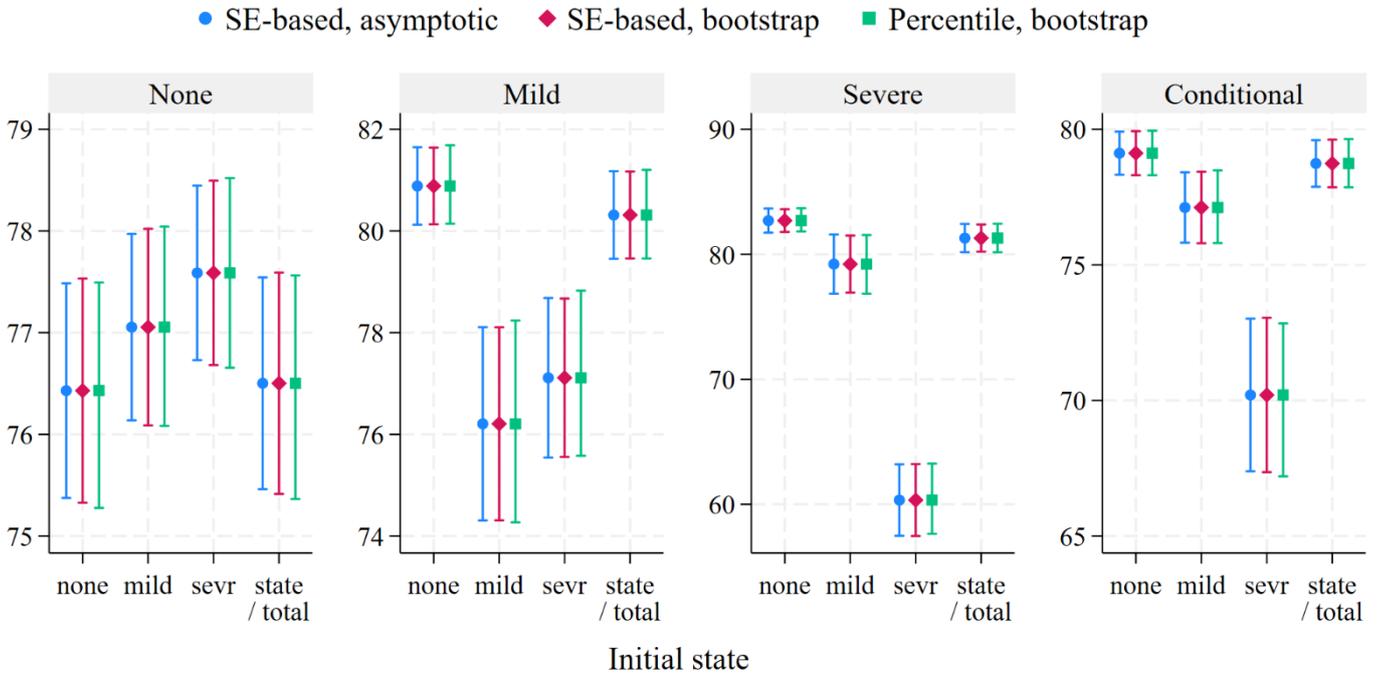
$$\ddot{\mathbf{G}}^X = \begin{bmatrix} \mathbf{G}^{X_1} & \dots & \mathbf{0} \\ \vdots & \ddots & \vdots \\ \mathbf{0} & \dots & \mathbf{G}^{X_K} \end{bmatrix}$$

where  $\mathbf{G}^{X_k} = \mathbf{G}_k^{cps}$  if the  $k$ -th final result is composite, and  $\mathbf{G}^{X_k} = \mathbf{I}$  if it is not, with appropriate dimensions for  $\mathbf{I}$ , depending on the result it operates on ( $2\bar{a}_{-1} + 2$  for MAFN and  $\bar{s}_{+1}^2$  for all other non-composite results).

#### 4.5 COMPARISON TO BOOTSTRAP RESULTS: COMPOSITE REWARDS

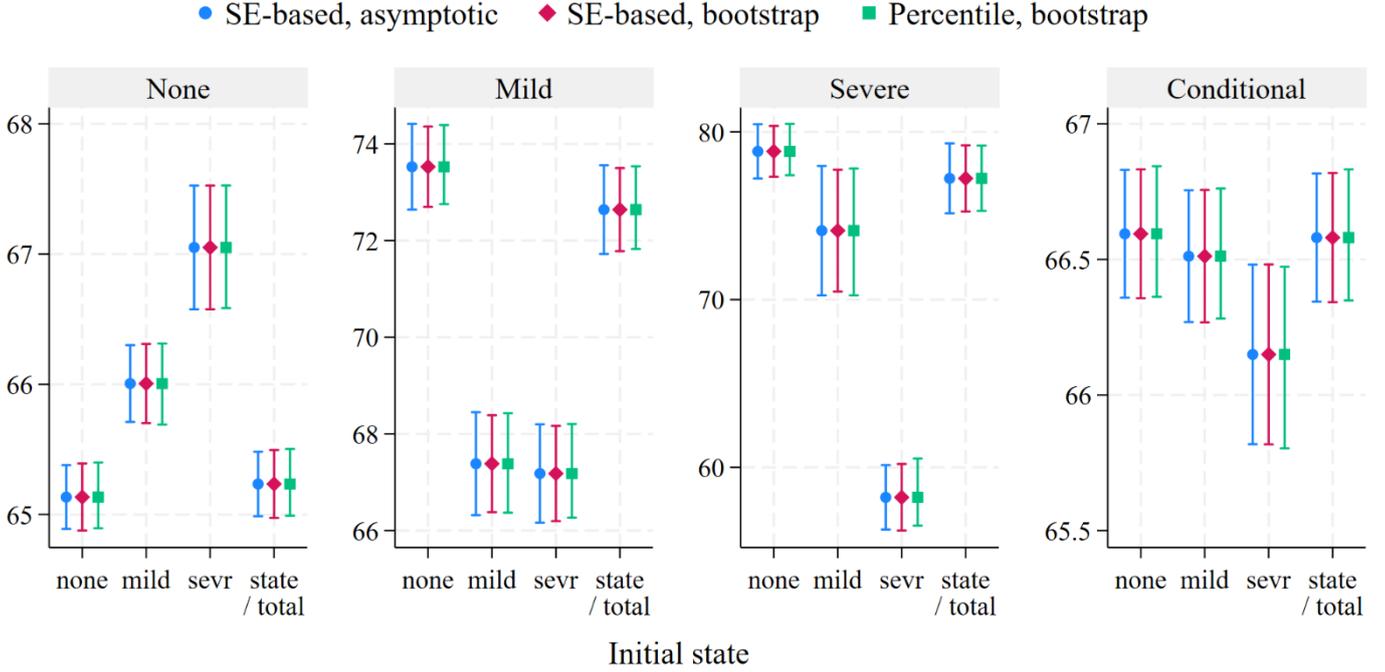
Based on the derivations of the previous subsections and continuing the multistate application on cognitive impairment, Figure 5 and Figure 6 compare 95% asymptotic and bootstrap CIs of the composite rewards 'maab' and 'mais', respectively. Asymptotic and bootstrap CIs exhibit only very small differences.

**Figure 5: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Composite Reward 'maab' (Mean Age at Absorption)**



Notes: The numbers and confidence intervals pertain to the composite reward 'maab', which calculates the mean age of subjects when entering the absorbing state, by state preceding the absorbing state and, nested, by initial state. Otherwise the notes from Figure 3 apply.

**Figure 6: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Composite Reward 'mais' (Mean Age in State)**



Notes: The numbers and confidence intervals pertain to the composite reward 'mais', which calculates the mean age of subjects of all time spent in a particular state. Otherwise the notes from Figure 3 apply.

## 5 PARTIAL AGE RANGES

A partial age range is defined by two ages  $z_b$  and  $z_e$ , called the beginning age and ending age, with  $b, e \in [1, \dots, \bar{a}]$  and  $z_b < z_e$ . We call a pair of age ranges disjunct if  $e_1 \leq b_2$  (note the weak inequality), where the subscript indexes the age range.

### 5.1 STANDARD REWARDS

Formulas for standard rewards apply unchanged when calculating a partial age range. The partial age range is solely introduced via a redefinition of the rewards matrix (5): A set of partial age range rewards matrices  $\mathbf{R}_a^{s,b,e}$  sets  $\mathbf{R}_a^{s,b,e} = \mathbf{0}$  if  $z_a \leq z_b$  or if  $z_a > z_e$ , and  $\mathbf{R}_a^{s,b,e} = \mathbf{R}_a^s$  otherwise.<sup>2</sup> We call an age partition a set of  $k$  disjunct age ranges for which it holds that  $\sum_k \sum_a \mathbf{R}_a^{s,b_k e_k} = \sum_a \mathbf{R}_a^s$  for all  $s$ ; or, equivalently, using (6),  $\sum_k \mathbf{R}^{s,b_k e_k} = \mathbf{R}^s$ .

We want to show the analogous results to section B-7.1: a) adding results of two partial age ranges  $\mathbf{R}^{s,b_1 e_1}$  and  $\mathbf{R}^{s,b_2 e_2}$  is equivalent to the result obtained by a single rewards definition  $\mathbf{R}^{s,b_1 e_1} + \mathbf{R}^{s,b_2 e_2}$ . For simplicity, but without loss of generality, as in BASE, we consider the case of adjacent age ranges, defined by  $e_1 = b_2$ . It follows that the point estimates and covariance matrix of a simple additive linear combination of the results of an age partition are identical to the result magnitudes for the full age range.

<sup>2</sup> These sign conditions are slightly different from section B-7.1. This is because rewards are assigned to (out-)transitions, whereas life expectancy calculations assign a "reward" to (the likelihood of reaching) a state directly.

From (10), we can see that  $\mathbf{E}_R^{b_1e_1} + \mathbf{E}_R^{b_2e_2} = \mathbf{E}_R^{b_1e_2}$  if and only if  $\mathbf{F}_R^{b_1e_1} + \mathbf{F}_R^{b_2e_2} = \mathbf{F}_R^{b_1e_2}$ . Considering our definition of partial age ranges and equations (9) and (8), it is easy to see that this holds true since from (7)

$$\bar{\mathbf{R}}_a^{s,e_1b_1} + \bar{\mathbf{R}}_a^{s,e_2b_2} = \mathbf{1}_{\bar{s}} \left( \bar{\mathbf{P}}_a \odot (\mathbf{R}_a^{s,b_1e_1} + \mathbf{R}_a^{s,b_2e_2}) \right) = \mathbf{1}_{\bar{s}} (\bar{\mathbf{P}}_a \odot \mathbf{R}_a^{s,b_1e_2}) \quad (28)$$

With respect to covariance matrices, recalling (22)-(24), and the fact that each partial age range result is based on the same set of transition probabilities, it is easy to show that the simple additive linear combination of two adjacent age ranges resolves to

$$\begin{aligned} & [\mathbf{I}_{\bar{s}^2} \quad \mathbf{I}_{\bar{s}^2}] \text{cov}(\text{vec}[\mathbf{E}_R^{b_1e_1} \quad \mathbf{E}_R^{b_2e_2}]) \begin{bmatrix} \mathbf{I}_{\bar{s}^2} \\ \mathbf{I}_{\bar{s}^2} \end{bmatrix} \\ &= [\mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1}] \left[ (\mathbf{G}_{b_1e_1}^{FR} + \mathbf{G}_{b_2e_2}^{FR}) \tilde{\mathbf{V}}^{tr} (\mathbf{G}_{b_1e_1}^{FR} + \mathbf{G}_{b_2e_2}^{FR})' \right] [\mathbf{I}_{\bar{s}^2} \otimes \mathbf{1}_{\bar{a}-1}]' \end{aligned} \quad (29)$$

This expression is equal to  $\text{cov}(\text{vec} \mathbf{E}_R^{b_1e_2})$  if and only if  $\mathbf{G}_{b_1e_1}^{FR} + \mathbf{G}_{b_2e_2}^{FR} = \mathbf{G}_{b_1e_2}^{FR}$ . This, in turn, is true if it holds for each component of (19), so the question becomes whether it holds for (18). For the blocks below the main block diagonal of (18), this can be deduced from basic arithmetic rules and (28). For the blocks on the main block diagonal, it can be deduced by applying simple arithmetic rules to (17).

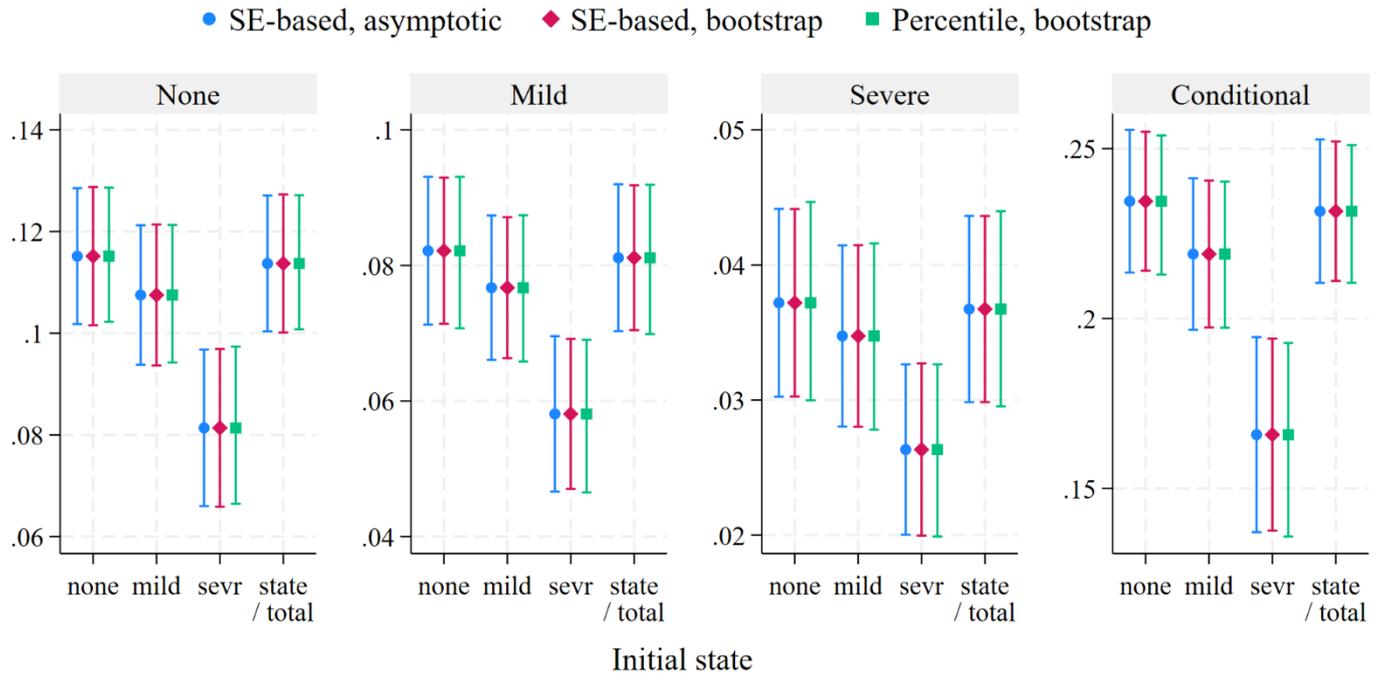
## 5.2 COMBINING PARTIAL AGE RANGE RESULTS

Partial age range results can be combined with other results in the usual way. The formulas of section 4 apply unchanged, with  $\mathbf{R}^{s,b,e}$  taking the place of  $\mathbf{R}^s$  whenever appropriate.

## 5.3 COMPARISON TO BOOTSTRAP RESULTS: PARTIAL AGE RANGES

Based on the derivations of the previous subsections and again using the multistate application on cognitive impairment, Figure 7 compares 95% asymptotic and bootstrap CIs of the alias reward 'stab', calculated over the partial age range 70-80 (the full age range is 50-110). Asymptotic and bootstrap CIs are very similar.

**Figure 7 Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results:  
Alias Reward 'stab' (State Proportion at Absorption), Partial Age Range 70-80, Women**

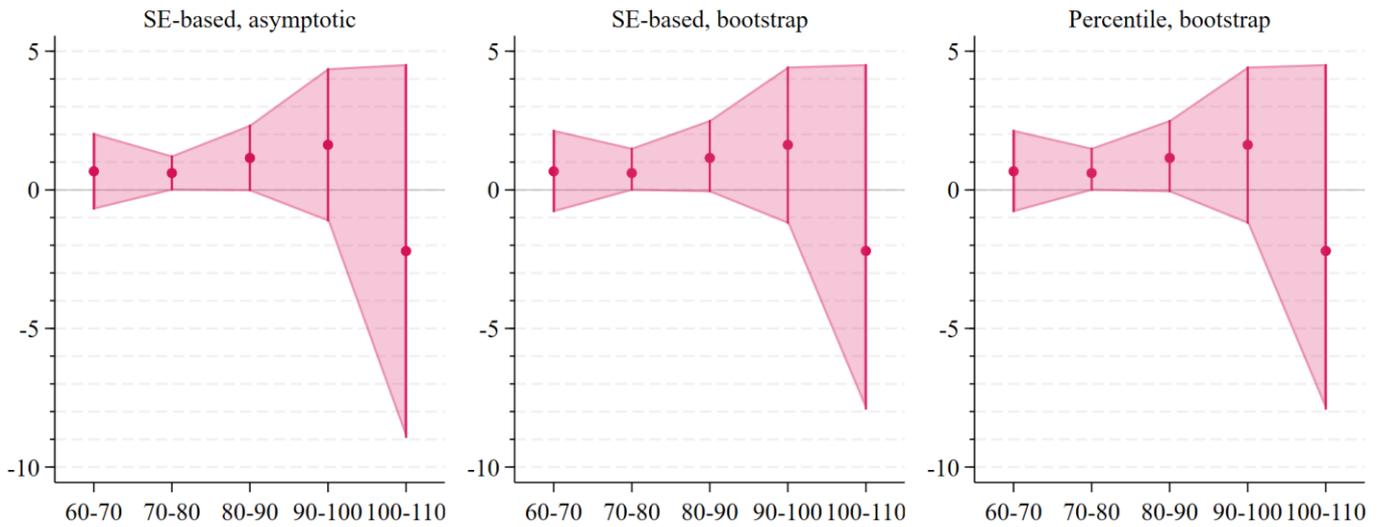


Notes: Partial age range (70-80) numbers and CIs for women pertaining to the alias reward 'stab', which calculates the proportions of the states at absorption. Otherwise the notes from Figure 3 apply.

## 6 COMPLEX NONLINEAR COMBINATIONS AND JOINT HYPOTHESIS TESTS

This section is in close analogy to section B-8: It illustrates asymptotic calculations of CIs for complex linear and nonlinear combinations based on many sets of results, based on a joint covariance matrix that covers all sets of results, as developed in earlier sections of this paper. As mentioned, the calculations of this section are completely analogous to section B-8, except that a different outcome is used. Section B-8 treats LEXP, here we focus on 'stab'. More specifically, section B-8 treated the fraction of lifetime spent in severe impairment (by dividing the severe impairment expectancy by total life expectancy). Here we technically perform the very same division, but since our result is 'stab' the outcome of this division is the fraction of deaths from the severely impaired state. The rest of the complex (non-)linear combinations are the same as in section B-8, too: The calculation of the fraction of deaths from severe impairment is done separately for 10-year partial age ranges, and separately for women and men. Next, separately for women and men, we calculate the percentage point increase in the fraction of deaths from severe impairment, by age decade. Finally, for each age range, we deduct the result for women from those for men. This procedure answers the following question: What are the age decades during which women's fraction of deaths from severe impairment increases particularly strongly in comparison to men? As the example in the BASE paper, the current one too may seem a little contrived; but its major point is simply to illustrate the possibilities that the calculation of joint covariance matrices across any type and number of results holds. Figure 8 compares the results based on analytical calculations (subgraph on the left) to bootstrap results (middle and right subgraphs). The only slightly visible differences appear at the very highest age range (100-110), where data scarcity leads to imprecision of estimation.

**Figure 8: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Complex Linear and Nonlinear Combinations Using Partial Age Ranges**



Notes: Each subgraphs shows sex differences (women minus men) for the percentage point increase, by age decade, in the fraction of deaths from severe impairment. Age decades are depicted on the horizontal axis. They are to be read as intervals [a, b), i.e., with a strong inequality on the right boundary.

As in section B-8, we will now consider the possibility of using the joint asymptotic covariance matrix for a joint test of several hypotheses. For example, one can ask whether all point estimates in (the left subgraph of) Figure 8 are zero. Visual inspection would suggest a positive answer. However, a corresponding asymptotic Wald test yields a  $\chi^2(5)$  statistic of 12.8 with associated p-value of 0.025, which would reject the hypothesis at the 5% level. This can be compared to the SE-based bootstrap results using the covariance matrix of coefficients calculated over the coefficient estimates of all bootstrap replications. A Wald test based on this covariance matrix yields a  $\chi^2(5)$  statistic of 11.57 with associated p-value of 0.041. While the agreement between the asymptotic and bootstrap statistics is not perfect, they would both lead to the rejection at the 5% level, but not at the 1% level.

## 7 REFERENCES

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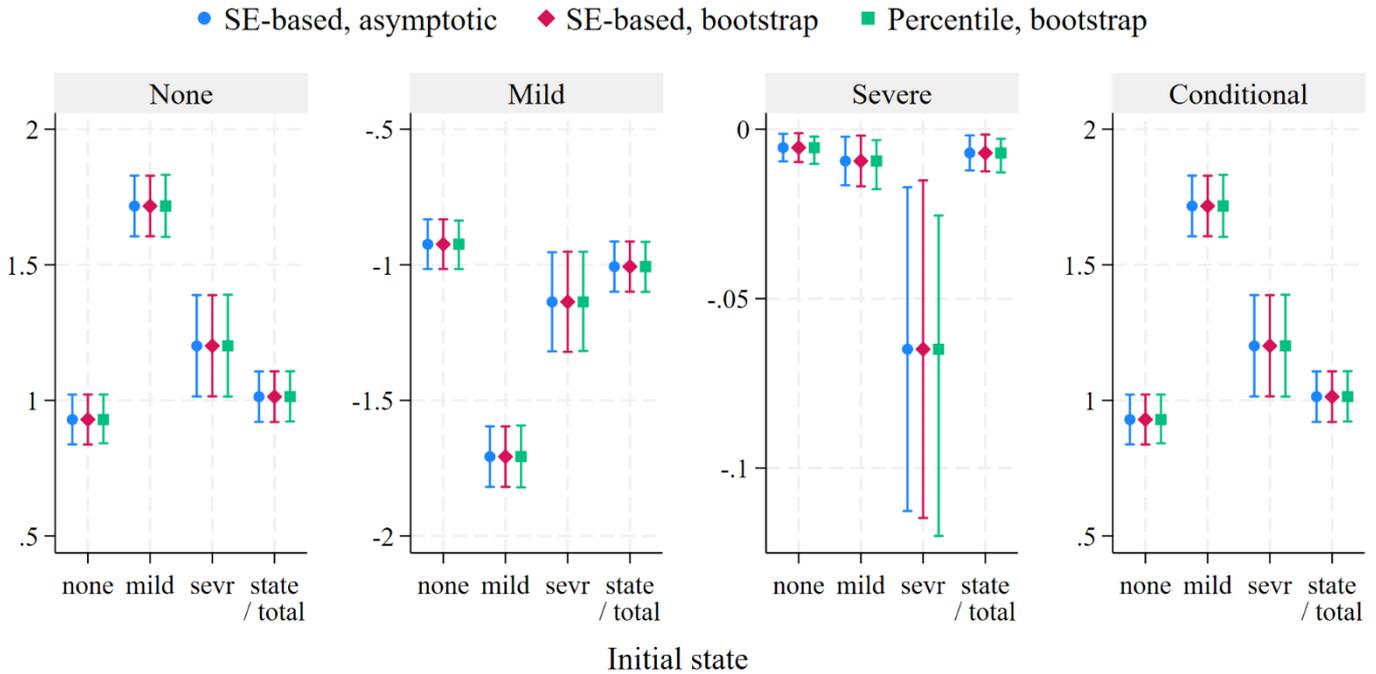
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# 8 APPENDIX

## 8.1 ADDITIONAL COMPARISONS TO BOOTSTRAP RESULTS

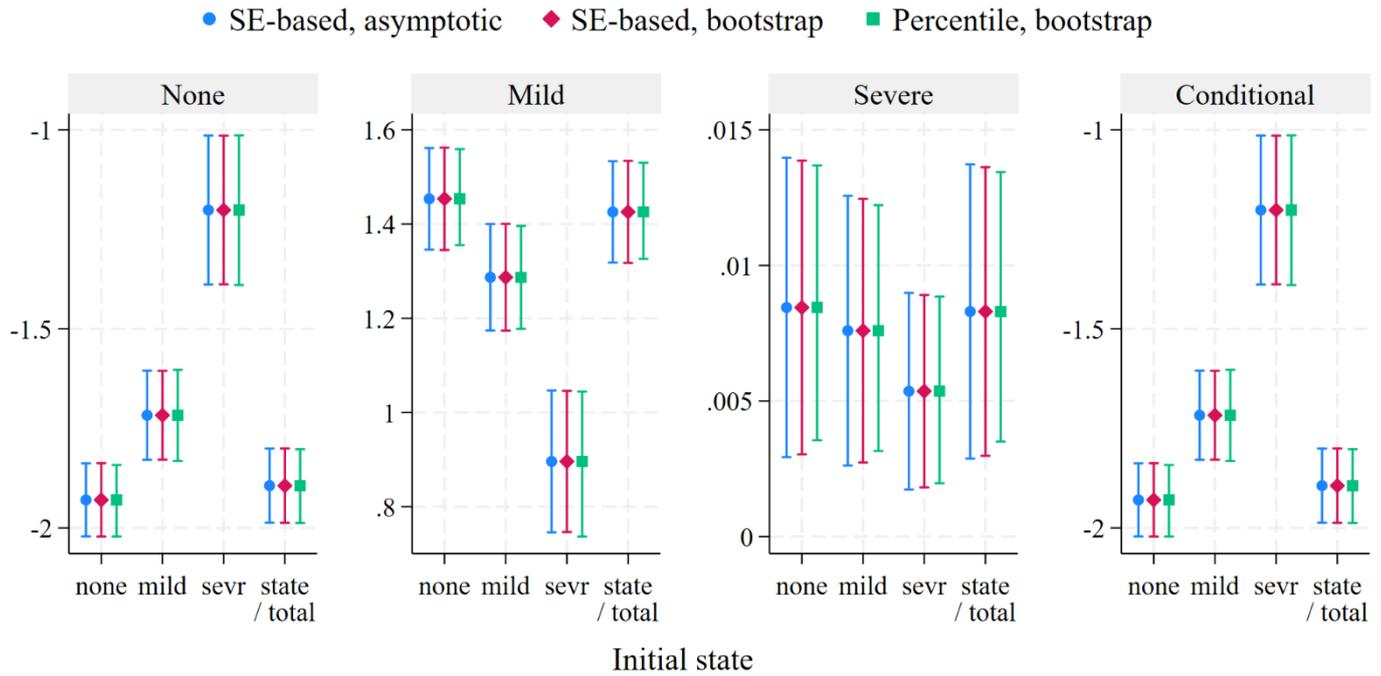
### 8.1.1 Standard Rewards

Figure A-1: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Standard Reward 'ncnt1' (Entry Count, Detail for State 1)



Notes: The numbers and confidence intervals pertain to the standard reward 'ncnt1', which counts the number of episodes of (entries into) state 1 ("none", no impairment), with corresponding exits from other states (i.e., recoveries): For each initial state, the sum of subgraphs 2-3 (states mild and severe) are the negatives of corresponding initial states in subgraph 1. Otherwise the notes from Figure 3 apply, with one exception: The totals (rightmost subgraph) are not the initial state-specific sum of subgraphs 1-3, but repeat the numbers for which state detail was calculated (state none, subgraph 1).

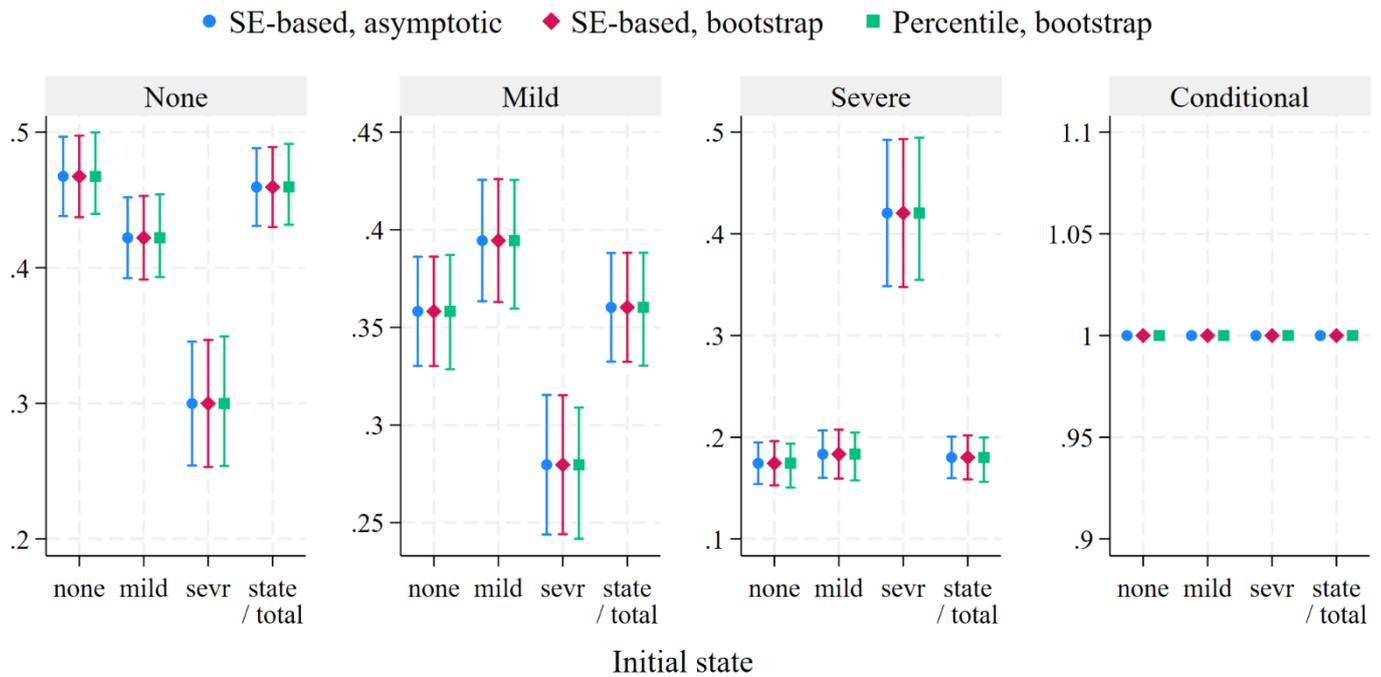
**Figure A-2: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results:  
Standard Reward 'xcnt1' (Exit Count, Detail for State 1)**



Notes: The numbers and confidence intervals pertain to the alias standard 'xcnt1', which counts the number of exits from state 1 ("none", no impairment), with corresponding entries to other transient states (i.e., incidences). Note that, unlike Figure A-1, the initial-state specific sum of subgraphs 2-3 (states mild and severe) are not the negatives of corresponding initial states in subgraph 1 since exits from state 1 to the absorbing state are not accounted for. Otherwise the notes from Figure 3 apply, with one exception: The totals (rightmost subgraph) are not the initial state-specific sum of subgraphs 1-3, but repeat the numbers for which state detail was calculated (state none, subgraph 1).

### 8.1.2 Alias Rewards

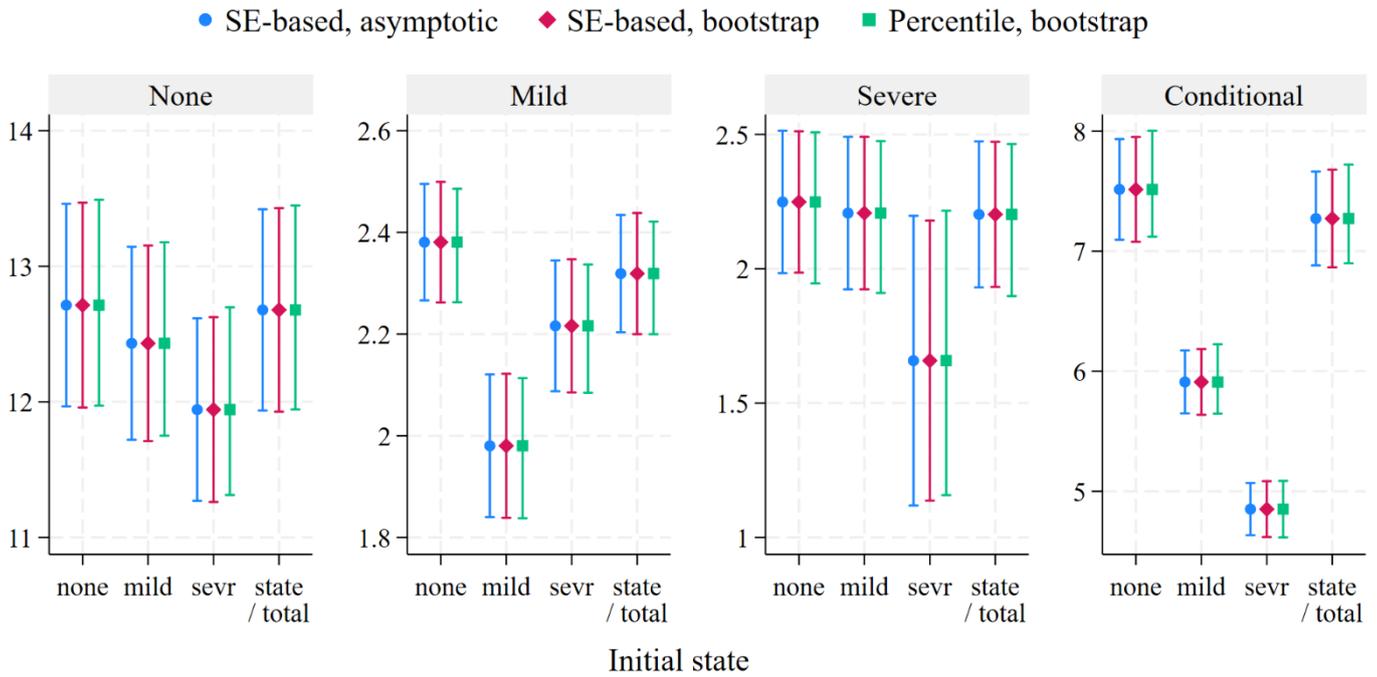
**Figure A-3: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results:  
Standard Reward 'stab' (State at Absorption)**



Notes: The numbers and confidence intervals pertain to the alias reward 'stab', which calculates the proportions of the states at absorption. Since these must sum to one, the totals (rightmost graph) have confidence intervals of length zero. Otherwise the notes from Figure 3 apply.

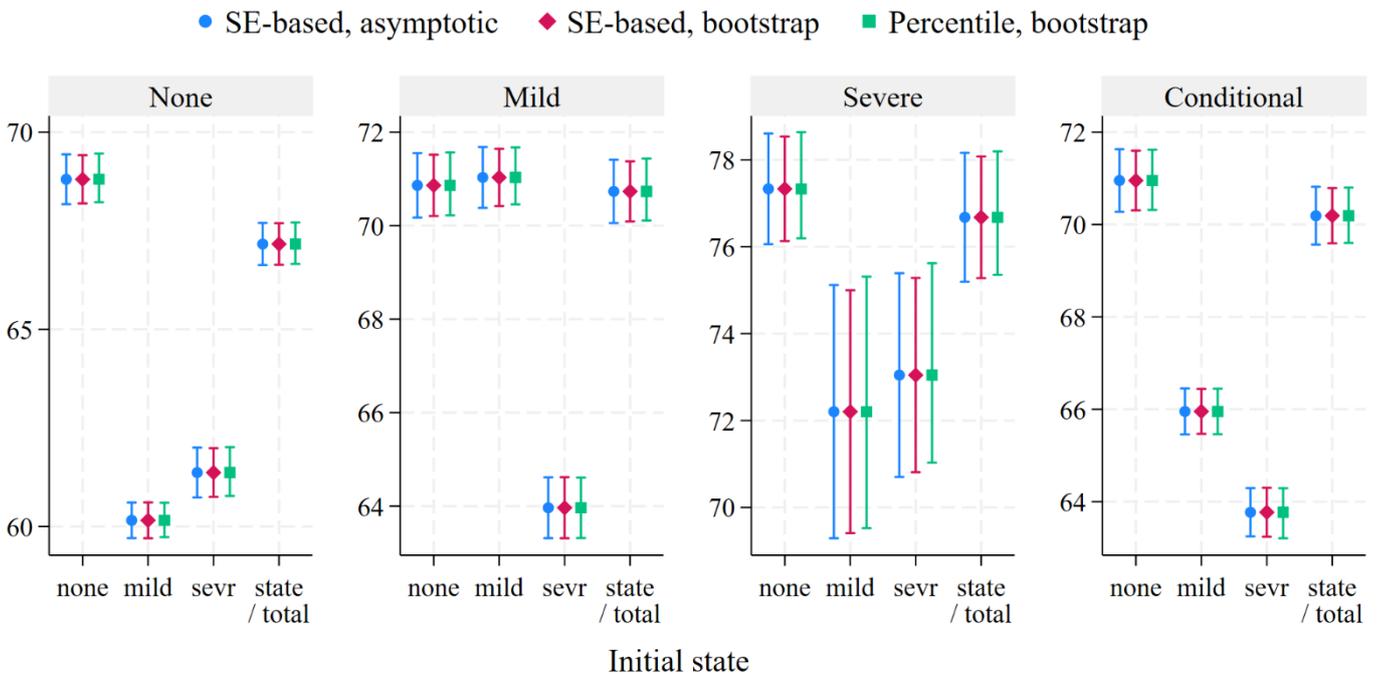
### 8.1.3 Composite Rewards

**Figure A-4: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Composite Reward 'mdur' (Mean Duration of Episodes)**



Notes: The numbers and confidence intervals pertain to the composite reward 'mdur', which calculates the mean duration of episodes. The rightmost graph shows the initial state-specific average duration, which is calculated as a ratio of sums (sums of numerators and sums of denominators), so its values are not directly deducible from subgraphs 1-3. Otherwise the notes from Figure 3 apply.

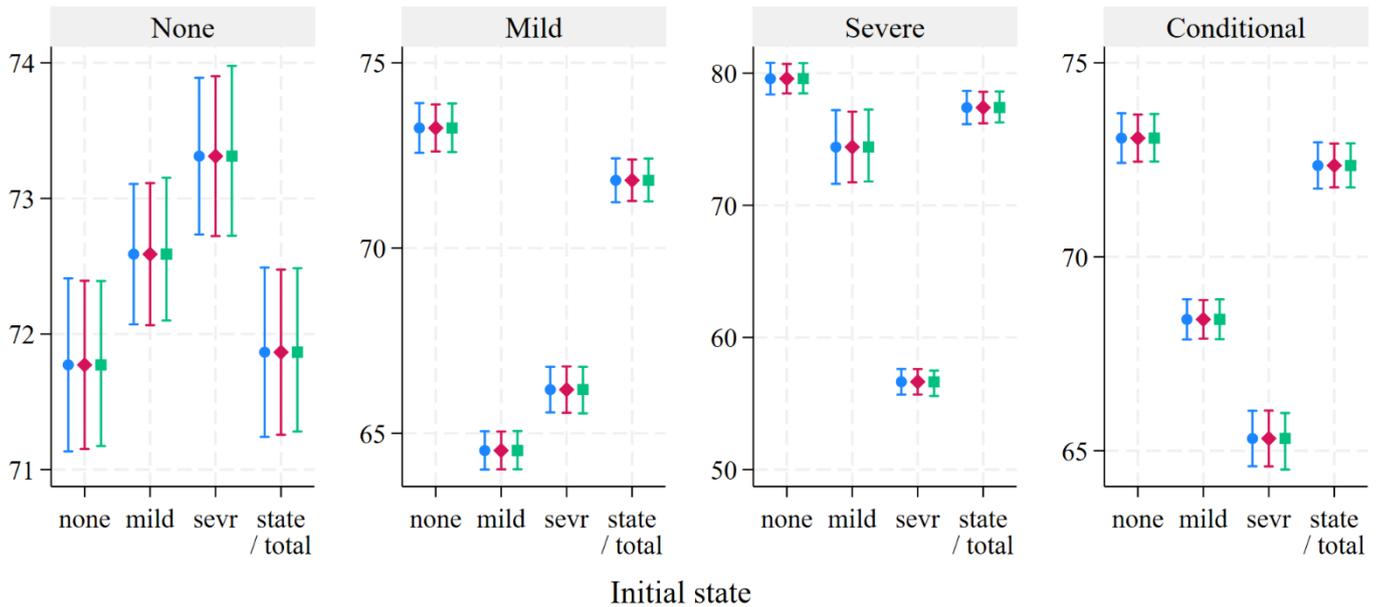
**Figure A-5: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Composite Reward 'maan' (Mean Age, All Entries)**



Notes: The numbers and confidence intervals pertain to the composite reward 'maan', which calculates the mean age at all entries to a state. The rightmost graph shows the initial state-specific mean age, which is calculated as a ratio of sums (sums of numerators and sums of denominators), so its values are not directly deducible from subgraphs 1-3. Otherwise the notes from Figure 3 apply.

**Figure A-6: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results:  
Composite Reward 'maax' (Mean Age, All Exits)**

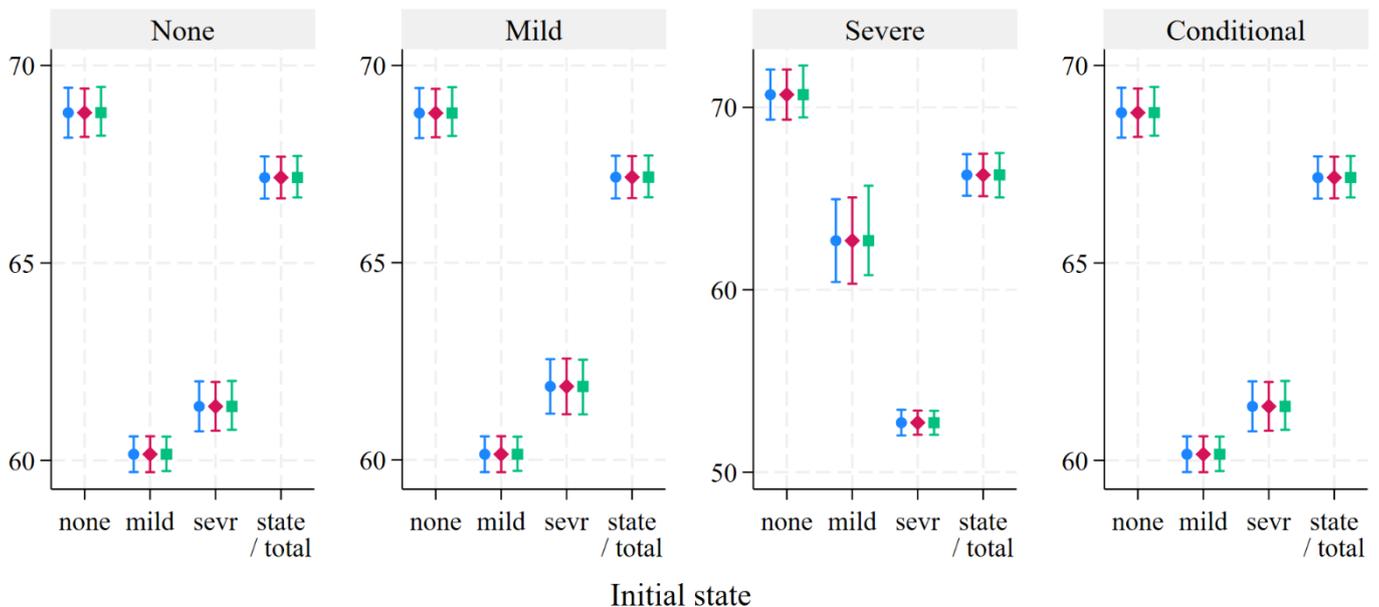
● SE-based, asymptotic    ◆ SE-based, bootstrap    ■ Percentile, bootstrap



Notes: The numbers and confidence intervals pertain to the composite reward 'maax', which calculates the mean age at all exits from a state. The rightmost graph shows the initial state-specific mean age, which is calculated as a ratio of sums (sums of numerators and sums of denominators), so its values are not directly deducible from subgraphs 1-3. Otherwise the notes from Figure 3 apply.

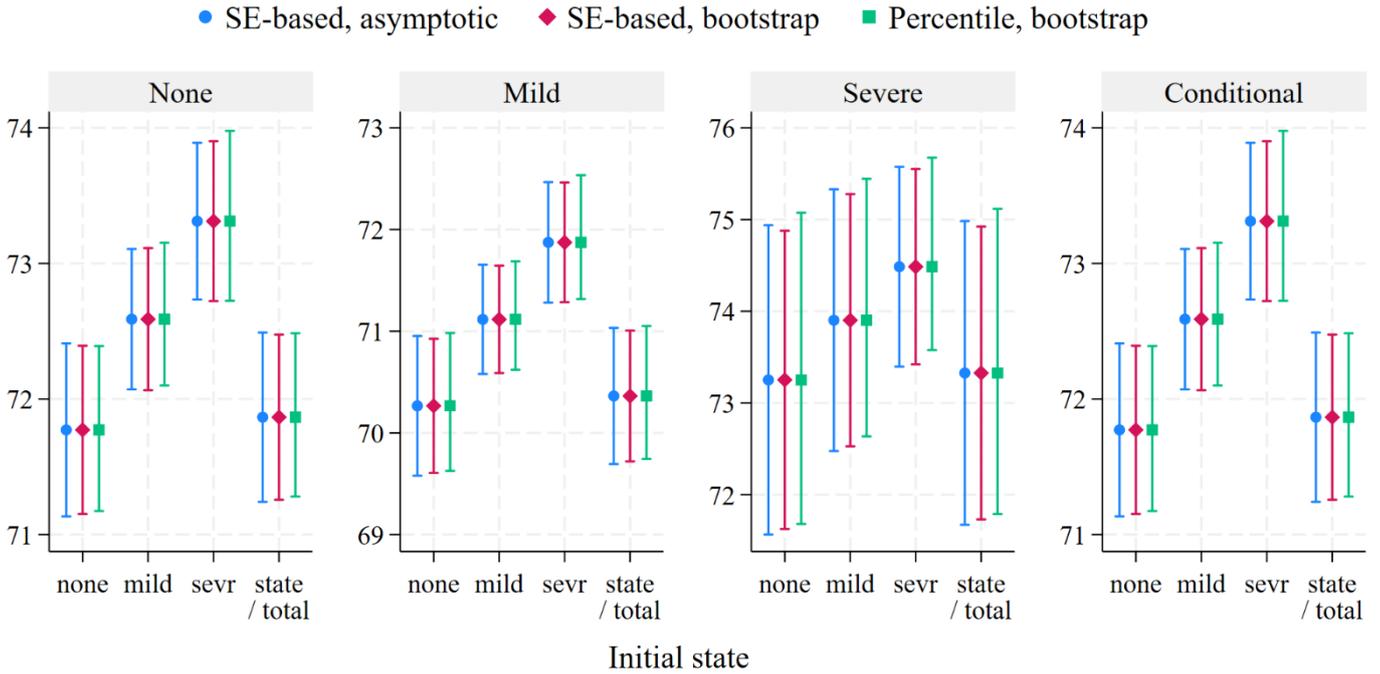
**Figure A-7: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results:  
Composite Reward 'maan1' (Mean Age, All Entries, Detail for State 1)**

● SE-based, asymptotic    ◆ SE-based, bootstrap    ■ Percentile, bootstrap



Notes: The numbers and confidence intervals pertain to the standard reward 'maan1', which calculates the mean age of all entries into state 1 ("none", no impairment), and shows mean ages of all corresponding exits from other states (i.e., recoveries). Otherwise the notes from Figure 3 apply, with one exception: The totals (rightmost subgraph) are not based on the initial state-specific numbers of subgraphs 1-3, but repeat the numbers for which state detail was calculated (state none, subgraph 1).

**Figure A-8: Comparison of 95% Confidence Intervals, Asymptotic v. Bootstrap Results: Composite Reward 'maax1' (Mean Age, All Exits, Detail for State 1)**



Notes: The numbers and confidence intervals pertain to the standard reward 'maax1', which calculates the mean age of all exits from state 1 ("none", no impairment), and shows mean ages of all corresponding entries to other transient states (i.e., recoveries). Otherwise the notes from Figure 3 apply, with one exception: The totals (rightmost subgraph) are not based on the initial state-specific numbers of subgraphs 1-3, but repeat the numbers for which state detail was calculated (state none, subgraph 1).

## 8.2 ADDITIONAL EXPLANATIONS FOR STANDARD REWARDS

### 8.2.1 Formal Expressions

A rewards matrix  $\hat{\mathbf{R}}$  is of dimension  $\bar{a} \times \bar{s}^2 \bar{s}_{+1}$  (see, for example, section 3.3.2). The elements of the first row are never used in calculations, hence they were indicated by a dot in previous sections; and similarly for elements of the last row that do not pertain to columns for transitions to the absorbing state. In the construction of rewards matrices below, we will set all of these irrelevant elements to zero. Assume a zero rewards matrix  $\hat{\mathbf{R}}_0 = \mathbf{0}$ . The below expressions specify vectors that replace columns of that zero matrix. They are either explicitly or implicitly taken to be of length  $\bar{a}_{-1}$ . It is understood that they replace the last  $\bar{a}_{-1}$  elements of a column (so that the first element always remains zero). Furthermore, if the column does not pertain to a transition into the absorbing state, the replacement uses only the first  $\bar{a}_{-2}$  elements of the vector, whose values fill rows 2 ...  $\bar{a}_{-1}$  of  $\hat{\mathbf{R}}_0$ . These conventions simplify the expressions below.

Think of the selection part as filling a first matrix  $\hat{\mathbf{R}}_0$ , and the value part as filling a second one. The final rewards matrix then results from an elementwise multiplication of these two matrices. The modifications by the sign part are trivial and therefore omitted. The expressions for the vectors are:

Selection part and state detail number:

$$\begin{aligned}
 \text{n:} \quad & \mathbf{r}_{ji}^s = \mathbf{1}' && \text{if } (i = s) \wedge (j \neq s) \\
 \text{x:} \quad & \mathbf{r}_{ji}^s = \mathbf{1}' && \text{if } (j = s) \wedge (i \neq s) \\
 \text{u:} \quad & \mathbf{r}_{ji}^s = \mathbf{1}' && \text{if } (i = s) \wedge (j = s) \\
 \text{n(cnt)\#:} \quad & \mathbf{r}_{ji}^s = \mathbf{1}' && \text{if } (i = \#) \wedge (i = s) \wedge (i \neq j) \\
 & \mathbf{r}_{ji}^s = -\mathbf{1}' && \text{if } (i = \#) \wedge (j = s) \wedge (i \neq j) \\
 \text{x(cnt)\#:} \quad & \mathbf{r}_{ji}^s = -\mathbf{1}' && \text{if } (j = \#) \wedge (j = s) \wedge (i \neq j) \\
 & \mathbf{r}_{ji}^s = \mathbf{1}' && \text{if } (j = \#) \wedge (i = s) \wedge (i \neq j)
 \end{aligned}$$

Value part:

$$\begin{aligned}
 \text{cnt:} \quad & \text{no modification} \\
 \text{atr:} \quad & \text{BOP: } \mathbf{r}_{ji}^s = \mathbf{z}_{-1} \\
 & \text{MID: } \mathbf{r}_{ji}^s = \mathbf{z}_{-1} + \frac{1}{2}\mathbf{n} \\
 & \text{EOP: } \mathbf{r}_{ji}^s = \mathbf{z}_{+1} \\
 \text{tbt:} \quad & \text{BOP: } \mathbf{r}_{ji}^s = \mathbf{n} \quad \text{if } (i = s) \\
 & \text{MID: } \mathbf{r}_{ji}^s = \mathbf{n} \quad \text{if } (i = s) \wedge (j = s) \\
 & \quad \mathbf{r}_{ji}^s = \frac{1}{2}\mathbf{n} \quad \text{if } [(i = s) \vee (j = s)] \wedge (i \neq j) \\
 & \text{EOP: } \mathbf{r}_{ji}^s = \mathbf{n} \quad \text{if } (j = s) \\
 \text{amp:} \quad & \text{BOP: } \mathbf{r}_{ji}^s = \mathbf{z}_{-1} + \frac{1}{2}\mathbf{n} \text{ if } (i = s) \\
 & \quad \mathbf{r}_{ji}^s = \mathbf{z}_{-1} \quad \text{if } (j = s) \wedge (i \neq j) \\
 & \text{MID: } \mathbf{r}_{ji}^s = \mathbf{z}_{-1} + \frac{1}{2}\mathbf{n} \text{ if } (i = s) \wedge (j = s) \\
 & \quad \mathbf{r}_{ji}^s = \mathbf{z}_{+1} + \frac{1}{4}\mathbf{n} \text{ if } (j = s) \wedge (i \neq j) \\
 & \quad \mathbf{r}_{ji}^s = \mathbf{z}_{+1} + \frac{3}{4}\mathbf{n} \text{ if } (i = s) \wedge (i \neq j) \\
 & \text{EOP: } \mathbf{r}_{ji}^s = \mathbf{z}_{-1} + \frac{1}{2}\mathbf{n} \text{ if } (j = s) \\
 & \quad \mathbf{r}_{ji}^s = \mathbf{z}_{+1} \quad \text{if } (i = s) \wedge (i \neq j) \\
 \text{att:} \quad & \text{calculated as the elementwise product of tbt and amp}
 \end{aligned}$$

## 8.2.2 Additional Example Rewards Matrices

Sections 3.1-3.3 contained several example rewards matrices that are based on two transient states. This section shows additional example rewards matrices that also consider ages  $\mathbf{z} = [50, 60, \dots, 100]$ , but for an expanded state space of three transient states. There is still only one absorbing state, as in the entirety of this document.

'ncnt':

	$r_{11}^1$	$r_{12}^1$	$r_{13}^1$	$r_{14}^1$	$r_{21}^1$	$r_{22}^1$	$r_{23}^1$	$r_{24}^1$	$r_{31}^1$	$r_{32}^1$	$r_{33}^1$	$r_{34}^1$
$\dot{R}^1 =$	50	.	.	.	.	.	.	.	.	.	.	.
60	0	0	0	0	1	0	0	0	1	0	0	0
70	0	0	0	0	1	0	0	0	1	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^2$	$r_{12}^2$	$r_{13}^2$	$r_{14}^2$	$r_{21}^2$	$r_{22}^2$	$r_{23}^2$	$r_{24}^2$	$r_{31}^2$	$r_{32}^2$	$r_{33}^2$	$r_{34}^2$
$\dot{R}^2 =$	50	.	.	.	.	.	.	.	.	.	.	.
60	0	1	0	0	0	0	0	0	0	1	0	0
70	0	1	0	0	0	0	0	0	0	1	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^3$	$r_{12}^3$	$r_{13}^3$	$r_{14}^3$	$r_{21}^3$	$r_{22}^3$	$r_{23}^3$	$r_{24}^3$	$r_{31}^3$	$r_{32}^3$	$r_{33}^3$	$r_{34}^3$
$\dot{R}^3 =$	50	.	.	.	.	.	.	.	.	.	.	.
60	0	0	1	0	0	0	1	0	0	0	0	0
70	0	0	1	0	0	0	1	0	0	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

'xcnt2':

	$r_{11}^1$	$r_{12}^1$	$r_{13}^1$	$r_{14}^1$	$r_{21}^1$	$r_{22}^1$	$r_{23}^1$	$r_{24}^1$	$r_{31}^1$	$r_{32}^1$	$r_{33}^1$	$r_{34}^1$
$\dot{R}^1 =$	50	.	.	.	.	.	.	.	.	.	.	.
60	0	0	0	0	-1	0	0	0	0	0	0	0
70	0	0	0	0	-1	0	0	0	0	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^2$	$r_{12}^2$	$r_{13}^2$	$r_{14}^2$	$r_{21}^2$	$r_{22}^2$	$r_{23}^2$	$r_{24}^2$	$r_{31}^2$	$r_{32}^2$	$r_{33}^2$	$r_{34}^2$
$\dot{R}^2 =$	50	.	.	.	.	.	.	.	.	.	.	.
60	0	0	0	0	1	0	1	1	0	0	0	0
70	0	0	0	0	1	0	1	1	0	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^3$	$r_{12}^3$	$r_{13}^3$	$r_{14}^3$	$r_{21}^3$	$r_{22}^3$	$r_{23}^3$	$r_{24}^3$	$r_{31}^3$	$r_{32}^3$	$r_{33}^3$	$r_{34}^3$
$\dot{R}^3 =$	50	.	.	.	.	.	.	.	.	.	.	.
60	0	0	0	0	0	0	-1	0	0	0	0	0
70	0	0	0	0	0	0	-1	0	0	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

'ttbt', mid-period transitions:

	$r_{11}^1$	$r_{12}^1$	$r_{13}^1$	$r_{14}^1$	$r_{21}^1$	$r_{22}^1$	$r_{23}^1$	$r_{24}^1$	$r_{31}^1$	$r_{32}^1$	$r_{33}^1$	$r_{34}^1$
$\dot{R}^1 = 50$	.	.	.	.	.	.	.	.	.	.	.	.
60	10	5	5	5	5	0	0	0	5	0	0	0
70	10	5	5	5	5	0	0	0	5	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^2$	$r_{12}^2$	$r_{13}^2$	$r_{14}^2$	$r_{21}^2$	$r_{22}^2$	$r_{23}^2$	$r_{24}^2$	$r_{31}^2$	$r_{32}^2$	$r_{33}^2$	$r_{34}^2$
$\dot{R}^2 = 50$	.	.	.	.	.	.	.	.	.	.	.	.
60	0	5	0	0	5	10	5	5	0	5	0	0
70	0	5	0	0	5	10	5	5	0	5	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^3$	$r_{12}^3$	$r_{13}^3$	$r_{14}^3$	$r_{21}^3$	$r_{22}^3$	$r_{23}^3$	$r_{24}^3$	$r_{31}^3$	$r_{32}^3$	$r_{33}^3$	$r_{34}^3$
$\dot{R}^3 = 50$	.	.	.	.	.	.	.	.	.	.	.	.
60	0	0	5	0	0	0	5	0	5	5	10	5
70	0	0	5	0	0	0	5	0	5	5	10	5
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

'tamp', mid-period transitions:

	$r_{11}^1$	$r_{12}^1$	$r_{13}^1$	$r_{14}^1$	$r_{21}^1$	$r_{22}^1$	$r_{23}^1$	$r_{24}^1$	$r_{31}^1$	$r_{32}^1$	$r_{33}^1$	$r_{34}^1$
$\dot{R}^1 = 50$	.	.	.	.	.	.	.	.	.	.	.	.
60	55	52.5	52.5	52.5	57.5	0	0	0	57.5	0	0	0
70	65	62.5	62.5	62.5	67.5	0	0	0	67.5	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^2$	$r_{12}^2$	$r_{13}^2$	$r_{14}^2$	$r_{21}^2$	$r_{22}^2$	$r_{23}^2$	$r_{24}^2$	$r_{31}^2$	$r_{32}^2$	$r_{33}^2$	$r_{34}^2$
$\dot{R}^2 = 50$	.	.	.	.	.	.	.	.	.	.	.	.
60	0	57.5	0	0	52.5	55	52.5	52.5	0	57.5	0	0
70	0	67.5	0	0	62.5	65	62.5	62.5	0	67.5	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	$r_{11}^3$	$r_{12}^3$	$r_{13}^3$	$r_{14}^3$	$r_{21}^3$	$r_{22}^3$	$r_{23}^3$	$r_{24}^3$	$r_{31}^3$	$r_{32}^3$	$r_{33}^3$	$r_{34}^3$
$\dot{R}^3 = 50$	.	.	.	.	.	.	.	.	.	.	.	.
60	0	0	57.5	0	0	0	57.5	0	52.5	52.5	55	52.5
70	0	0	67.5	0	0	0	67.5	0	62.5	62.5	65	62.5
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮