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ORIGINAL PAPER

Accounting for increased non-target-disease-specific mortality in decision-analytic screening models for economic evaluation

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Abstract
Background Positive screening results are often associated not only with target-disease-specific but also with non-target-disease-specific mortality. In general, this association is due to joint risk factors. Cost-effectiveness estimates based on decision-analytic models may be biased if this association is not reflected appropriately.
Objective To develop a procedure for quantifying the degree of bias when an increase in non-target-disease-specific mortality is not considered.
Methods We developed a family of parametric functions that generate hazard ratios (HRs) of non-target-disease-specific mortality between subjects screened positive and negative, with the HR of target-disease-specific mortality serving as the input variable. To demonstrate the efficacy of this procedure, we fitted a function within the context of coronary artery disease (CAD) risk screening, based on HRs related to different risk factors extracted from published studies. Estimates were embedded into a decision-analytic model, and the impact of 'modelling increased non-target-disease-specific mortality' was assessed.
Results In 55-year-old German men, based on a risk screening with 5 % positively screened subjects, and a CAD risk ratio of 6 within the first year after screening, incremental quality-adjusted life–years were 19 % higher and incremental costs were 8 % lower if no adjustment was made. The effect varied depending on age, gender, the explanatory power of the screening test and other factors.
Conclusion Some bias can occur when an increase in non-target-disease-specific mortality is not considered when modelling the outcomes of screening tests.

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Introduction

In medicine, there are several fields in which screening methods are used [1–12]. For example, screening is used to predict the risk of developing coronary artery disease (CAD) [1, 2] or to detect early markers of several types of cancer [3–5]. All these screening methods have in common that they are used to identify subpopulations at greater risk, for which an intervention (treatment or prevention) is intended to take place. Furthermore, decision-analytic models have been published for many screening methods [1–13]. The corresponding models differ greatly in terms of model assumptions, input data and complexity. However, they show that there is a need for accurate decision-analytic models to assess the consequences of screening [14].

In several settings, it may be that subjects with a positive screening result have increased mortality for diseases other than the target disease. Subjects with an enhanced risk of developing CAD, for example, also have enhanced mortality due to lung cancer, because smoking is a risk factor for both CAD and lung cancer [15, 16]. Furthermore, target-disease-specific mortality may be affected by other diseases and non-target risk factors. CAD, for example, is affected by diabetes and hypertension. However, this issue is frequently addressed in decision models [17, 18].

Another example can be found in risk screening for cervical cancer. The risk of developing and dying from cervical cancer may be associated with mortality resulting from venereal diseases in general, because cervical cancer may be caused by infection with the human papillomavirus (HPV), a cause of venereal disease [19].

When screening for colorectal cancer, one should keep in mind that some risk factors for colorectal cancer are smoking, eating red meat, physical inactivity, inflammatory bowel disease, environmental factors and alcohol consumption. These risk factors are also risk factors for mortality from causes other than colorectal cancer. Many other examples can be found where mortality from causes other than the target disease is increased in positively screened subjects.

The typical approach used in decision-analytic models is to consider non-target-disease-specific mortality using data from a life table of the general population. However, even when target-disease-specific mortality is subtracted from the life table data, this approach does not consider that subjects with a positive screening result have increased mortality for diseases other than the target disease [15, 16, 19, 20]. For this reason, traditional models can easily overestimate the number of life–years gained from screening.

Especially in early-stage decision making, it may be unknown to what degree non-target-disease-specific mortality is increased in subjects with positive screening results.

Our intention was to develop a new tool that can be used to estimate the extent to which mortality from other causes is increased in subjects with positive screening results. This tool can be applied to patient groups for whom empirical data on the increase in mortality from other causes do not exist. That is, this tool can be used to extrapolate screening cost-effectiveness to different patient groups who might get more or less benefit from screening than the observed patients.

Originally, this tool was developed for a special early stage decision-making model that allows the assessment of CAD risk screening strategies [21]. The aim of this modelling tool is not to explain the specific causes of increased non-target-disease-specific mortality, but to quantify the overall extent to which mortality from other causes is increased.

As changes in target-disease-specific mortality are frequently modelled via hazard ratios (or similarly, via relative risks or odds ratios) [22, 23], non-target-disease-specific mortality is, in our approach, also modelled via the hazard ratio. In our approach, this hazard ratio is estimated via a function that assigns for each target-disease-specific hazard ratio a non-target-disease-specific hazard ratio. The parameters of this function are estimated based on observed data (i.e. observed combinations of target- and non-target-specific hazard ratios, which are extracted from the literature, based on different risk groups as defined in the underlying publications). There are several properties that this function needs to fulfil. These properties are defined in Sect. 2. In Sect. 3, we develop a family of parametric functions that satisfies these properties. To demonstrate the relevance of considering an increase in non-target-disease-specific mortality, we quantified the degree of bias when such an increase is not considered in a case example (Sect. 4).

Definition of desired properties

We estimated the hazard ratio of mortality from other causes (HR_{other}) based on the hazard ratio of mortality due to the target disease being screened (HR_{target}). Both these hazard ratios compare subjects with positive to subjects with negative screening results. For the purpose of consistency, let the numerators of both hazard ratios represent subjects with positive and the denominators represent subjects with negative screening results. That is, according to our definition, a valid screening method will increase

HR_{target}. Further, let HR_{other} be expressed as a function of HR_{target}.

The properties that $HR_{other}(HR_{target})$ are to fulfil are as follows:

Property 1 If the screening method has no discriminatory power concerning mortality due to the target disease, it also has no discriminatory power concerning mortality due to other causes:

$$HR_{other}(1) = 1.$$

Such screening methods may always exist, for example flipping a coin.

Property 2 If screening method B has a higher discriminatory power with respect to the target disease compared with screening method A, then screening method B also has a higher discriminatory power concerning mortality due to other causes:

$$HR^{B}_{target} > HR^{A}_{target} \Rightarrow HR_{other}(HR^{B}_{target}) > HR_{other}(HR^{A}_{target}).$$

Thus, the function $HR_{other}(HR_{target})$ is strictly increasing.

Property 3 If HR_{target} of a misdirected screening method A is equal to the reciprocal value of HR_{target} of a screening method B, then HR_{other} of screening method A is equal to the reciprocal value of HR_{other} of screening method B:

$$HR^{B}_{target} = \frac{1}{HR^{A}_{target}} \Rightarrow HR_{other}\left(HR^{B}_{target}\right) = \frac{1}{HR_{other}(HR^{A}_{target})}.$$

Property 3 was set up for consistency. The range of hazard ratios HR_{target} below 1 may not be relevant in practical experience because hazard ratios HR_{target} below 1 indicate misdirected screening methods. Subjects with negative screening results would have a higher incidence than subjects with positive screening results. Misdirected screening methods may be derived from valid screening methods by switching all screening results from positive to negative and vice versa. By doing so, the numerator and denominator of both hazard ratios are implicitly switched as well.

Property 4 The hazard ratio of non-target-disease-related mortality has an upper bound B:

$$\exists b < \infty : HR_{other}(HR_{target}) \leq b.$$

The rationale of this property is as follows: if a screening test perfectly predicts target-disease-specific mortality, this is accompanied by an infinitely large target-disease-specific hazard ratio (i.e. $HR_{target} = \infty$). If, furthermore, the function $HR_{other}(HR_{target})$ does not have an upper bound, $HR_{target} = \infty$ would yield $HR_{other}(\infty) = \infty$. In other words, a screening method that perfectly explains target-disease-specific mortality would also perfectly explain non-target-disease-specific mortality. This, of course, is unlikely to happen, and therefore this property was set up.

Property 5 If HR_{target} is larger than 1 (i.e. the screening method is not misdirected), then HR_{target} exceeds HR_{other}:

$$HR_{other}(HR_{target}) < HR_{target} \text{ for } HR_{target} > 1.$$

Property 5 may be interpreted as follows: the screening methods that we consider have a higher explanatory power concerning target-disease-specific mortality than concerning mortality from other causes. Although this property may be relaxed depending on the screening test considered, the set of functions fitted to the empirical data should at least allow for property 5 to hold when it is appropriate. Graphically, property 5 means that $HR_{other}(HR_{target})$ takes a course below a 45 degree angle (i.e. the curve falls below the straight line $f(x) = x$).

Property 6 $HR_{other}(HR_{target})$ is continuously differentiable.

Property 6 makes the function $HR_{other}(HR_{target})$ appear smoother. However, it may not be essential for the purpose of approximating reality.

A family of parametric functions satisfying the desired properties

When estimating the function $HR_{other}(HR_{target})$, a flexible family of parametric functions is desired in order to allow a close fit to empirical data. When designing such a family, one may focus on submapping over the interval $(1, \infty)$, as this interval covers all screening tests that are not misdirected. For misdirecting screening tests (i.e. $HR_{target} \in (0, 1)$), the function $HR_{other}(HR_{target})$is defined implicitly via property 3. Furthermore, if $HR_{other}(HR_{target})$ is differentiable over $(1, \infty)$, it is also differentiable over $(0, 1)$, and in particular for $HR_{target} = 1$ (for a proof, see "Appendix").

A family of parametric functions $HR_{other}(HR_{target})$ over the interval $[1, \infty)$ may be designed by first setting a smallest upper bound (i.e. the supremum) of this function (property 4). We define a first parameter θ_1 as $\theta_1 := \sup(HR_{other}(\cdot))$, with $\theta_1 \geq 1$.

Thus, θ_1 is the upper bound of HR_{other}. From the supremum, one may subtract a term that converges to 0 when HR_{target} goes to infinity. This term has to be positive and monotone decreasing in order to guarantee property 2 (i.e. $HR_{other}(HR_{target})$ is strictly increasing. Such a term, which also guarantees that the function runs through the point (1, 1) (property 1), is given by $(\theta_1 - 1)\left(HR_{target}\right)^{-\theta_2}$,

where the power $\theta_2 \geq 0$ defines a second parameter. However, the resulting function y with

$$y = \theta_1 - (\theta_1 - 1)\left(\mathrm{HR}_{\mathrm{target}}\right)^{-\theta_2} \quad (1)$$

does not always run below the 45 degree angle (property 5). This may be corrected by first solving Eq. (1) for $\mathrm{HR}_{\mathrm{target}}$:

$$\mathrm{HR}_{\mathrm{target}} = \left(\frac{\theta_1 - 1}{\theta_1 - y}\right)^{1/\theta_2}$$

and then adding the term $(y-1)(1+\theta_3)$ on the right-hand side, where $\theta_3 \geq 0$ denotes a further arbitrary parameter. If property 5 needs to be relaxed, the range of θ_3 can be extended to $\theta_3 \in [-1, \infty]$. The resulting equation describes a curve that fulfils all the desired properties:

$$\mathrm{HR}_{\mathrm{target}} = \left(\frac{\theta_1 - 1}{\theta_1 - \mathrm{HR}_{\mathrm{other}}}\right)^{1/\theta_2} + (\mathrm{HR}_{\mathrm{other}} - 1)(1 + \theta_3). \quad (2)$$

The solution of solving Eq. (2) for $\mathrm{HR}_{\mathrm{other}}$ will be denoted as $\mathrm{HR}_{\mathrm{other}}(\mathrm{HR}_{\mathrm{target}}|\theta_1, \theta_2, \theta_3)$. Examples are shown in Figs. 1, 2 and 3. The parameters θ_1, θ_2 and θ_3 can be interpreted as follows: θ_1 gives an upper bound of $\mathrm{HR}_{\mathrm{other}}(\mathrm{HR}_{\mathrm{target}})$; θ_2 allows that $\mathrm{HR}_{\mathrm{other}}(\mathrm{HR}_{\mathrm{target}})$ comes arbitrarily close to the point where the upper bound and the bisector (i.e. the line $\mathrm{HR}_{\mathrm{other}}(\mathrm{HR}_{\mathrm{target}}) = \mathrm{HR}_{\mathrm{target}}$) cross, without violating property 5; θ_3 shifts the function to the left or to the right, while the function is fixed in $(\mathrm{HR}_{\mathrm{target}} = 1, \mathrm{HR}_{\mathrm{other}} = 1)$. The combination of θ_2 and θ_3 allows a wide flexibility of the fitted function's shape.

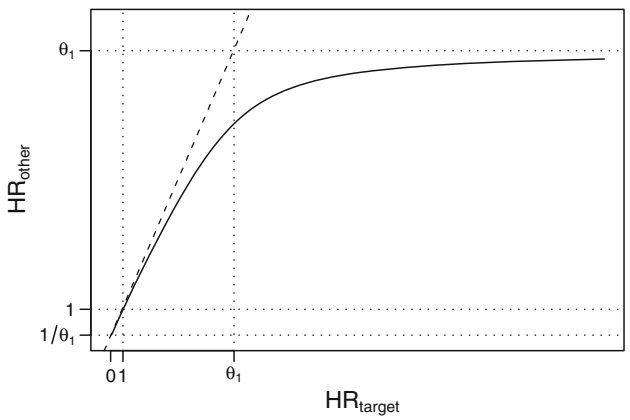

Fig. 1 Relationship between the hazard ratios concerning disease-specific mortality and mortality from other causes with constant parameters $\theta_2 = 1$ and $\theta_3 = 0$. $\mathrm{HR}_{\mathrm{target}}$ = hazard ratio between subjects with positive and negative screening results concerning the target disease being screened; $\mathrm{HR}_{\mathrm{other}}$ = hazard ratio concerning mortality from other causes; *dashed line* = bisector (i.e. $x = y$)

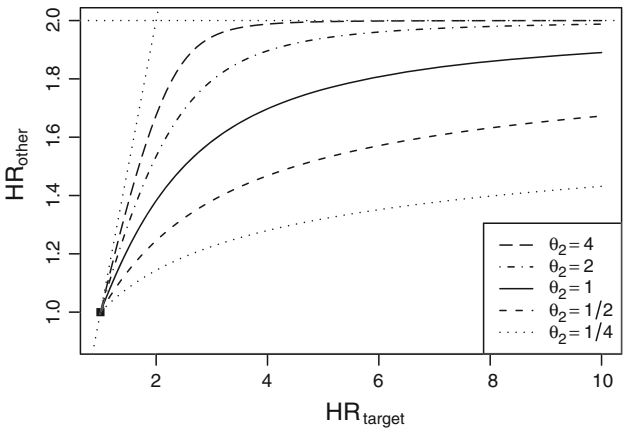

Fig. 2 Function describing the relationship between the hazard ratios concerning disease-specific mortality and mortality from other causes with varying parameter θ_2 and constant parameters $\theta_1 = 2$ and $\theta_3 = 0$. $\mathrm{HR}_{\mathrm{target}}$ = hazard ratio between subjects with positive and negative screening results concerning the target disease being screened; $\mathrm{HR}_{\mathrm{other}}$ = hazard ratio concerning mortality from other causes; *dotted lines* = bisector (i.e. $x = y$) or upper bound respectively

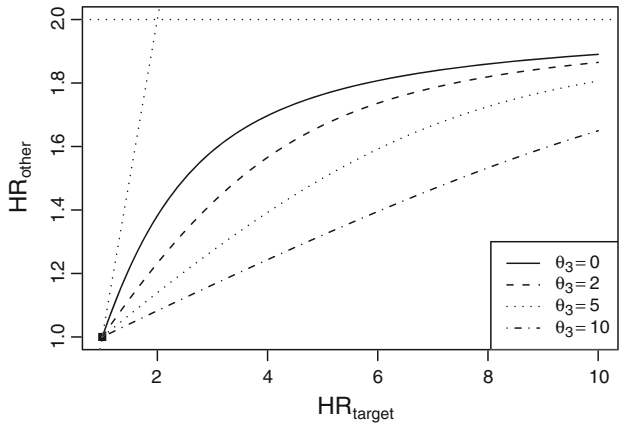

Fig. 3 Function describing the relationship between the hazard ratios concerning disease-specific mortality and mortality from other causes with varying parameter θ_3 and constant parameters $\theta_1 = 2$ and $\theta_2 = 1$. $\mathrm{HR}_{\mathrm{target}}$ = hazard ratio between subjects with positive and negative screening results concerning the target disease being screened; $\mathrm{HR}_{\mathrm{other}}$ = hazard ratio concerning mortality from other causes; *dotted lines* = bisector (i.e. $x = y$) or upper bound respectively

Applied case example

In this section, we will demonstrate how the function $\mathrm{HR}_{\mathrm{other}}(\mathrm{HR}_{\mathrm{target}})$ may be used in decision-analytic modelling. Basically, this can be done in five steps. First, in the disease-specific context, pairs of hazard ratios $(\mathrm{HR}_{\mathrm{target}}, \mathrm{HR}_{\mathrm{other}})$ have to be identified. Second, these observed pairs are used to estimate the parameter vector $\boldsymbol{\theta} := (\theta_1, \theta_2, \theta_3)'$. Third, the value of $\mathrm{HR}_{\mathrm{target}}$ that will be applied in the decision-analytic model has to be defined.

Fourth, the fitted function $HR_{other}(HR_{target})$ and the defined value of HR_{target} are used to estimate HR_{other}. Fifth, the hazard ratios HR_{target} and HR_{other} can be incorporated into decision-analytic models by multiplying mortality rates.

Structure and purpose of the decision-analytic model

In our applied example, we focus on a published CAD risk screening model (Fig. 4) [21]. The health outcome is measured in quality-adjusted life–years (QALYs), and the costs are measured in 2011 euros. This model was designed for early decision making to assess the long-term consequences of innovative CAD risk screening procedures in a male cohort aged 50 years. We compare screening with no screening. However, the model could also be used to compare an innovative CAD risk screening procedure with established ones, such as the screening strategies using the Framingham risk equation [15] or the PROCAM score [24].

Although risk screening per se does not have an effect on health, in this model, an intervention takes place for those who were identified as high-risk subjects (i.e. subjects with a positive screening result). In this case, they receive statins to reduce their CAD incidence. Both fatal and non-fatal CAD incidence is reduced through statin intake. A risk reduction of 33 % is assumed [25] and applied to compliant subjects (90 % compliance). Primary prevention (i.e. additional statin intake) stops at CAD onset or at death. In the base case scenario, non-target-disease-specific mortality is not reduced by primary prevention. The model had a lifetime horizon, although shorter horizons were applied for sensitivity analysis.

Two versions of the model were run: one in which subjects with a positive screening result had the same non-target-disease-specific mortality as subjects with a negative screening result and one with increased non-target-disease-specific mortality for high-risk patients. In both these versions, a scenario with prevention is compared with a scenario without prevention and incremental effects are calculated.

Key parameters of the decision-analytic model are displayed in Table 1. Transition probabilities are not displayed as they were re-calculated for each cycle and each set of parameters. The transition probabilities of the Markov model were derived by disaggregating cause-specific mortality (i.e. target- and non-target-disease-specific mortality) as published by the German Federal Statistical Office [26]. This was done by assuming a constant age- and gender-specific CAD prevalence [27, 28] and by applying a ratio of CAD incidence between subjects with positive and negative screening results [21, 29]. This incidence ratio (which also corresponds to fatal CAD incidence, i.e. target-disease-specific mortality) was assumed to decrease as time passes, based on the Framingham risk equation [15, 21] (Fig. 6). This assumption was made because the explanatory power of a risk screening decreases over time (as a weighted average between HR_{target} of the previous cycle and the value 1). A hazard ratio closer to 1 indicates fewer differences between subjects with positive and negative screening results. As the fatal CAD incidence ratio HR_{target} changed over time, $HR_{other}(HR_{target})$ changed implicitly (Figs 5, 6).

Apart from the CAD incidence ratio, the proportion of subjects who receive a positive screening result was used for disaggregation (5 % in the base case scenario). Further details of the disaggregation process are presented elsewhere [21].

Estimation of the parameters of the hazard ratio function

To estimate the degree to which non-target-disease-specific mortality is increased in subjects with a positive screening result, pairs of hazard ratio estimates were extracted from four empirical studies [30–33]. All these studies reported CAD-specific mortality and all-cause-specific mortality for

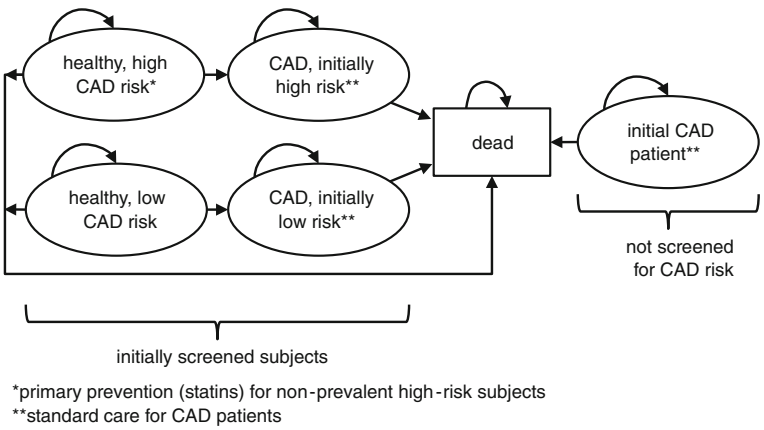

Fig. 4 Illustration of the Markov model

Table 1 Key parameters of the decision-analytic model

Parameter	Value	SE	Source
CAD risk reduction due to statins	0.33	0.05	[25]
CAD prevalence	Age and gender specific		[21, 27, 28]
Cause-specific mortality	Age and gender specific		[26]
Log(OR) of annual CAD mortality between CAD prevalent and non-prevalent subjects	−2.37	0.20	[21, 29]
Log(OR) of annual HF mortality between CAD prevalent and non-prevalent subjects	−1.44	0.02	[21, 29]
Log(OR) of annual further mortality between CAD prevalent and non-prevalent subjects	−0.06	0.29	[21, 29]
Weighting parameter to consider the decrease in the explanatory power of the screening over time (HR_{target} of the new cycle is a weighted average of HR_{target} of the previous cycle and the value 1)	0.96	0.01	[15, 21, 28]
Compliance	0.90	0.05	[21] (Assumption)
Health expenditures	Age and gender specific, based on sickness funds data		[39]
Ratio of health expenditures between CAD prevalent and non-prevalent subjects	Age and gender specific, based on sickness funds data		[29, 34]
CAD attributable share of health expenditures	Age and gender specific		[34]
Annual prevention costs with statins (including drug costs and health work force)	€436	€30.2	[40]
Screening costs	€70	€13	Assumption
Utility weight of CAD	0.90	0.03	[58–60]

CAD coronary artery disease, *OR* odds ratio, *HF* heart failure, *HR* hazard ratio

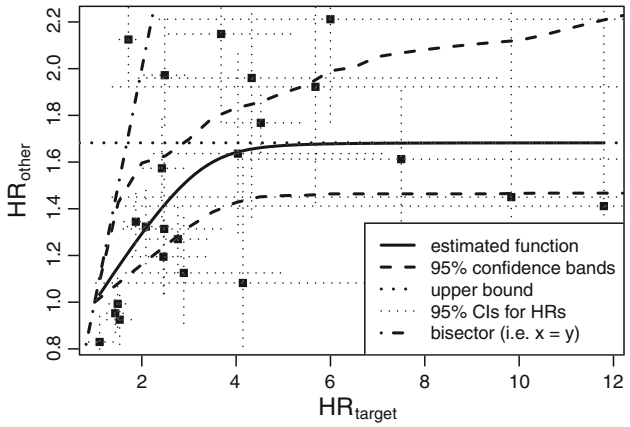

Fig. 5 Estimated function describing the relationship between the hazard ratios concerning coronary artery disease-specific mortality and mortality from other causes plus confidence bands derived via bootstrapping. HR_{target} = hazard ratio between subjects with positive and negative screening results concerning the target disease being screened; HR_{other} = hazard ratio concerning mortality from other causes

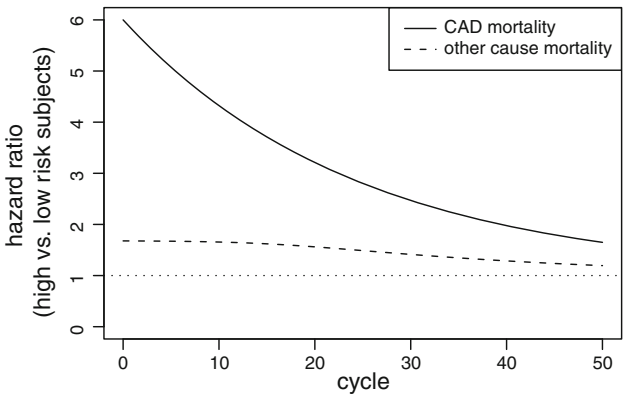

Fig. 6 Course of the hazard ratios between positively and negatively screened CAD non-prevalent subjects over time. The illustrated *curves* correspond to the base case scenario

different risk groups. The definition of subjects with a positive versus subjects with a negative screening result was based on the risk groups that were defined in the identified studies ("Appendix"; Table 4). Hazard rates were estimated by dividing the number of fatal events by the number of person–years under observation, and hazard ratios were derived by dividing the corresponding hazard rates ("Appendix"; Tables 5, 6). Confidence intervals of these hazard ratios were derived based on the assumption of Poisson-distributed events for a given time under observation. The error propagation law was applied to derive variance estimates on the log-hazard ratio scale [34]. The number of fatal non-CAD-specific events was calculated by subtracting CAD-specific events from the overall number of events.

Based on these observed pairs $(HR_{target}, HR_{other})$ of hazard ratios, the function $HR_{other}(HR_{target}|\theta_1, \theta_2, \theta_3)$ was fitted by applying the method of least squares to the

log-transformed hazard ratios (natural logarithm). The method of least squares is the standard approach for fitting linear regression models [35]. Minimisation was based on the Nelder and Mead algorithm [36] using the R function 'optim' [37]. Within optimisation, we considered the valid range specified for the parameters. For this reason, θ_1 was optimised on the $\log(\theta_1 - 1)$ scale, θ_2 was optimised on the $\log(\theta_2)$ scale, and θ_3 was optimised on the $\log(\theta_3 + 1)$ scale. With respect to the allowed range of θ_3, property 5 has been relaxed. The uncertainty of the parameter estimates was assessed by bootstrapping the extracted hazard ratios based on 1,000 runs [38]. Furthermore, 95 % pointwise confidence bands of the function $HR_{other}(HR_{target})$ were calculated based on the bootstrap approach.

Costs

A cost analysis was applied from the social health insurance (SHI) perspective. The age- and gender-specific costs of the SHI [39] were disaggregated via the age- and gender-specific cost ratio between CAD prevalent and non-prevalent subjects [34]. The share of CAD attributable SHI costs was derived via a complex regression approach based on sickness funds data [34]. CAD attributable costs were omitted if CAD was prevented. Screening costs were assumed to be €70 per person screened. Costs of prevention with statins included personnel costs and drug costs [40]. Costs for prevention were only applied to compliant subjects. All costs were inflated to 2011 euros [41].

Sensitivity analysis

To test the robustness of the results, several sensitivity analyses were performed. A deterministic sensitivity analysis was performed with respect to the initial value of HR_{target}, share of subjects screened positive, risk reduction due to intervention, compliance and time horizon. Subgroup analyses were performed according to age and gender. As screening and prevention may not only affect target-disease-specific mortality, but also other cause-specific mortality, we reduced mortality from other causes within a structural sensitivity analysis by 1, 5 and 10 %.

Furthermore, a probabilistic sensitivity analysis (PSA) has been performed in which all uncertain parameters were sampled according to reasonable distributions. Costs were assumed to be gamma distributed, probabilities were assumed to be beta distributed, and log odds ratios and log relative risks were assumed to be normally distributed [23, 42]. Corresponding parameters were approximated via expected value and standard error.

PSA was performed for both the adjusted and the unadjusted scenarios. Within the adjusted scenario, the parameters describing the function $HR_{other}(HR_{target})$ were derived via bootstrapping. To assess the effect of the function $HR_{other}(HR_{target})$, the same sampled parameter values were used for the adjusted and the unadjusted PSA.

As the structure of the Markov model was quite complex (several sets of equations had be solved for each cycle), the number of runs of PSA was restricted to 115.

Results of the application

The regression model to fit the function $HR_{other}(HR_{target})$ has an R square (log–log scale) of 0.37. The corresponding regression coefficients are presented in Table 2. The fitted curve including 95 % confidence limits is displayed in Fig. 5. The upper bound of HR_{other} is 1.68. However, at $HR_{target} = 12$, the 95 % confidence interval of HR_{other} ranges from 1.5 to 2.2. In 100 % of the bootstrapped cases, θ_3 fulfils property 5.

In the base case analysis, which corresponds to 50-year-old men with an initial CAD mortality rate ratio of 6 and with 5 % of subjects having a positive screening result, ignoring increased other-cause mortality in subjects at high risk for CAD increased the incremental health benefit (i.e. QALYs) by 19 %. At the same time, the incremental costs were estimated to be 8 % lower, compared with the scenario with adjustment. In consequence, the incremental cost-effectiveness ratio (ICER) decreased from €10,416 per QALY to €9,518 per QALY when no adjustment was made. Although always present, the effect varied depending on age, gender, explanatory power of the screening (i.e. HR_{target}), share of subjects with a positive screening result, risk reduction due to medical prevention, discounting (Table 3), compliance and whether non-target-disease-specific mortality was also reduced via prevention. If a short time horizon (i.e. less than 10 years) was applied, the effect became negligible.

Compared with the overall model uncertainty, the effect of not adjusting for increased non-target-disease-specific mortality appeared small (Fig. 7). The scatter plots of incremental costs and health outcome overlapped substantially for both scenarios. However, for each run of the PSA, the effect of not adjusting for increased non-target-disease-specific mortality was apparent (Fig. 8).

Table 2 Parameter estimates of the regression model quantifying the relationship between target- and non-target-disease-specific mortality ratios

Parameter	Estimate[a]	Mean[b]	SE[b]
$\log(\theta_1 - 1)$	−0.38	2.23	4.87
$\log(\theta_2)$	1.28	7.99	7.17
$\log(\theta_3 + 1)$	1.04	−1.14	6.04

[a] Used for the base case analysis

[b] Based on the bootstrap algorithm

Table 3 Deterministic, methodological and structural sensitivity analyses and subgroup analysis

	Incremental health outcome (QALYs gained)			Incremental costs (€)			ICER (€ per life–year gained)		
	With adjustment	Without adjustment	Ratio	With adjustment	Without adjustment	Ratio	With adjustment	Without adjustment	Ratio
Base case	0.024	0.028	1.19	246	266	0.92	10,416	9,518	0.91
Initial hazard ratio of CAD mortality (base case: HR = 6)									
2	0.016	0.017	1.06	312	318	0.98	19,985	19,159	0.96
12	0.026	0.030	1.16	196	214	0.92	7,599	7,168	0.94
Share of subjects with a positive screening result (base case: 5 %)									
10 %	0.043	0.050	1.17	425	460	0.92	9,911	9,177	0.93
20 %	0.075	0.086	1.14	825	884	0.93	10,966	10,276	0.94
CAD risk reduction due to medical prevention with statins (base case: 33 %)									
23 %	0.016	0.019	1.18	256	273	0.94	16,258	14,665	0.90
42 %	0.031	0.037	1.19	236	260	0.91	7,559	7,008	0.93
Discounting (base case: 3 %)									
0 %	0.044	0.055	1.23	337	388	0.87	7,578	7,060	0.93
5 %	0.016	0.019	1.16	213	225	0.95	13,141	11,980	0.91
Compliance (base case: 90 %)									
80 %	0.021	0.024	1.18	224	241	0.93	10,836	9,877	0.91
100 %	0.027	0.032	1.19	268	292	0.92	10,080	9,232	0.92
Subgroup analyses (base case: male, 50 years)									
40 years, male	0.022	0.026	1.14	326	343	0.95	14,606	13,418	0.92
55 years, male	0.022	0.027	1.21	208	229	0.91	9,473	8,606	0.91
60 years, male	0.020	0.024	1.24	169	188	0.90	8,609	7,784	0.90
40 years, female	0.013	0.015	1.12	346	356	0.97	26,082	23,832	0.91
50 years, female	0.016	0.019	1.16	259	271	0.95	16,147	14,551	0.90
55 years, female	0.016	0.019	1.19	222	235	0.94	13,571	12,144	0.89
60 years, female	0.016	0.020	1.21	180	194	0.93	11,104	9,925	0.89
Time horizon (base case: lifetime)									
2 years	<0.001	<0.001	1.00	98	98	1.00	2,949,252	2,939,521	1.00
5 years	0.001	0.001	1.01	132	132	1.00	241,886	240,657	0.99
10 years	0.003	0.003	1.02	171	172	0.99	63,610	62,960	0.99
20 years	0.011	0.011	1.05	197	200	0.99	18,460	17,805	0.96
Health outcome 'life–years gained' (base case: 'QALYs')									
CAD utility 1	0.019	0.023	1.21	246	266	0.92	13,023	11,664	0.90
Reduction in non-target-disease-specific mortality via prevention (base case: no reduction, i.e. 0 %)									
1 %	0.025	0.029	1.17	251	270	0.93	10,158	9,380	0.92
5 %	0.029	0.032	1.11	272	287	0.95	9,317	8,898	0.96
10 %	0.035	0.037	1.05	299	309	0.97	8,560	8,418	0.98
Costs for screening (base case: €70)									
€50	0.024	0.028	1.19	226	246	0.92	9,568	8,803	0.92
€90	0.024	0.028	1.19	266	286	0.93	11,263	10,234	0.91

Table 3 continued

	Incremental health outcome (QALYs gained)			Incremental costs (€)			ICER (€ per life–year gained)		
	With adjustment	Without adjustment	Ratio	With adjustment	Without adjustment	Ratio	With adjustment	Without adjustment	Ratio
Annual costs for prevention (base case: €436)									
€381	0.024	0.028	1.19	216	235	0.92	9,163	8,405	0.92
€490	0.024	0.028	1.19	275	297	0.93	11,668	10,632	0.91

ICER incremental cost-effectiveness ratio, *CAD* coronary artery disease, *QALYs* quality-adjusted life–years, *HR* hazard ratio

Discussion

In order to assess the bias by ignoring increased non-target-disease-specific mortality in subjects with a positive screening result, we designed a function that describes the relationship between target and non-target-disease-specific mortality between subjects with positive and negative screening results. Furthermore, we fitted this function to empirical data and applied it in a case example. We show that ignoring an increase in non-target-disease-specific mortality may lead to a bias in estimating the cost-effectiveness of screening (€10,416 per QALY vs. €9,518 per QALY).

The alternative approach to accommodating non-target-disease-specific mortality would be to adjust non-target-disease-specific mortality for covariates using a regression model. This approach, however, was not feasible because it would have required individual-level data. For the same reason, we did not use information on the correlation between risk factors to adjust non-target-disease-specific mortality.

To our knowledge, similar tools for related purposes do not yet exist. However, recently, there have been several approaches with respect to uncertainty within decision-analytic modelling and cost-effectiveness analysis [34, 43, 44]. Kim et al. [44] focused on estimating life–years gained based on clinical trials. They showed that life–years gained are overestimated when competing risk (non-target-disease-specific mortality) is not considered [44]. In contrast to our study, which used decision-analytic modelling to estimate survival time, the authors estimated survival time directly, using survival functions. Other authors have focussed on the methodology of quantifying parameter uncertainty [34] or on structuring decision-analytic models [45]. Bilcke et al. [43] presented a 'practical guide' to account for methodological, structural and parameter uncertainty in decision-analytic models. None of the references [34, 43–45] specifically dealt with the question of adjusting non-target-disease-specific mortality.

As in any estimation model, we had to rely on certain assumptions. For example, we have assumed a positive relationship between target- and non-target-disease-specific mortality. This assumption is not self-evident: some risk factors exist that are both positively associated with some causes of mortality, but negatively associated with other causes of mortality. For example, the risk factor obesity is positively associated with CAD, chronic heart failure and stroke, but negatively associated with osteoporosis and hip fractures [46, 47].

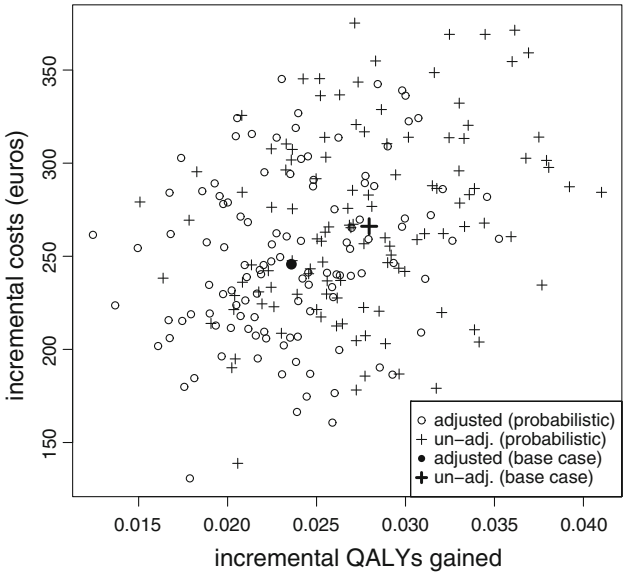

Fig. 7 Scatter plot of incremental costs and incremental effects of primary prevention with statins with and without consideration of an increase in non-target-disease-specific mortality

However, our approach was developed for early decision making, where no precise data on HR_{other} are available. Our approach helps in getting a rough estimate. In the case of obesity, overall non-CAD-specific mortality is still negatively associated with this risk factor.

One might also question the assumption that a screening method has a higher explanatory power concerning target-disease-specific mortality than concerning mortality from other causes (property 5). For example, the influence of smoking on overall mortality may be very large but, for some specific illnesses, it may be relatively small. However, the empirical data for the CAD scenario support

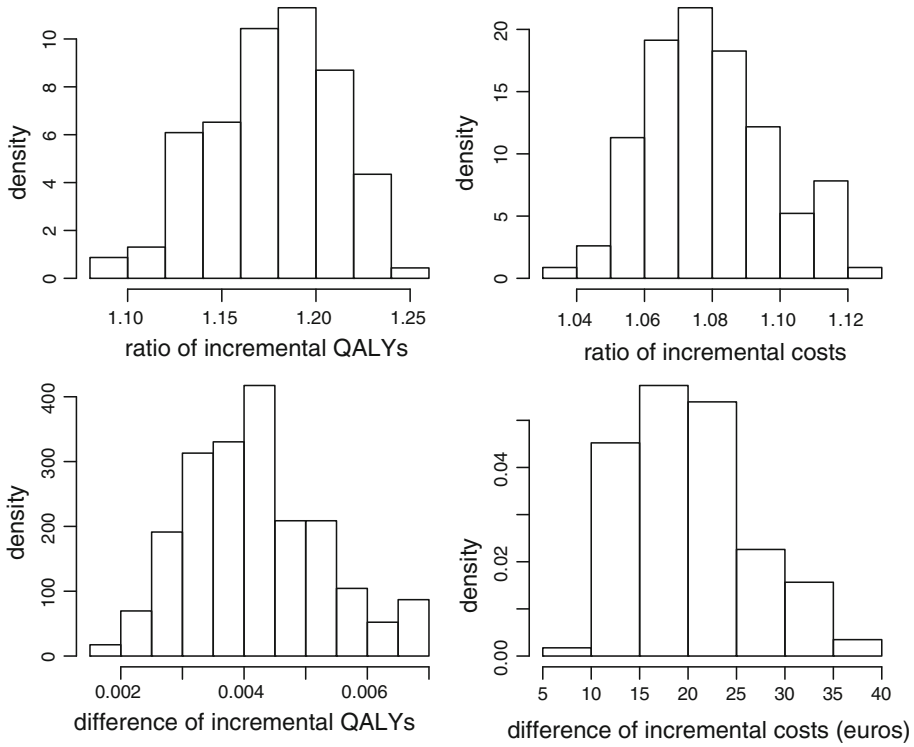

Fig. 8 Effect of adjusting for increased non-target-disease-specific mortality in high CAD risk patients

Table 4 Definition of risk groups used to estimate hazard ratios

ID	Study (first author)	Population characteristics	Definition of risk groups
D1	Daviglus	Women	Risk: very high, high, normal versus low
D2	Daviglus	Women	Risk: very high, high versus normal, low
D3	Daviglus	Women	Risk: very high versus high, normal, low
L1	Lowe	Women	Blood pressure: high, high/normal, normal versus optimal
L2	Lowe	Women	Blood pressure: high, high/normal versus normal, optimal
L3	Lowe	Women	Blood pressure: high versus high/normal, normal, optimal
L4	Lowe	Women	Serum cholesterol: <5.20 versus ≥5.20 mmol/l
L5	Lowe	Women	Serum cholesterol: <6.20 versus ≥6.20 mmol/l
L6	Lowe	Women	Smoking status: yes versus no
L7	Lowe	Men	Blood pressure: high, high/normal, normal versus optimal
L8	Lowe	Men	Blood pressure: high, high/normal versus normal, optimal
L9	Lowe	Men	Blood pressure: high versus high/normal, normal, optimal
L10	Lowe	Men	Serum cholesterol: <5.20 versus ≥5.20 mmol/l
L11	Lowe	Men	Serum cholesterol: <6.20 versus ≥6.20 mmol/l
L12	Lowe	Men	Smoking status: yes versus no
R1	Rosengren	Men	Risk: high, moderate, low versus optimal
R2	Rosengren	Men	Risk: high, moderate versus low, optimal
R3	Rosengren	Men	Risk: high versus moderate, low, optimal
S1	Stamler	Men, 40–57 years (MRFIT)	Risk: non-low versus low
S2	Stamler	Men, 40–59 years (CHA)	Risk: non-low versus low
S3	Stamler	Women, 40–59 years (CHA)	Risk: non-low versus low

MRFIT Multiple Risk Factor Intervention Trial, *CHA* Chicago Heart Association Detection Project in Industry, *ID* identification label for the extracted data point

Table 5 Person–years and number of cause-specific deaths subdivided according to the screening result

ID	Person–years		No. of CAD deaths		No. of deaths from other causes	
	'+'	'−'	'+'	'−'	'+'	'−'
D1	170,954	43,168	45	2	373	49
D2	124,918	89,204	42	5	319	103
D3	30,803	183,319	19	28	91	331
L1	163,399	15,663	392	13	1,080	92
L2	137,779	41,282	361	44	937	235
L3	105,882	73,179	324	81	759	413
L4	139,328	43,415	316	89	852	20
L5	65,614	117,129	187	218	400	472
L6	56,032	130,667	209	196	537	635
L7	187,214	8,974	1,084	21	1,973	72
L8	163,076	33,112	1,007	98	1,773	272
L9	129,104	67,084	865	240	1,475	570
L10	124,825	71,202	791	314	1,279	766
L11	41,842	154,184	318	787	434	1,611
L12	70,812	126,742	541	564	1,110	935
R1	138,344	2,414	676	1	1,456	18
R2	119,624	21,134	646	31	1,362	112
R3	14,666	126,092	149	528	228	1,246
S1	4,813,065	286,364	9,578	126	21,456	722
S2	135,433	6,818	516	6	1,168	30
S3	124,828	5,714	181	2	662	28

ID substudy identification codes, '+' = subjects with a positive risk score/enhanced risk; '−' = subjects with a negative risk score/lower risk; *CAD* coronary artery disease

Table 6 Cause-specific hazard rates and hazard ratio estimates

ID	CAD mortality rate		Mortality rate from other causes		Hazard ratio estimates	
	'+'	'−'	'+'	'−'	HR_{target}	HR_{other}
D1	0.26	0.05	2.18	1.14	5.68	1.92
D2	0.34	0.06	2.55	1.15	6.00	2.21
D3	0.62	0.15	2.95	1.81	4.04	1.64
L1	2.40	0.83	6.61	5.87	2.89	1.13
L2	2.62	1.07	6.80	5.69	2.46	1.19
L3	3.06	1.11	7.17	5.64	2.76	1.27
L4	2.27	2.05	6.12	0.46	1.11	13.27
L5	2.85	1.86	6.10	4.03	1.53	1.51
L6	3.73	1.50	9.58	4.86	2.49	1.97
L7	5.79	2.34	10.54	8.02	2.47	1.31
L8	6.18	2.96	10.87	8.21	2.09	1.32
L9	6.70	3.58	11.42	8.50	1.87	1.34
L10	6.34	4.41	10.25	10.76	1.44	0.95
L11	7.60	5.10	10.37	10.45	1.49	0.99
L12	7.64	4.45	15.68	7.38	1.72	2.12
R1	4.89	0.41	10.52	7.46	11.80	1.41
R2	5.40	1.47	11.39	5.30	3.68	2.15
R3	10.16	4.19	15.55	9.88	2.43	1.57
S1	1.99	0.44	4.46	2.52	4.52	1.77
S2	3.81	0.88	8.62	4.40	4.33	1.96
S3	1.45	0.35	5.30	4.90	4.14	1.08

ID substudy identification codes; '+' = subjects with a positive risk score/enhanced risk; '−' = subjects with a negative risk score/lower risk; *CAD* coronary artery disease, *HR* hazard ratio

property 5 [30, 31], even though it was not demanded when fitting the model.

The assumption that the function $HR_{other}(HR_{target})$ has an upper bound (property 4) is especially useful when it is used to extrapolate the relationship between both hazard ratios into regions beyond the range of observed pairs of $(HR_{target}, HR_{other})$. However, in our case study, the upper bound of HR_{other} varied widely, i.e. extrapolation in areas far beyond observed values of HR_{target} was accompanied by a significant degree of uncertainty. However, in the case of extrapolation, the robustness of estimates can be examined.

There might be other families of parametric functions satisfying the desired properties, which could, for example, be based on the arctangent function or on the Hill equation [48, 49]. However, the family of parametric functions that we have presented already has a high degree of flexibility, so that the benefit of identifying further parametric functions appears negligible. As a side effect, the flexible design led to unstable parameter estimates (Table 2). However, this is an appropriate reflection of uncertainty if the function is used for extrapolation.

There are some technical requirements that have to be fulfilled to apply the function, which are not always given. First, HR_{target} needs to be known. Second, empirical data are needed to fit the function. To identify such data, we suggest performing a literature review based on the keywords 'mortality', 'risk' and the name of the target disease. The identified studies can be checked to establish whether they are suitable to extract pairs of hazard ratios. An example of how hazard ratios can be estimated from such publications is given in the "Appendix".

Our application example referred to CAD risk screening. However, there are other areas of screening to which this function may also apply. As stated before, some risk factors for cervical cancer, colorectal cancer and inflammatory bowel disease are also associated with a higher risk of other causes of mortality [19, 50, 51]. Also, when modelling hepatitis C, one should bear in mind that it has common risk factors with other causes of death, such as HIV or death resulting from drug abuse [52, 53].

Regarding our application example, one might question whether the observed difference of 0.004 QALYs per

person screened is of clinical relevance. However, this corresponds to 19 % additional QALYs compared with no adjustment. Furthermore, many well-accepted preventive measures show only a small benefit, for example, mumps vaccination—while uncontroversial—yields a health gain of less than 0.001 life–years [54].

In the Markov model, it was not considered whether subjects who participate in a screening programme might differ from the general population. In particular, participating individuals may receive better care for diseases other than CAD and may have smaller non-target-disease-specific mortality than predicted. This might affect the incremental cost and health outcome ratios that we have presented.

The regression approach to fit the function $HR_{other}(HR_{target})$ also has several limitations. All observed pairs of hazard ratios entered the regression equation with an equal weight. Therefore, one might suggest performing a meta-regression [55]. However, fixed effects meta-regression did not seem appropriate as heterogeneity among the hazard ratio pairs was present: the confidence limits crossed the fitted function significantly less often than expected. Mixed effects meta-regression, on the other hand, is a complex procedure that requires an iterative proceeding. Standard approaches of mixed meta-regression could not be applied, as we did not perform linear but non-linear regression. Furthermore, the regression approach did not reflect the fact that both HR_{other} and HR_{target} were measured with error. Solutions that exist for meta-analysis of diagnostic tests again could not be transferred, as we conducted a non-linear regression [56, 57]. However, the approach of giving equal weight to all observations was found to be relatively robust [55]. In particular, in the presence of heterogeneity, equal weighting appears suitable, as heterogeneity shifts the weights towards equal weights [55].

In conclusion, some bias can occur when an increase in non-target-disease-specific mortality is not considered when modelling the outcomes of screening tests. The proposed function may support decision-analytic modelling and result in more valid modelling results.

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Appendix

Data collection

Details regarding the observed pairs of HR_{target} and HR_{other} can be found in Tables 4, 5 and 6.

Proof of $HR_{other}(HR_{target})$ being differentiable

If $HR_{other}(HR_{target})$ satisfies all desired properties over $[1, \infty)$, then it is automatically differentiable (property 6) over (0, 1) and also in $HR_{target} = 1$, which can be shown as follows. Let $HR_{other}^{[1,\infty)}(HR_{target})$ be the function $HR_{other}(HR_{target})$ as defined over $[1, \infty)$, and let $HR_{other}^{(0,1)}(HR_{target})$ be $HR_{other}(HR_{target})$ as defined over (0, 1). Via property 3, $HR_{other}^{(0,1)}(HR_{target})$ is defined as follows:

$$HR_{other}^{(0,1)}(HR_{target}) := \frac{1}{HR_{other}^{[1,\infty)}(1/HR_{target})}. \tag{3}$$

If $HR_{other}^{[1,\infty)}(HR_{target})$ is differentiable, then $HR_{other}^{[1,\infty)}(HR_{target})$ is also differentiable:

$$\begin{aligned}\frac{\partial HR_{other}^{(0,1)}(HR_{target})}{\partial HR_{target}} &= \frac{\partial \frac{1}{HR_{other}^{[1,\infty)}(1/HR_{target})}}{\partial HR_{target}} \\ &= \frac{\frac{\partial HR_{other}^{[1,\infty)}}{\partial HR_{target}}(1/HR_{target})}{\left(HR_{target} \cdot HR_{other}^{[1,\infty)}(1/HR_{target})\right)^2}.\end{aligned} \tag{4}$$

To prove that $HR_{other}(HR_{target})$ is differentiable in $HR_{target} = 1$, it has to be shown that:

$$\lim_{HR_{target}\uparrow 1} \frac{\partial HR_{other}^{(0,1)}(HR_{target})}{\partial HR_{target}} = \lim_{HR_{target}\downarrow 1} \frac{\partial HR_{other}^{[1,\infty)}(HR_{target})}{\partial HR_{target}}. \tag{5}$$

The right-hand side of Eq. (5) can furthermore be written as:

$$\lim_{HR_{target}\downarrow 1} \frac{\partial HR_{other}^{[1,\infty)}(HR_{target})}{\partial HR_{target}} = \frac{\partial HR_{other}^{[1,\infty)}}{\partial HR_{target}}(1), \tag{6}$$

meaning that it represents the derivation of $HR_{other}^{[1,\infty)}$ at $HR_{target} = 1$. From the left-hand side of Eq. (5) and from Eq. (4), it follows that:

$$\begin{aligned}&\lim_{HR_{target}\uparrow 1} \frac{\partial HR_{other}^{(0,1)}(HR_{target})}{\partial HR_{target}} \\ &= \lim_{HR_{target}\uparrow 1} \frac{\frac{\partial HR_{other}^{[1,\infty)}}{\partial HR_{target}}(1/HR_{target})}{\left(HR_{target} \cdot HR_{other}^{[1,\infty)}(1/HR_{target})\right)^2} \\ &= \frac{\frac{\partial HR_{other}^{[1,\infty)}}{\partial HR_{target}}(1/1)}{\left(1 \cdot HR_{other}^{[1,\infty)}(1/1)\right)^2} = \frac{\partial HR_{other}^{[1,\infty)}}{\partial HR_{target}}(1)\end{aligned} \tag{7}$$

Equations (6) and (7) show that Eq. (5) holds. Thus, $HR_{other}(HR_{target})$ is differentiable in $HR_{target} = 1$.

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