

Decision thresholds and increases in risk for preventive treatment

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Abstract

This paper investigates the notion of treatment threshold for preventive treatment with potential side effects in the context of increases in risk. Changes in risk are defined by the concept of n th-order stochastic dominance and concern the effectiveness of preventive treatment, side effects, severity of the potential disease and comorbidity risk. The impact of a riskier environment on the probability of disease threshold above which the preferable decision is to undergo preventive treatment is shown to depend on both mixed risk averse individual preferences and the configuration of increase in risk considered. These results suggest that neglecting differences between risks when evaluating the treatment threshold is likely to lead to substantial errors in most cost-benefit applications for preventive treatment.

1 Introduction

The decision to undergo medical treatment has many consequences on the health of individuals; this is particularly true in the case of preventive treatment, as they are likely to incur side effects (see Waters et al., 2009). Side effects are unintended and often harmful effects of medical treatment that are secondary to the effect intended. For instance, in the case of vaccines, several problems are usually reported within a few weeks of getting a vaccine including headaches, upper respiratory tract infection or even pneumonia, or inflammation of the stomach or intestines (CDC, 2014). Hence, as administering preventive treatment for a specific disease can be harmful for an individual in good health, a trade-off between the benefit of treatment and its side effect has to be faced before administering treatment. Depending on this trade-off and his own preferences, a decision-maker will decide to undergo the treatment or not. In the literature, a useful notion known as the treatment threshold has been defined by Pauker and Kassirer (1975) to help the physician to decide whether or not to treat a patient who may or may not have a disease. This notion defines a probability of disease threshold above which the preferable course of action is to undergo treatment, otherwise to withhold treatment. This notion has been initially defined for curative treatment in the absence of precise diagnosis and in relation to individual preferences, in particular, risk attitudes (see also Eeckhoudt, 2002; Felder and Mayrhofer, 2014). The aim of this paper is to investigate the notion of treatment threshold in the case of preventive care with potential side effects as a tool to help a decision-maker in deciding to administer or not a preventive treatment. More particularly, we consider preventive treatment administered ex-ante that reduces the severity of the disease should

the disease occur, and we investigate the concept of treatment threshold for preventive treatment when the environment of the decision-maker becomes riskier.

We consider various situations of increase in risk that are encountered in the case of preventive treatment. First, we consider the case where the effectiveness of preventive treatment in reducing the severity of the potential disease is uncertain. Indeed, as the effect of treatment occurs in the future, there is still some uncertainty as to how this treatment will affect health in case of disease. Intuitively, the more uncertain or risky the effectiveness of the treatment, the less often the treatment should be administered and therefore the higher the treatment threshold. Second, we consider the side effects of preventive treatment to be uncertain and extend the notion of treatment threshold to the case of risky side effects of treatment. In that context, we investigate how an increase in risk of a detrimental effect affects the probability of undergoing the preventive treatment. Intuitively, the riskier the side effect, the less likely the preventive treatment should be administered and the higher the treatment threshold. Third, we consider the severity of the potential disease to be risky. Indeed, when deciding to administer preventive treatment, it is unlikely that the decision-maker knows with certainty the severity of the potential disease. This might also arise in the presence of comorbidity risks. We then investigate how higher uncertainty about the severity of the potential disease influences the treatment threshold. Intuitively, the riskier or the more uncertain the gravity of the potential disease, the less often the preventive treatment should be administered as the more uncertain is the health improvement from preventive treatment in case of the disease, and the higher the treatment threshold should be. Finally, we generalise part of our results by considering the case where preventive treatment reduces uncertainty on the severity of the potential disease and by introducing comorbidity risks.

So as to define increases in risk, we use the concept of n th-order stochastic dominance. This approach makes it possible to define a statistical link between random variables, and to link it to individual preferences. In particular, n th-order stochastic dominance includes the concepts of mean-preserving increase in risk introduced by Rothschild and Stiglitz (1970) as well as of increase in downside risk as defined by Menezes et al. (1980). Such an approach has been recently used to address various economic decisions in the face of changes in risk (e.g. Eeckhoudt and Schlesinger, 2008; Courbage and Rey, 2012; Jouini et al., 2013). In addition, changes in risk of higher orders are particularly relevant in the context of health since it implies higher statistical moments and the health econometric literature is paying greater attention to higher order statistical moments of health and health care probability distributions (see e.g. Cantoni and Ronchetti, 2006).

We then show that the decision to undergo preventive treatment when the environment becomes riskier depends both on individual preferences and on the configuration of increase in risk considered. We show that utility of higher orders drives the decision to engage in prevention activities, and in particular preferences that are commonly referred to as mixed risk averse (see Caballé and Pomansky, 1996). We consider risk preferences of higher orders than the one of risk aversion, prudence and temperance as previously used in the literature of treatment threshold (Felder and Mayrhofer, 2014). Although intuitively, one may think that a riskier environment always increases the treatment threshold, this paper shows that this is not necessarily the case and that results strongly depend on the risky environment considered.

This paper provides some interesting results in terms of public health policy. It offers conditions on individual preferences and on higher order risk increases under which

preventive treatment would be used less or more often in the population confronted to riskier effectiveness of treatment, to riskier side effect of the treatment, to riskier severity of the potential disease or to riskier comorbid conditions. Such results are helpful for the decision-maker in terms of cost-benefit analysis, whether he be the physician or the patient. Indeed, these results suggest that neglecting differences between risks when evaluating the decision threshold is likely to lead to substantial errors in most cost-benefit applications.

This paper is organised as follows. In the next section, we introduce the benchmark model of probability threshold in the case of preventive treatment. Section 3 presents the concepts of n th-order stochastic dominance and of increase in n th-degree risk defined by Ekern (1980). Section 4 investigates the effect of uncertainty on the effectiveness of treatment. Section 5 addresses the impact of riskier side effects. Section 6 presents the effect of uncertainty on the severity of the potential disease. Section 7 deals with the more general case of the effect of an increase in comorbidity risk when the preventive treatment reduces uncertainty. Finally, some concluding remarks are provided in the last section.

2 The benchmark model

This section introduces the basic hypothesis of the model based on Pauker and Kassirer's (1975) framework in which we substitute curative treatment by preventive treatment. Consider a patient who faces the risk of developing a specific disease with probability p . We assume that health can be quantified, for instance, through quality-adjusted life-years (QALY)¹. Let H_0 be the level of health in case of disease and H_2 the level of health if no disease, with obviously $H_2 > H_0$. The difference between H_2 and H_0 indicates the severity of the potential disease without treatment. A well-defined preventive treatment for the disease is available reducing the severity of the disease should it occur. This treatment is to be initiated ex-ante, i.e. before knowing whether the patient has already developed the disease. We denote by b the beneficial effect of the treatment reducing the severity of the disease should it occur. Hence, the health level in case of disease becomes $H_0 + b$. We denote by c the possible side effect of the treatment reducing the level of health in the state of no disease when the preventive treatment has been administered. This form of prevention is often referred to as secondary prevention in the health literature (Kenkel, 2000) and as self-insurance in the risk economics literature (Ehrlich and Becker, 1972).

A good illustration is a person who is at risk of developing tuberculosis but who has no signs or symptoms of clinically or radiologically active tuberculosis. Administrating preventive chemotherapy reduces the development of the disease should it occur in the future. However, chemotherapy can incur side effects in the form of nausea, hair loss and hearing impairment or even anemia or thrombocytopenia (CDC, 2014). Another illustration could be the use of mefloquine prophylaxis to prevent malaria, a mosquito-borne disease caused by a parasite. Mefloquine does not reduce the probability of being bitten by a mosquito and exposed to malaria parasites, but reduces the adverse effect on health should a person be exposed to malaria parasites. However, mefloquine is often

¹Recent developments regarding QALY can be found in Hammitt (2013).

associated with serious adverse reactions such as gastrointestinal disturbance, headache, insomnia or even psychoses and neuropsychiatric disorders (Juckett, 1999).

Going back to our model, the decision-maker (DM) must decide whether or not to administer the preventive treatment. The DM's utility function is given by v (verifying the usual assumption $v'(x) > 0 \forall x$). In this analysis, we do not differentiate between physician and patient, in the sense that we assume that the DM decides purely in the interest of the patients².

Hence, the agent faces two lotteries. In the case where no preventive treatment is administered, he faces the lottery \tilde{H}^{NT} defined as:

$$\tilde{H}^{NT} = [H_2, H_0; 1 - p, p],$$

In the case where a preventive treatment is administered, he faces the lottery \tilde{H}^T defined as:

$$\tilde{H}^T = [H_2 - c, H_0 + b; 1 - p, p],$$

We make the assumption that $H_0 + b < H_2 - c$, i.e. a DM receiving preventive treatment never ends up in a better health status if the disease occurs than if the disease does not occur.

The agent accepts the treatment if and only if the expected utility with treatment is at least as high as the expected utility without treatment, i.e. $E[v(\tilde{H}^T)] \geq E[v(\tilde{H}^{NT})]$, or equivalently if and only if:

$$p \geq \frac{v(H_2) - v(H_2 - c)}{(v(H_2) - v(H_2 - c)) + (v(H_0 + b) - v(H_0))} = p^A \quad (1)$$

The treatment threshold, denoted p^A , is the value of the probability of disease such that one is indifferent between undergoing the preventive treatment or not, i.e. such as $E[v(\tilde{H}^T)] = E[v(\tilde{H}^{NT})]$. Hence, p^A is the probability threshold above which the preferable course of action is to undergo the preventive treatment³.

From Eq. (1), it is easy to show that if $c = 0$, i.e. if there is no side effect of the treatment, then $p^A = 0$ meaning that the DM will always choose to treat whatever his attitude to risk. Analogously, if $b = 0$, i.e. if there is no beneficial effect of the treatment, then $p^A = 1$ and the DM will always refuse to treat whatever his attitude to risk. Naturally, the relevance of the treatment threshold concept arises when there exists a trade-off between treatment and side effect, i.e. when $b > 0$ and $c > 0$. We therefore make the assumptions that $H_0 < H_0 + b < H_2 - c < H_2$. In such a case, $p^A > 0$ whatever the DM's attitude to risk.

In what follows, we assume a strictly risk-averse DM, i.e. v such that $v''(x) < 0 \forall x$. More precisely, we assume that the utility function is n -times differentiable of order n and such that $(-1)^{(n+1)}v^{(n)} > 0 \forall n \geq 1$, i.e. such that the successive higher derivatives alternate in signs. Such utility function is referred to as a mixed risk-averse utility function (Caballé and Pomansky, 1996). Brockett and Golden (1987) noted that all commonly used risk-averse utility functions are mixed risk-averse utility functions (see also Ebert,

²As stressed by one referee, this assumption ignores the fact that often there might be different (financial) incentives for the one treatment over the other from the perspective of the healthcare provider.

³This concept focuses on the health consequences of preventive treatment only, without consideration for the financial consequences.

2013). The logarithmic function ($v(x) = \ln(x)$), the power function ($v(x) = x^a$ with $0 < a < 1$), and the negative exponential function ($v(x) = -\exp^{-ax}$ with $a > 0$), which are widely referenced utility functions in medical decision-making (see Bleichrodt et al., 2005) have the property of having their successive higher derivatives alternate in signs. Such properties of the utility function also capture the notion of preferences for harms disaggregation or preferences to combine good with bad as showed by Eeckhoudt and Schlesinger (2006) and Eeckhoudt et al. (2009).

In this article we investigate how a riskier environment influences the probability threshold. To that aim, we present in the next section the concept of change in risk that is used throughout this paper.

3 Higher order degree change in risk

The changes in risk we consider in this paper are based on the concept of stochastic dominance. Stochastic dominance establishes a partial ordering of probability distributions. It makes it possible to compare distributions that differ in their conditional moments of higher orders. A special case of stochastic dominance is the notion of increase in risk as developed by Ekern (1980).

The standard notion of n th-degree stochastic dominance and n th-degree risk increase (Ekern, 1980) are defined as follows. Consider two random variables X and Y with F and G respectively their two cumulative distribution functions defined over a probability support contained within the interval $[a, b]$. Define $F_1 = F$ and $G_1 = G$. Now define $F_{k+1}(z) = \int_a^z F_k(t)dt$ and $G_{k+1}(z) = \int_a^z G_k(t)dt$ for $k \geq 1$.

The variable X is dominated by the variable Y by n th-degree stochastic dominance ($X \preceq_{SD-n} Y$) if $F_n(z) \geq G_n(z)$ for all z in $[a, b]$ where the inequality is strict for some z .

A special case of stochastic dominance is the notion of increase in risk as developed by Ekern (1980). According to Ekern (1980), the variable X is an increase in n th-order risk over Y ($X \succeq_n Y$) if $X \preceq_{SD-n} Y$ and the first $(n - 1)$ moments of G and F are identical ($E(X^k) = E(Y^k) \forall k = 1, 2, \dots, n - 1$). Ekern's (1980) definition includes the cases of mean preserving increase in risk of Rothshild and Stiglitz (1970) as well as of increase in downside risk defined by Menezes et al. (1980) as respectively a 2^{nd} -degree and a 3^{rd} -degree increase in risk.

The known characterizing properties of these concepts are the following⁴ ($f^{(s)}$ denotes the s th derivative of f):

(i) For all X and Y such that $X \preceq_{SD-n} Y$, $E[f(X)] < E[f(Y)]$ for any function f such that $(-1)^{s+1} f^{(s)} > 0 \forall s = 1, 2, \dots, n$.

(ii) For all X and Y such that $X \succeq_n Y$, $E[f(X)] < E[f(Y)]$ for any function f such that $(-1)^{n+1} f^{(n)} > 0$.

⁴A proof can be found in Ingersoll (1987) for example.

To illustrate higher order increase in risk and the link between the properties of the utility function, we rely on Eeckhoudt and Schlesinger's (2006) framework which provides a unified approach based on preferences over specific class of lotteries⁵.

Let us consider an individual with an initial health status a facing the binary lottery $\tilde{H}_1 = [a - \delta_1, a; \frac{1}{2}, \frac{1}{2}]$, meaning that the individual has a fifty per cent chance of contracting a disease that decreases a by δ_1 units. Now, let us assume that this individual faces a second disease that decreases his health by δ_2 units. This second disease could occur either in the state of good health or in the state of bad health, where the first disease had already occurred, with equiprobable probability. Equivalently, this means that the individual faces the lottery $\tilde{H}_1^0 = [a - \delta_1, a - \delta_2; \frac{1}{2}, \frac{1}{2}]$ or $\tilde{H}_2^0 = [a, a - \delta_1 - \delta_2; \frac{1}{2}, \frac{1}{2}]$, where both lotteries have the same expected mean. The change from \tilde{H}_1^0 to \tilde{H}_2^0 illustrates a mean-preserving increase in risk (Rothschild and Stiglitz, 1970) or an increase in risk of order 2. From Rothschild and Stiglitz (1970), we know that all risk-averse individuals prefer \tilde{H}_1^0 to \tilde{H}_2^0 , i.e. $E[v(\tilde{H}_1^0)] > E[v(\tilde{H}_2^0)]$ for all concave functions v . Hence, a risk-averse individual prefers to face the second disease in the state of good health, i.e. \tilde{H}_1^0 , rather than in the state of bad health, where the first disease had already occurred, i.e. \tilde{H}_2^0 .

Now consider a 3rd-degree increase in risk which is equivalent to what Menezes et al. (1980) call "downside risk". Consider still an individual with an initial health status a facing the binary lottery $\tilde{H}_1 = [a - \delta_1, a; \frac{1}{2}, \frac{1}{2}]$. This individual is now forced to undergo an additional health risk $\tilde{\epsilon}$ with $E(\tilde{\epsilon}) = 0$ where $\tilde{\epsilon}$ is also a number of life years. This risk could occur either in the state of good health, or in the state of bad health where the first disease already occurred with equiprobable probability. Equivalently, this means that the individual faces the lottery $\tilde{H}_1^* = [a + \tilde{\epsilon}, a - \delta_1; \frac{1}{2}, \frac{1}{2}]$ or $\tilde{H}_2^* = [a, a - \delta_1 + \tilde{\epsilon}; \frac{1}{2}, \frac{1}{2}]$, where both lotteries have the same expected mean and the same variance. The change from \tilde{H}_1^* to \tilde{H}_2^* represents an increase in downside risk (Menezes et al., 1980) or an increase in risk of order 3. From Menezes et al. (1980), we know that $E[v(\tilde{H}_1^*)] > E[v(\tilde{H}_2^*)]$ for all prudent individual, i.e. $v'''(x) > 0$ as defined by Kimball (1990). The intuitive explanation is that a prudent individual prefers to see the additional health risk $\tilde{\epsilon}$ attached to the good state of health (health level a) rather than to the bad one (health level $a - \delta_1$).

To illustrate a 4th-degree increase in risk, let the health loss δ_1 be replaced in \tilde{H}_1^* and \tilde{H}_2^* by another health risk $\tilde{\epsilon}_1$ such as $E(\tilde{\epsilon}_1) = 0$. The change from \tilde{H}_1^* to \tilde{H}_2^* now represents a 4th-degree increase in risk, where both lotteries have the same expected mean, variance and skewness. A patient whose preferences verify temperance, i.e. $v''''(x) < 0$ as defined by Kimball (1992), prefers to see the additional health risk $\tilde{\epsilon}$ attached to the no risk state of health (health level a) rather than to the risky one (health level $a + \tilde{\epsilon}_1$), i.e. he prefers \tilde{H}_1^* to \tilde{H}_2^* . A 4th-degree increase in risk is equivalent to what Menezes and Wang (2005) call an increase in "outer risk".

More generally, the passage from the lottery $\tilde{H}_1^* = [\tilde{\epsilon}_1 + \tilde{\theta}_2, \tilde{\epsilon}_2 + \tilde{\theta}_1; \frac{1}{2}, \frac{1}{2}]$ to the lottery $\tilde{H}_2^* = [\tilde{\epsilon}_1 + \tilde{\theta}_1, \tilde{\epsilon}_2 + \tilde{\theta}_2; \frac{1}{2}, \frac{1}{2}]$ (where $\tilde{\epsilon}_2 \preceq_{n_1} \tilde{\epsilon}_1$ and $\tilde{\theta}_2 \preceq_{n_2} \tilde{\theta}_1$) represents a $(n_1 + n_2)$ th-degree increase in risk (Eeckhoudt et al., 2009). A patient with a utility function v such that $(-1)^{(n_1+n_2+1)}v^{(n_1+n_2)} > 0$ prefers \tilde{H}_1^* to \tilde{H}_2^* i.e. $E[v(\tilde{H}_1^*)] > E[v(\tilde{H}_2^*)]$. The intuitive explanation is the following: consider a patient facing a risky health status modeled by the lottery $[\tilde{\epsilon}_1, \tilde{\epsilon}_2; \frac{1}{2}, \frac{1}{2}]$, then he prefers to combine a "relative good risk" $\tilde{\theta}_1$ to the "relative bad state" $\tilde{\epsilon}_2$ and the "relative bad risk" $\tilde{\theta}_2$ to the "relative good state" $\tilde{\epsilon}_1$ rather

⁵See also Eeckhoudt et al. (2009) and Ebert (2013).

than to combine “good” with “good” ($\tilde{\theta}_1$ and $\tilde{\epsilon}_1$) and “bad” with “bad” ($\tilde{\theta}_2$ and $\tilde{\epsilon}_2$). Such preferences capture the notion of preferences for harms disaggregation following the terminology of Eeckhoudt and Schlesinger (2006).

Eeckhoudt et al. (2009) generalize this result to stochastic dominance, i.e. in the case where $\tilde{\epsilon}_2 \preceq_{SD-n_1} \tilde{\epsilon}_1$ and $\tilde{\theta}_2 \preceq_{SD-n_2} \tilde{\theta}_1$, then $E[v(\tilde{H}_1^*)] > E[v(\tilde{H}_2^*)]$ for all mixed risk-averse patients with v such that $(-1)^{(s+1)}v^{(s)} > 0$ for $s = 1, 2, \dots, n_1 + n_2$.

It should be stressed that a higher statistical moment of order n of one random variable over another is a necessary but not sufficient condition for the first random variable to be a n^{th} -degree increase in risk of the other random variable.

4 Uncertain effectiveness of preventive treatment

Since the seminal work of Arrow (1963), uncertainty in health care is known to relate mainly to uncertainty surrounding the effectiveness of medical treatment and uncertainty surrounding the severity of disease. In this section, we investigate the effect of uncertain effectiveness of preventive treatment on the probability threshold, and in particular how an increase in the risk of the effectiveness of treatment modifies the treatment threshold. Increase in the risk of effectiveness can be due for instance to the use of new technological discoveries or simply to a better knowledge of the effectiveness of preventive treatment.

In order to introduce uncertain effectiveness of treatment, we consider that b becomes random of the form \tilde{b}_i with $i = 1, 2$. We consider two situations under which the DM faces either \tilde{b}_1 or \tilde{b}_2 as a risk on the effectiveness of treatment with \tilde{b}_2 being riskier than \tilde{b}_1 in the sense of n th-order stochastic dominance or in the sense of an Ekern increase in risk of order n , i.e. $\tilde{b}_2 \preceq_{SD-n} \tilde{b}_1$ or $\tilde{b}_2 \preceq_n \tilde{b}_1$. We then compare the treatment threshold associated to \tilde{b}_1 and \tilde{b}_2 . In the situation with \tilde{b}_i as a risk on the treatment effectiveness ($i = 1, 2$), the DM faces the two following lotteries in case he undergoes a treatment or not:

$$\begin{aligned}\tilde{H}_{b_i}^T &= [H_2 - c, H_0 + \tilde{b}_i; 1 - p, p], \\ \tilde{H}^{NT} &= [H_2, H_0; 1 - p, p],\end{aligned}$$

with \tilde{b}_i such that $v(H_2 - c) > E[v(H_0 + \tilde{b}_i)] \forall i = 1, 2$ to ensure that a DM receiving a risky preventive treatment never ends up in a better health status if the disease occurs than if the disease does not occur.

We denote by $p_{b_i}^A$ the treatment threshold associated to \tilde{b}_i and given by

$$p_{b_i}^A = \frac{v(H_2) - v(H_2 - c)}{(v(H_2) - v(H_2 - c)) + (E[v(H_0 + \tilde{b}_i)] - v(H_0))} \quad (2)$$

Using the properties (i) and (ii) of section 3, we obtain the following proposition.

Proposition 1

A riskier effectiveness of preventive treatment in the sense of n th-degree stochastic dominance ($\tilde{b}_2 \preceq_{SD-n} \tilde{b}_1$) increases the treatment threshold ($p_{b_2}^A > p_{b_1}^A$) for all DMs with a utility function v such that $(-1)^{(1+s)}v^{(s)} > 0 \forall s = 1, 2, \dots, n$.

A riskier effectiveness of preventive treatment in the sense of an Ekern increase in n th-degree risk ($\tilde{b}_2 \preceq_n \tilde{b}_1$) increases the treatment threshold ($p_{b_2}^A > p_{b_1}^A$) for all DMs with a utility function v such that $(-1)^{(1+n)}v^{(n)} > 0$.

The proof is straightforward. Using Eq. (2), we see that $p_{b_2}^A > p_{b_1}^A$ iff $E[v(H_0 + \tilde{b}_2)] < E[v(H_0 + \tilde{b}_1)]$. Using the properties (i) and (ii) of section 3, we directly obtain the result.

The explanation of Proposition 1 is that the riskier the effectiveness of preventive treatment, the lower the gain of welfare from the treatment in case of disease. Indeed, let us define $h(H_0, \tilde{b}_i) = E[v(H_0 + \tilde{b}_i)] - v(H_0)$ the gain of welfare from the risky treatment \tilde{b}_i in case of disease⁶ when the DM's health level in case of disease is H_0 . Intuition suggests that the DM will undergo less preventive treatment in the presence of a more uncertain effectiveness whenever the gain from the treatment is weaker i.e. $h(H_0, \tilde{b}_2) < h(H_0, \tilde{b}_1)$ or equivalently, $E[v(H_0 + \tilde{b}_2)] < E[v(H_0 + \tilde{b}_1)]$, which is true for all function v such that $(-1)^{(1+s)}v^{(s)} > 0 \forall s = 1, 2, \dots, n$ when $\tilde{b}_2 \preceq_{SD-n} \tilde{b}_1$ or such that $(-1)^{(1+n)}v^{(n)}(x) > 0$ when $\tilde{b}_2 \preceq_n \tilde{b}_1$ according to Ekern (1980). Hence, the riskier the effectiveness of preventive treatment, the less often the DM will decide to undergo preventive treatment.

In the case of $n = 1$ (\tilde{b}_2 and \tilde{b}_1 being two degenerated random variables such that $\tilde{b}_2 = \underline{b}$ and $\tilde{b}_1 = \bar{b}$ with $\bar{b} > \underline{b}$), a first-order increase in risk corresponds to a lower effectiveness of treatment. Then according to Proposition 1, the lower the effectiveness of the treatment, the higher the treatment threshold and the less often the treatment threshold for all DM such that $v'(\cdot) > 0$. In the case of $n = 2$, Proposition 1 means that the introduction of uncertainty on the effectiveness of the treatment increases the treatment threshold for all risk-averse DMs compared to the case where the effectiveness of the treatment is certain.

The results above suggest that policy measures which result in a reduction in the uncertainty or the risk surrounding the effectiveness of preventive treatment would cause preventive care to rise.

5 Uncertain side effects

While the side effect of preventive treatment c is assumed to be certain in the benchmark model, it is most likely that the intensity of this effect is uncertain. This is mainly why people are deterred from pursuing prevention as they are uncertain about the degree of side effects. Waters et al. (2009) even defined the concept of side effect aversion to express the inability of people to invest in prevention due to uncertain side effects. We therefore assume here that the side effect becomes \tilde{c}_i . We then investigate how the treatment threshold reacts to a riskier side effect. To that end, we compare the treatment threshold

⁶ $h(H_0, \tilde{b}_i)$ is related to the concept of utility premium introduced by Friedman and Savage (1948) which defines a non-monetary measure of risk aversion (i.e. the degree of pain of facing a risk).

associated with two uncertain side effects, \tilde{c}_1 and \tilde{c}_2 such that \tilde{c}_2 is riskier than \tilde{c}_1 . We also assume that \tilde{c}_i is such that $E[v(H_2 - \tilde{c}_i)] > v(H_0 + b) \forall i = 1, 2$.

With uncertainty on the side effect, the DM faces the two following lotteries in case he undergoes a preventive treatment or not:

$$\tilde{H}_{c_i}^T = [H_2 - \tilde{c}_i, H_0 + b; 1 - p, p],$$

$$\tilde{H}^{NT} = [H_2, H_0; 1 - p, p],$$

We denote by $p_{c_i}^A$ the treatment threshold associated with \tilde{c}_i ($i = 1, 2$). It writes as

$$p_{c_i}^A = \frac{v(H_2) - E[v(H_2 - \tilde{c}_i)]}{(v(H_2) - E[v(H_2 - \tilde{c}_i)]) + (v(H_0 + b) - v(H_0))}. \quad (3)$$

We obtain the following proposition (see proof in Appendix 1):

Proposition 2

For all DMs with a utility function v such that $(-1)^{(1+n)}v^{(n)} > 0$, a riskier side effect of preventive treatment in the sense of an Ekern increase in n th-degree risk ($\tilde{c}_2 \preceq_n \tilde{c}_1$) increases the treatment threshold ($p_{c_2}^A > p_{c_1}^A$) if n is even, and decreases the treatment threshold ($p_{c_2}^A < p_{c_1}^A$) if n is odd.

In order to explain this result, let us define $f(H_2, \tilde{c}_i) = v(H_2) - E[v(H_2 - \tilde{c}_i)]$ the loss of welfare due to the presence of a side effect \tilde{c}_i in case of no disease when the health level in case of no disease is H_2 . As it is intuitive, the DM will treat less often in the presence of riskier side effects ($p_{c_2}^A < p_{c_1}^A$) whenever the loss of welfare is higher in case of riskier side effect, i.e. whenever $f(H_2, \tilde{c}_2) > f(H_2, \tilde{c}_1)$.

Hence according to Proposition 2, a riskier side effect ($\tilde{c}_2 \preceq_n \tilde{c}_1$) will lead to a higher loss of welfare from preventive treatment ($f(H_2, \tilde{c}_2) > f(H_2, \tilde{c}_1)$) if n is odd, but to a lower loss of welfare from preventive treatment ($f(H_2, \tilde{c}_2) < f(H_2, \tilde{c}_1)$) if n is even. In other words, when n is even, the passage from \tilde{c}_1 to \tilde{c}_2 is bad news for the DM leading to an increase in the probability threshold; when n is odd, the passage from \tilde{c}_1 to \tilde{c}_2 is good news for the DM, leading to a decrease in the probability threshold. While this result seems rather surprising at first sight, a simple interpretation can be provided in terms of preferences for harms disaggregation.

In the case of a certain side effect, we know from Eq. (1) that the lower the certain side effect c , the lower the probability threshold p^A (since $v'(x) > 0 \forall x$). Then replacing c by $c - k$ with $k > 0$, which corresponds to an Ekern increase in risk of order one is good news for the DM. In the same spirit, replacing c by $c + \tilde{\epsilon}$ (with $E(\tilde{\epsilon}) = 0$) corresponds to an Ekern increase in risk of order 2. The introduction of uncertainty on the side effect is bad news for a risk-averse DM. Indeed, the DM will treat less often in the presence of uncertain side effects ($p_c^A > p^A$) whenever the loss of welfare is higher in case of uncertain side effect, i.e. whenever $f(H_2, \tilde{c}) > f(H_2, c)$. This inequality may be rewritten equivalently as $E[v(H_2 - \tilde{c})] < v(H_2 - c)$ which is true for all risk-averse DM by Jensen inequality. To summarize, the DM prefers to have $(-k)$ attached to c rather than 0 to c , and he prefers to have 0 attached to c rather than $\tilde{\epsilon}$ to c .

Let us now consider the two random variables \tilde{c}_1 and \tilde{c}_2 such that $\tilde{c}_1 = [c - k, c + \tilde{\epsilon}; \frac{1}{2}, \frac{1}{2}]$ and $\tilde{c}_2 = [c, c - k + \tilde{\epsilon}; \frac{1}{2}, \frac{1}{2}]$. The passage from \tilde{c}_1 to \tilde{c}_2 is an Ekern increase in risk of order

3. According to Proposition 2, as $\tilde{c}_2 \preceq_3 \tilde{c}_1$, for a prudent DM ($v'''(x) > 0 \forall x$), $p_{c_2}^A < p_{c_1}^A$ which is equivalent to $f(H_2, \tilde{c}_2) > f(H_2, \tilde{c}_1)$. In other words, the passage from \tilde{c}_1 to \tilde{c}_2 is good news for the DM. The explanation is that a prudent DM prefers to see attached $\tilde{\epsilon}$ which is bad news for him to the good state of nature c rather than to the bad state of nature $(c - k)$. He prefers to disaggregate the two adverse outcomes. That is why he prefers being confronted with the side effect captured by \tilde{c}_2 than the one captured by \tilde{c}_1 , explaining that $f(H_2, \tilde{c}_2) < f(H_2, \tilde{c}_1)$, and therefore $p_{c_2}^A < p_{c_1}^A$.

Finally, let us consider the two random variables \tilde{c}_1 and \tilde{c}_2 such that $\tilde{c}_1 = [c + \tilde{\theta}, c + \tilde{\epsilon}; \frac{1}{2}, \frac{1}{2}]$ and $\tilde{c}_2 = [c, c + \tilde{\theta} + \tilde{\epsilon}; \frac{1}{2}, \frac{1}{2}]$. The passage from \tilde{c}_1 to \tilde{c}_2 is an Ekern increase in risk of order 4. According to Proposition 2, as $\tilde{c}_2 \preceq_4 \tilde{c}_1$, for a temperant DM ($v''''(x) < 0 \forall x$), $p_{c_2}^A > p_{c_1}^A$ which is equivalent to $f(H_2, \tilde{c}_2) < f(H_2, \tilde{c}_1)$, i.e. the passage from \tilde{c}_1 to \tilde{c}_2 is bad news for the DM. The explanation is that a temperant DM prefers to see attached $\tilde{\epsilon}$ which is bad news for him to the good state of nature c rather than to the bad state of nature $(c + \tilde{\theta})$. He prefers to disaggregate the two adverse outcomes.

To sum-up, a more adverse side effect is not equivalent for the individual to the statistical definition of the notion of more risk. Proposition 2 shows that a more adverse side effect is equivalent to an Ekern increase in risk for even orders and to an Ekern decrease in risk for odd orders. Proposition 2 could then be restated as: for all DMs with a utility function v such that $(-1)^{(1+n)}v^{(n)} > 0$, a more adverse side effect (as defined previously) of preventive treatment always increases the treatment threshold ($p_{c_2}^A > p_{c_1}^A$).

Let us illustrate Proposition 2 in light of the clinical example presented earlier. A physician examines a person who is at risk of developing tuberculosis but who has no signs or symptoms of clinically or radiologically active tuberculosis. The physician has the possibility to prescribe preventive chemotherapy that reduces the development of the disease should it occur in the future. However, chemotherapy can incur side effects in the form of nausea, hair loss and hearing impairment or even anemia or thrombocytopenia. Following Sox et al. (2007) and Felder and Mayrhofer (2014), consider that the utility function of the DM is $v(x) = \frac{x^{0.6}}{6.212}$ verifying that $(-1)^{(1+n)}v^{(n)}(x) > 0 \forall x$. Let assume that the health level in good health is $H_2 = 21$ and that the health level if the disease occurs without treatment is $H_0 = 2$. The benefit of the treatment on health is assumed to be $b = 11$ and the side effects to be $c = 3$. The probability threshold in the benchmark case is $p_A = 16,8969\%$. Hence, if the physician consider that the a priori probability of the patient to develop tuberculosis in the future is at least 16,8969%, then preventive chemotherapy is the optimal strategy.

Consider now that the DM is uncertain about the potential side effect, where uncertainty on side effect is captured by $\tilde{c} = [1, 5; \frac{1}{2}, \frac{1}{2}]$, with $E(\tilde{c}) = c = 3$. In this case, the probability threshold is $p_c^A = 17,1118\%$. Hence, as claimed by Proposition 2, introducing uncertainty on side effect makes preventive chemotherapy an optimal strategy for a higher probability of developing tuberculosis.

Consider now two uncertain side effects \tilde{c}_1 and \tilde{c}_2 such that \tilde{c}_2 is riskier than \tilde{c}_1 in the sense of Ekern increase in risk at order 3 ($\tilde{c}_2 \preceq_3 \tilde{c}_1$) with $\tilde{c}_1 = [2, 4; \frac{3}{4}, \frac{1}{4}]$ and $\tilde{c}_2 = [1, 3; \frac{1}{4}, \frac{3}{4}]$. We obtain $p_{c_2}^A = 14,463\% < 14,466\% = p_{c_1}^A$ as claimed by Proposition 2 with n odd.

If we consider now two uncertain side effects \tilde{c}_1 and \tilde{c}_2 such that $\tilde{c}_2 \preceq_4 \tilde{c}_1$ with $\tilde{c}_1 = [2, 4; \frac{1}{2}, \frac{1}{2}]$ and $\tilde{c}_2 = [1, 3, 5; \frac{1}{8}, \frac{6}{8}, \frac{1}{8}]$, we obtain $p_{c_2}^A = 16,9508\% > 16,9506\% = p_{c_1}^A$, as claimed by Proposition 2 since $n = 4$ is even.

It should be noted that Proposition 2 cannot be generalized to the case where \tilde{c}_2 and

\tilde{c}_1 are related by a relation of stochastic dominance. Indeed, the successive derivatives of the function g (see Appendix 1) do not have signs that alternate (but that are always negative) as is required by the generalization to stochastic dominance.

6 Uncertainty on the severity of the potential disease

Another well referenced source of uncertainty regarding health care is uncertainty surrounding the severity of the potential disease (Arrow, 1963). A frequent reason for this uncertainty comes from the presence of comorbidity risk. If the severity of the potential disease is not known with certainty, then H_0 becomes random. We investigate how a riskier severity of the potential disease modifies the treatment threshold.

Let us consider two risks of severity of the potential disease, \tilde{H}_{01} and \tilde{H}_{02} such that \tilde{H}_{02} is riskier than \tilde{H}_{01} . Consider two situations, under which the DM faces either \tilde{H}_{01} or \tilde{H}_{02} as a severity risk, and define the treatment threshold for each situation. In the situation with \tilde{H}_{0i} as a risk on the severity ($i = 1, 2$), the DM faces the two following lotteries in case he undergoes preventive treatment or not:

$$\tilde{H}_{H_{0i}}^T = [H_2 - c, \tilde{H}_{0i} + b; 1 - p, p],$$

$$\tilde{H}_{H_{0i}}^{NT} = [H_2, \tilde{H}_{0i}; 1 - p, p],$$

We denote by $p_{H_{0i}}^A$ the threshold associated to \tilde{H}_{0i} and given by:

$$p_{H_{0i}}^A = \frac{v(H_2) - v(H_2 - c)}{(v(H_2) - v(H_2 - c)) + (E[v(\tilde{H}_{0i} + b)] - E[v(\tilde{H}_{0i})])} \quad (4)$$

We obtain the following proposition (see proof in Appendix 2):

Proposition 3

A riskier severity of the potential disease in the sense of n th-degree stochastic dominance ($\tilde{H}_{02} \preceq_{SD-n} \tilde{H}_{01}$) decreases the treatment threshold ($p_{H_{02}}^A < p_{H_{01}}^A$) for all DMs with a utility function v such that $(-1)^{(s)}v^{(s+1)} > 0 \forall s = 1, 2, \dots, n$.

A riskier severity of the potential disease in the sense of an Ekern increase in n th-degree risk ($\tilde{H}_{02} \preceq_n \tilde{H}_{01}$) decreases the treatment threshold ($p_{H_{02}}^A < p_{H_{01}}^A$) for all DMs with a utility function v such that $(-1)^{(n)}v^{(n+1)} > 0$.

Contrary to the case where a riskier effectiveness of the treatment increases the treatment threshold of a mixed risk-averse DM, a riskier severity of the potential disease decreases the treatment threshold of a mixed risk-averse DM. The explanation of Proposition 3 is that for a mixed risk-averse individual, the riskier the severity of the potential disease, the higher the gain of welfare from preventive treatment in case of disease ($h(\tilde{H}_{02}, b) > h(\tilde{H}_{01}, b)$) and thus the more often the DM will decide to undergo preventive treatment.

In the case of $n = 1$, a first-order increase in risk corresponds to a lower severity of the potential disease. Then according to Proposition 3, the higher the severity of the

potential disease, the lower the treatment threshold and the more often a risk-averse DM will treat. In the case of $n = 2$, Proposition 3 means that the introduction of uncertainty on the severity of the potential disease decreases the treatment threshold for all prudent DMs compared to the case where the effectiveness of the treatment is certain.

Hence, if the basic level of health of the population tends to be riskier overtime, e.g. as environmental conditions deteriorate, there will be a tendency for preventive care to increase overtime.

7 A more general context

Finally, instead of considering preventive treatment exogenous to the change of risk, a more general context is to consider preventive treatment that reduces uncertainty of the potential disease. It then makes it possible to consider changes in risk on the health level in case of disease \tilde{H}_0 , and changes in risk on the effectiveness of preventive care \tilde{b} together.

We assume now that the health level in case of disease without treatment is written as \tilde{H}_0 , and with treatment as \tilde{H}_1 (with $\tilde{H}_0 \preceq_{SD-n} \tilde{H}_1$ or $\tilde{H}_0 \preceq_n \tilde{H}_1$). This means that the treatment is efficient in the sense that the health level is improved, i.e. $E[v(\tilde{H}_1)] > E[v(\tilde{H}_0)]$ for all utility function v such that $(-1)^{s+1}f^{(s)} > 0 \forall s = 1, 2, \dots, n$ when $\tilde{H}_0 \preceq_{SD-n} \tilde{H}$ and such that $(-1)^{n+1}f^{(n)} > 0$ when $\tilde{H}_0 \preceq_n \tilde{H}_1$. In other words, preventive treatment allows decreasing the risk on the health level in case of disease. By analogy with previous sections where $H + b < H_2 - c$, we assume that \tilde{H}_1 is such that $E[v(\tilde{H}_1)] < H_2 - c$. Note that the benchmark model is a particular case of this one where $\tilde{H}_0 = H_0$ and where $\tilde{H}_1 = H_0 + b$.

The treatment threshold is given by:

$$p^{*A} = \frac{v(H_2) - v(H_2 - c)}{(v(H_2) - v(H_2 - c)) + (E[v(\tilde{H}_1)] - E[v(\tilde{H}_0)])} \quad (5)$$

In order to make the risky environment more general, we consider the possibility of a comorbidity risk, $\tilde{\epsilon}_i$ with $i = 1, 2$. Indeed, it often happens that patients are confronted with comorbid conditions (Harris and Nease (1997), Coeberg et al. (1999)) and $\tilde{\epsilon}_i$ is a random element that reflects the potential comorbid conditions associated to the disease if it occurs (see Eeckhoudt, 2002). The comorbidity risk $\tilde{\epsilon}_i$ is an exogenous risk with no link with the first disease. In other words, the initial disease and its treatment do not affect the random element $\tilde{\epsilon}_i$, meaning that random variables $\tilde{\epsilon}_i$, \tilde{H}_0 and \tilde{H}_1 are mutually independent⁷. Let us consider the two comorbidity risks $\tilde{\epsilon}_1$ and $\tilde{\epsilon}_2$ with $\tilde{\epsilon}_2$ being riskier than $\tilde{\epsilon}_1$ ($\tilde{\epsilon}_2 \preceq_{SD-m} \tilde{\epsilon}_1$ or $\tilde{\epsilon}_2 \preceq_m \tilde{\epsilon}_1$). The DM faces then the two following lotteries in case he undergoes a treatment or not ($i = 1, 2$):

$$\begin{aligned} \tilde{H}_{*\epsilon_i}^T &= [H_2 - c, \tilde{H}_1 + \tilde{\epsilon}_i; 1 - p, p], \\ \tilde{H}_{*\epsilon_i}^{NT} &= [H_2, \tilde{H}_0 + \tilde{\epsilon}_i; 1 - p, p]. \end{aligned}$$

⁷With a more general terminology, $\tilde{\epsilon}_i$ is a state-contingent background risk. See for example Fei and Schlesinger (2008) and Courbage and Rey (2012) for recent studies with state-contingent background risks.

The probability threshold becomes ($i = 1, 2$):

$$p_{\epsilon_i}^{*A} = \frac{v(H_2) - v(H_2 - c)}{(v(H_2) - v(H_2 - c)) + (E[v(\tilde{H}_1 + \tilde{\epsilon}_i)] - E[v(\tilde{H}_0 + \tilde{\epsilon}_i)])} \quad (6)$$

We then obtain the following proposition (see proof in Appendix 3).

Proposition 4

*When preventive treatment reduces the risk of the potential disease in the sense of n th-degree stochastic dominance (passage from \tilde{H}_0 to \tilde{H}_1 such that $\tilde{H}_0 \preceq_{SD-n} \tilde{H}_1$), a riskier comorbidity risk in the sense of m th-degree stochastic dominance ($\tilde{\epsilon}_2 \preceq_{SD-m} \tilde{\epsilon}_1$) decreases the treatment threshold ($p_{\epsilon_2}^{*A} < p_{\epsilon_1}^{*A}$) for all DMs with a utility function v such that $(-1)^{(1+s_1+s_2)}v^{(s_1+s_2)} > 0 \quad \forall s_1 = 1, 2, \dots, n; \forall s_2 = 1, 2, \dots, m$.*

*When preventive treatment reduces the risk of the potential disease in the sense of an Ekern change in n th-degree risk (passage from \tilde{H}_0 to \tilde{H}_1 such that $\tilde{H}_0 \preceq_n \tilde{H}_1$), a riskier comorbidity risk in the sense of an Ekern increase in m th-degree risk ($\tilde{\epsilon}_2 \preceq_m \tilde{\epsilon}_1$) decreases the treatment threshold ($p_{\epsilon_2}^{*A} < p_{\epsilon_1}^{*A}$) for all DMs with a utility function v such that $(-1)^{(1+n+m)}v^{(n+m)} > 0$.*

The intuition of the result of Proposition 4 is that the benefit of the treatment is higher in the presence of a riskier comorbidity risk for a mixed risk-averse DM⁸. Indeed, let us define the function $w(\tilde{H}_0 + \tilde{\epsilon}, \tilde{H}_1 + \tilde{\epsilon}) = E[v(\tilde{H}_1 + \tilde{\epsilon}_i)] - E[v(\tilde{H}_0 + \tilde{\epsilon}_i)]$ as the welfare gain due to the treatment in the presence of a comorbidity risk $\tilde{\epsilon}_i$, i.e. the welfare gain due to the passage from \tilde{H}_0 to the less riskier disease \tilde{H}_1 . From Eq. (6), the DM will treat more often in the presence of a riskier comorbidity risk ($p_{\epsilon_2}^{*A} < p_{\epsilon_1}^{*A}$) whenever the welfare gain due to treatment is higher in presence of a riskier comorbidity risk, i.e. $w(\tilde{H}_0 + \tilde{\epsilon}_2, \tilde{H}_1 + \tilde{\epsilon}_2) > w(\tilde{H}_0 + \tilde{\epsilon}_1, \tilde{H}_1 + \tilde{\epsilon}_1)$.

Hence, individuals who tend to be exposed to riskier comorbidities are more likely to undergo preventive treatment, all other things being equal.

8 Conclusion

This paper has addressed the concept of treatment threshold in the case of preventive treatment with potential side effects as a tool to help the DM administering preventive treatment. It has considered various configurations of increase in risk that are encountered in the case of preventive treatment, whether it concerns the efficiency of preventive care, side effect, the severity of the potential disease and comorbidity risks. To define changes in risk, we used the concepts of n th-order stochastic dominance and of n th-order increase in risk developed by Ekern (1980).

We showed that under mixed risk-averse preferences, conditions on risk preferences of orders higher than the one of risk aversion, prudence and temperance need to be considered to investigate how the treatment threshold reacts to a changing risky environment. In

⁸Bleichrodt et al. (2003) in a related but different framework looked at the effect of comorbidity on the optimal curative treatment intensity when the effectiveness of the treatment is risky.

particular, we showed that both mixed risk-averse preferences and the configuration of increase in risk considered drive the results. If intuitively, one would think that a riskier environment always increases the decision threshold, this paper has shown that results strongly depend on the risky environment. For instance, a prudent DM will undergo preventive treatment more often when the effectiveness of treatment is riskier, but less often when the side effect is riskier when higher risk is defined by a third order increase in risk. On the other hand, a risk-averse DM will undergo more often preventive treatment when either the effectiveness of treatment or side effect are riskier when higher risk is defined by a second order increase in risk.

While these conditions seem rather complex, they encompass many common assumptions used in health literature, whether it concerns the conditions on the utility function of the DM or the changes in risk. Indeed, many utility functions used in medical decision-making (Bleichrodt et al., 2005) are mixed risk-averse, i.e. having their successive higher derivatives alternate in signs. In addition, the changes in risk we consider in this paper are well documented in the health econometric literature that is paying greater attention to higher order conditional moments of health and health care probability distributions (Manning et al., 2005; Cantoni and Ronchetti, 2006). The results of this paper therefore suggest that neglecting differences between risks when evaluating the decision threshold is likely to lead substantial errors in most cost-benefit applications.

Finally, while these results are obtained in the context of treatment decisions, they could also apply to a large set of other decisions confronted to a riskier environment, whether these are environmental decisions or financial decisions.

Appendix 1

$p_{c_2}^A > (<) p_{c_1}^A \Leftrightarrow E[v(H_2 - \tilde{c}_2)] < (>) E[v(H_2 - \tilde{c}_1)]$. Lets' define the function g as follows: $g(c) = v(H_2 - c) \forall c$ for given H_2 . The previous inequality rewrites as: $E[g(\tilde{c}_2)] < E[g(\tilde{c}_1)]$. For v such that $(-1)^{(n+1)}v^{(n)} > 0 \forall n$, we obtain:

$$g'(c) = -v'(H_2 - c) < 0,$$

$$g''(c) = v''(H_2 - c) < 0,$$

$$g'''(c) = -v'''(H_2 - c) < 0,$$

$$g^{(4)}(c) = v^{(4)}(H_2 - c) < 0,$$

...

$$g^{(n)}(c) = v^{(n)}(H_2 - c) \text{ if } n \text{ is even with } v^{(n)}(H_2 - c) < 0,$$

$$g^{(n)}(c) = -v^{(n)}(H_2 - c) \text{ if } n \text{ is odd with } -v^{(n)}(H_2 - c) < 0.$$

Since $\tilde{c}_2 \preceq_n \tilde{c}_1$, using properties (i) and (ii) of section 3, we obtain $E[g(\tilde{c}_2)] < E[g(\tilde{c}_1)]$ if n is even, and $E[g(\tilde{c}_2)] > E[g(\tilde{c}_1)]$ if n is odd, that is equivalent to $p_{c_2}^A > p_{c_1}^A$ if n is even, and $p_{c_2}^A < p_{c_1}^A$ if n is odd.

Appendix 2

From Eq. (4), $p_{\tilde{H}_{02}}^A < p_{\tilde{H}_{01}}^A$ iff $h(\tilde{H}_{02}, b) > h(\tilde{H}_{01}, b)$ that rewrites equivalently as $E[g(\tilde{H}_{02})] > E[g(\tilde{H}_{01})]$ where $g(x) = v(x + b) - v(x) \forall x$ for a given b . Using properties (i) and (ii) of section 3, assuming $\tilde{H}_{02} \preceq_n \tilde{H}_{01}$, and g such that $(-1)^{(n+1)}g^{(n)} < 0$, the inequality is verified. g such that $(-1)^{(n+1)}g^{(n)} < 0$ is equivalent to v such that $(-1)^{(n)}v^{(n+1)} > 0$ that provides the result stated in Proposition 3. Considering the case where $\tilde{H}_{02} \preceq_{SD-n} \tilde{H}_{01}$ requires g such that $(-1)^{(s+1)}g^{(s)} < 0 \forall s = 1, 2, \dots, n$.

Appendix 3

$$p_{\epsilon_2}^{*A} < p_{\epsilon_1}^{*A} \Leftrightarrow E[v(\tilde{H}_0 + \tilde{\epsilon}_1)] + E[v(\tilde{H}_1 + \tilde{\epsilon}_2)] > E[v(\tilde{H}_0 + \tilde{\epsilon}_2)] + E[v(\tilde{H}_1 + \tilde{\epsilon}_1)].$$

If we pose $Y_N = \tilde{H}_0$, $X_N = \tilde{H}_1$, $Y_M = \tilde{\epsilon}_2$, $X_M = \tilde{\epsilon}_1$, the application of Theorem 3 of Eeckhoudt et al. (2009) provides the result.

References

- Arrow K. 1963. Uncertainty and the welfare economics of medical care. *American Economic Review* **53**: 941-973.
- Brockett P., Golden L. 1987. A class of utility functions containing all the common utility functions. *Management Science* **33**: 955-964.
- Bleichrodt H, Crainich D, Eeckhoudt L. 2003. The effect of comorbidities on treatment decision. *Journal of Health Economics* **22**: 805-820.
- Bleichrodt H, Doctor J, Stolk E. 2005. A nonparametric elicitation of the equity-efficiency trade-off in cost-utility analysis. *Journal of Health Economics* **24**: 655-678.
- Caballé J., Pomansky A. 1996. Mixed risk aversion. *Journal of Economic Theory* **71**: 485-513.
- Cantoni E, Ronchetti E. 2006. A robust approach for skewed and heavy-tailed outcomes in the analysis of health care expenditures. *Journal of Health Economics* **25**: 198-213.
- Centers for Disease Control and Prevention (CDC). Possible side-effects from vaccines. <http://www.cdc.gov/vaccines/vac-gen/side-effects.htm> [10 September 2014].
- Coebergh JW, Jansse M, Post P, Razenberg P. 1999. Serious comorbidity among unselected cancer patients newly diagnosed in the southeastern part of the Netherlands in 93-96. *Journal of Clinical Epidemiology* **52**: 1131-1136.
- Courbage C, Rey B. 2012. Optimal prevention and other risks in a two-period model. *Mathematical Social Sciences* **63**: 213-217.
- Ebert S. 2013. Moment characterization of higher-order risk preferences. *Theory and Decision* **74**, 267-284.
- Eeckhoudt L. 2002. *Risk and Medical Decision Making*. Kluwer: Boston.
- Eeckhoudt L, Schlesinger H. 2008. Changes in risk and the demand for saving. *Journal of Monetary Economics* **55**: 1329-1336.
- Eeckhoudt L, Schlesinger H. 2006. Putting risk in its proper place. *American Economic Review* **96**: 280-289.
- Eeckhoudt L, Schlesinger H, Tsetlin I. 2009. Apportioning risks via stochastic dominance. *Journal of Economic Theory* **144**: 994-1003.
- Ehrlich I, Becker G. 1972. Market insurance, self-insurance and self-protection. *Journal of Political Economy* **80**: 623-649.
- Ekern S. 1980. Increasing Nth degree risk. *Economics Letters* **6**: 329-333.
- Fei W, Schlesinger H. 2008. Precautionary insurance demand with state-dependent background risk. *Journal of Risk and Insurance* **75**: 1-16.
- Felder S, Mayrhofer T. 2014. Risk preferences: Consequences for test and treatment thresholds and optimal cutoffs. *Medical Decision Making* **34**: 33-41.
- Friedman M, Savage L. 1948. The utility analysis of choice involving risk. *Journal of Political Economy* **56**: 279-304.
- Hammit J. 2013. Admissible utility functions for health, longevity and wealth: integrating monetary and life-year measures. *Journal of Risk and Uncertainty* **47**: 311-325.
- Harris R, Nease R. 1997. The importance of patient preferences for comorbidities in cost effectiveness analyses. *Journal of Health Economics* **16**: 113-120.
- Ingersoll J. 1987. *Theory of Financial Decision Making*. Rowman & Littlefield: New Jersey.

- Jouini E, Napp C, Nocetti D. 2013. Economic consequences of Nth-degree risk increases and Nth-degree risk attitudes. *Journal of Risk and Uncertainty* **47**: 199-224.
- Juckett G. (1999). Malaria prevention in travelers. *American Family Physician* **59**: 2523-2530.
- Kenkel D. 2000. Prevention. In: Culyer A.J., Newhouse J.P. (eds), *Handbook of Health Economics*, vol. 1B, chap. 31. North Holland: Amsterdam.
- Kimball M. 1992. Precautionary motives for holding assets. In: Newman, P. Milgate, M., Falwell, J. (Eds.), *The New Palgrave Dictionary and Finance*. Palgrave Macmillan: London.
- Kimball M. 1990. Precautionary saving in the small and in the large. *Econometrica* **58**: 53-73.
- Manning W, Basu A, Mullahy J. 2005. Generalized modeling approaches to risk adjustment of skewed outcome data. *Journal of Health Economics* **24**: 465-488.
- Menezes C, Geiss C, Tressler J. 1980. Increasing downside risk. *American Economic Review* **70**: 921-932.
- Menezes C, Wang XH. 2005. Increasing outer risk. *Journal of Mathematical Economics* **41**, 875-886.
- Pauker S, Kassirer J. 1975. Therapeutic decision making: A cost benefit analysis. *New England Journal of Medicine* **293**: 229-234.
- Rothschild M, Stiglitz J. 1970. Increasing risk: I. A definition. *Journal of Economic Theory* **2**: 225-243.
- Sox HS, Blatt MA, Higgins MC, Marton, K.I. 2007. *Medical Decision Making*. American College of Physicians: Philadelphia.
- Waters EA, Weinstein ND, Colditz GA, Emmons K. 2009. Explanation for side effect aversion in preventive medical treatment. *Health Psychology* **28**: 201-209.