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The effect of comorbidities on treatment decisions

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Abstract

Medical decision analyses typically focus on one disease, that is, on one source of risk. In many medical decisions multiple sources of risk co-exist, however. This paper analyzes the effect of such comorbidities on treatment decisions. The effect of comorbidities on treatment decisions depends primarily on the way in which the patient's attitude to health status risks varies with duration. In the QALY model comorbidities do not affect treatment decisions. This property of the QALY model can be used as a diagnostic test of its descriptive and prescriptive validity.

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1. Introduction

Medical decision analyses and economic evaluations of health care typically focus on one disease, that is, they assume that there is only one source of risk. Many medical decisions are taken, however, in the presence of other, often uncontrollable, health risks. A few papers have hinted at the importance of incorporating such comorbidities into medical decision making (Fryback and Lawrence, 1997; Harris and Nease, 1997), but to date the impact of comorbidities on medical decisions has been unexplored and in economic evaluations of health care they are, often implicitly, assumed to have no effect on treatment recommendations.

Research in savings and insurance theory shows that the existence of multiple sources of risk can have substantial effects on optimal decisions (Kimball, 1990; Eeckhoudt and Kimball, 1992; Eeckhoudt et al., 1996) and, therefore, an economic analysis of the impact

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of comorbidities on medical decisions seems warranted. The purpose of this paper is to perform such an analysis.

We analyze the behavior of a patient who has to make an optimal treatment decision in the face of a comorbidity. For analytical convenience and to clarify the main concepts involved, we assume that treatment only affects quality of life whereas the comorbidity only affects life duration. An example is hip replacement for a patient who also suffers from coronary artery disease (CAD). If successful, hip replacement improves quality of life, without affecting its length, while the comorbidity CAD may affect life duration.

In what follows, [Section 2](#) describes the model and the main assumptions made throughout the paper. In [Section 3](#), we analyze the patient's optimal treatment decision when the effect of the comorbidity is known and held constant. This case corresponds to the usual practice in economic evaluation where comorbidities are assumed to have no effect on treatment recommendations. We show that in this case a risk-averse patient will be less treatment-prone than a risk-neutral patient. This is according to intuition: treatment is risky and because a risk-averse patient dislikes risk more than a risk-neutral patient, we expect the former to take less treatment.

In [Section 4](#), we analyze the case in which the effect of the comorbidity is still known but is no longer constant, that is, we analyze the effect of changes in life duration on optimal treatment selection. We derive that the effect of (known) changes in the comorbidity depends on how the patient's aversion to health status risks changes with duration. Empirical evidence on this relationship does not exist, but we argue that it is intuitively plausible that a patient's aversion to health status risks increases with duration. Then, optimal treatment intensity will fall with changes in the comorbidity that increase duration.

The most widely used utility function over health status and duration in economic evaluations of health care is the QALY model. In [Section 5](#), we show that under the QALY model changes in the comorbidity do not affect treatment selection. This holds both for the QALY model with linear utility of duration, that is, neutrality with respect to duration risk, and for the more general QALY model in which the utility function over duration can be curved to reflect risk aversion with respect to duration or time preference.

In [Sections 6–8](#), we analyze the case where the comorbidity is risky. Intuition may suggest that, by comparison with the situation where the comorbidity is known, a risk-averse patient will accept less treatment risk to compensate for the risk in the comorbidity. We show that this intuition is not generally true. Once again, we find that the way the patient's aversion to health status risks varies with duration plays a crucial role.

Under the QALY model, the introduction of background duration risk does not affect the optimal treatment decision. This is a strong result that can be used to test the descriptive and the prescriptive validity of the QALY model.

[Section 9](#) concludes. Formal derivations of the results presented throughout the paper are given in the appendices.

2. The basic model

We consider a patient who has a particular disease and whose health state is equal to H_A . There exists a treatment for his disease, but its effects are risky. Treatment affects

only the patient's health status, not his life duration. Treatment can either be beneficial, in which case it improves the patient's health by b units per unit dose of treatment, or it can be harmful, in which case it deteriorates the patient's health by c units per unit dose of treatment. The probability that the treatment is beneficial is equal to P . This probability is given and is beyond the patient's control. Let n denote treatment intensity. We assume that n is continuous and nonnegative.¹

Assume that health has been quantified, for example, by a health utility index. Without loss of generality, let health be scaled so that $H_A = 0$. If treatment with intensity n is applied, the patient's final health will be nb if treatment is beneficial and $-nc$ if treatment is harmful.

The patient's decision problem is to select the optimal treatment intensity in the face of risk concerning the effects of treatment. We assume that the patient maximizes expected utility. The patient's utility is a function both of health status H and of duration T , $U = U(H, T)$. The utility function U is at least four times differentiable. First derivatives with respect to health status and duration are denoted by U_1 and U_2 , respectively, second derivatives by U_{11} and U_{22} , respectively and cross-product derivatives by U_{12} , etc. The utility function is increasing in both its arguments, that is, $U_1 > 0$ and $U_2 > 0$. Unless otherwise stated, we assume that the patient is risk averse both with respect to health status ($U_{11} < 0$) and with respect to duration ($U_{22} < 0$).

We assume that the marginal utility of duration increases with health status, that is, $U_{12} > 0$. Empirical support for this assumption can be derived from the studies of McNeil et al. (1981) and Sutherland et al. (1982). McNeil et al. (1981) found that for small durations people are unwilling to give up life-years for improvements in health status. For longer durations, people are willing to trade-off life-years against improvements in health status. Such preferences are displayed in Fig. 1A. Up to duration T_1 people are not willing to trade-off duration for a change from health state B to health state A . For durations that exceed T_1 , they are willing to trade-off duration for an improvement in health status from B to A .

Sutherland et al. (1982) observed that there is a so-called 'maximal endurable time' for health states of low quality. Beyond this maximal endurable time additional increases in duration are valued negatively. The findings from Sutherland et al. are illustrated in Fig. 1B. For health state B there is a maximal endurable time, which is equal to T_2 . Beyond T_2 additional life-years in B are valued negatively.

Fig. 1 shows that both the findings from McNeil et al. (1981) and those from Sutherland et al. (1982) imply that the slope of the utility function for duration under the bad health state B never exceeds that obtained under the good health state A , that is, $U_{12} \geq 0$.

3. Treatment decisions when the comorbidity is riskless

When the effects of the comorbidity are known, the patient's decision problem is

$$\max_n EU = PU(nb, T) + (1 - P)U(-nc, T) \quad (1)$$

¹ The assumption of continuous treatment intensity seems plausible in many medical decision contexts, for example, decisions about the administration of drugs. Our conclusions are not affected when the assumption does not hold. Then, we can no longer take derivatives with respect to n , but we can approximate partial derivatives with respect to n by considering discrete increments.

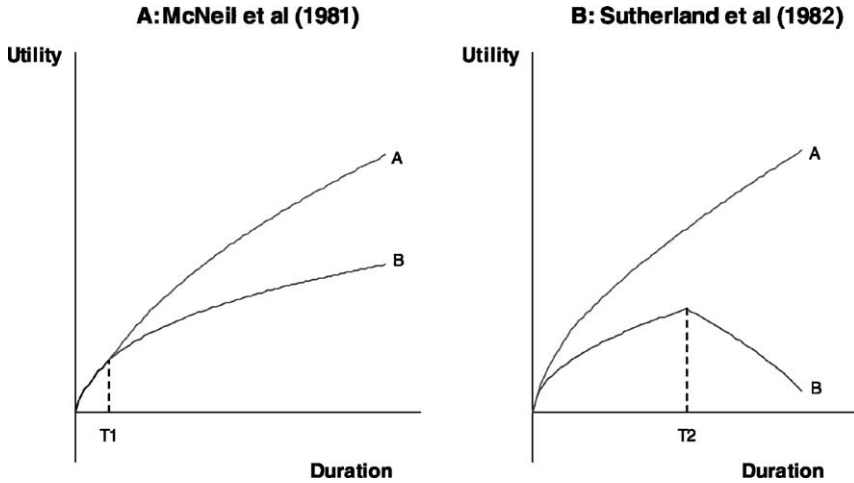


Fig. 1. Empirical findings.

The first-order condition is

$$\frac{\partial EU}{\partial n} = PbU_1(nb, T) - c(1 - P)U_1(-nc, T) = 0 \tag{2}$$

Let us start with the simple case in which the patient is risk neutral with respect to health status. In that case, his utility function is equal to $U(H, T) = W(T) \times H$, where $W(T)$ is a (positive) utility function over duration, and the first-order condition becomes

$$W(T)(Pb - c(1 - P)) = 0 \tag{3}$$

It follows from Eq. (3) that the *treatment threshold*, that is, the minimum probability P for which treatment intensity is strictly positive, is equal to $c/(b + c)$. If $P < c/(b + c)$, the first-order condition is negative and the patient will not take treatment. If $P > c/(b + c)$, the first-order condition is positive and the patient will take as much treatment as possible, that is, he will take treatment with maximal intensity. Fig. 2 illustrates the above argument.

Let us suppose that now the patient is risk averse. Then, $U_{11} < 0$ and it follows that $U_1(nb, T) < U_1(-nc, T)$. Consequently, $PbU_1(nb, T) - c(1 - P)U_1(-nc, T)$ is negative if $P = c/(b + c)$ and the patient takes no treatment at this value of P . A necessary condition for a risk-averse patient to take treatment is $P > c/(b + c)$, and thus the treatment threshold of the risk-averse patient exceeds $c/(b + c)$. Throughout the paper, we assume that $P > c/(b + c)$. Concavity of U then ensures that Eq. (1) has an interior solution.

Let α be the treatment threshold for a risk-averse patient. Contrary to a risk-neutral patient, a risk-averse patient will not jump from no treatment to treatment with maximal intensity if P exceeds α . For sufficiently small differences between P and α the patient will take less than maximal treatment. Formally, this follows because we obtain from (2) that

$$\frac{\partial n}{\partial P} = \frac{-bU_1(nb, T) - cU_1(-nc, T)}{Pb^2U_{11}(nb, T) + c^2(1 - P)U_{11}(-nc, T)} \tag{4}$$

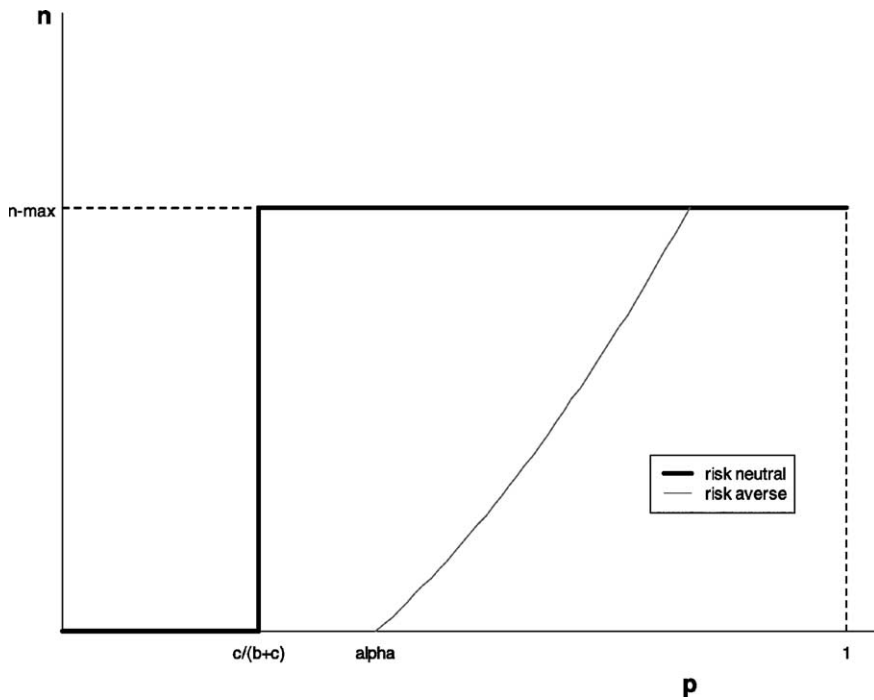


Fig. 2. Optimal treatment intensity and risk attitude.

which is positive and, because of the assumptions of our model, is not infinite. Hence, $\partial n/\partial P$ makes no sudden jump but increases in a continuous way until the maximum treatment intensity is reached. Intuitively, this gradual increase in treatment intensity follows because increases in n make treatment more risky. Because a risk-averse patient dislikes risk, he will not move immediately to the maximum treatment intensity if P is sufficiently close to α . Fig. 2 displays the above argument.

Summarizing, we observe that for each value of P , a risk-neutral patient will take at least as much treatment as a risk-averse patient. In other words, the introduction of risk aversion in the model makes the patient less treatment prone.

4. Changes in the comorbidity that are known with certainty

Let us now examine what happens to the patient’s optimal treatment selection when there is a change in the effect of the comorbidity. As before, we assume that the effect of the comorbidity is known. Recall that the comorbidity only affects duration. The impact of a change in duration on the optimal amount of treatment is given by (5), which is obtained by totally differentiating (2) and rearranging.

$$\frac{dn}{dT} = -\frac{1}{S}(PbU_{12}(nb, T) - c(1 - P)U_{12}(-nc, T)) \tag{5}$$

where $S \equiv \partial^2 EU / \partial n^2 = Pb^2 U_{11}(nb, T) - c^2(1 - P)U_{11}(-nc, T)$, which is negative by the assumption that the patient is risk averse with respect to health status ($U_{11} < 0$). The sign of (5) is, therefore, determined by the sign of $PbU_{12}(nb, T) - c(1 - P)U_{12}(-nc, T)$, which is not known a priori. However, we will next show that it is possible to relate dn/dT to the way the patient’s aversion to health status risks varies with duration.

From Eq. (2) we know that

$$\frac{c(1 - P)}{Pb} = \frac{U_1(nb, T)}{U_1(-nc, T)} \tag{6}$$

If we substitute (6) into (5) we obtain

$$\frac{dn}{dT} \begin{matrix} \leq \\ \geq \end{matrix} 0 \Leftrightarrow \frac{U_{12}(nb, T)}{U_1(nb, T)} - \frac{U_{12}(-nc, T)}{U_1(-nc, T)} \begin{matrix} \leq \\ \geq \end{matrix} 0 \tag{7}$$

The sign of $(U_{12}(nb, T))/(U_1(nb, T)) - (U_{12}(-nc, T))/(U_1(-nc, T))$ is determined by the way the ratio U_{12}/U_1 varies with health status. Now

$$\frac{\partial(U_{12}/U_1)}{\partial H} = \frac{U_{121}U_1 - U_{11}U_{12}}{U_1^2} \tag{8}$$

The responsiveness of the ratio U_{12}/U_1 to changes in health status is not intuitively clear and it is hard to conceive of empirical tests to examine this responsiveness. However, by using Young’s theorem ($U_{121} = U_{112}$) we can write

$$\frac{U_{121}U_1 - U_{11}U_{12}}{U_1^2} = \frac{U_{112}U_1 - U_{11}U_{12}}{U_1^2} = -\frac{\partial(-U_{11}/U_1)}{\partial T} \tag{9}$$

The term $\partial(-U_{11}/U_1)/\partial T$ indicates how the patient’s aversion to health status risks varies with duration. Combining (7) and (9), we obtain that improvements in the comorbidity, that is, increases in duration, will lead to an increase (decrease) in optimal treatment intensity if the patient’s aversion to health status risks decreases (increases) with duration.

To our knowledge, no tests of how changes in duration affect a patient’s aversion to health status risks have been performed as yet. A priori, it seems reasonable to expect that a patient becomes more averse to health status risks when duration increases. The longer duration, the longer bad outcomes of treatment last, and hence, the larger the differences between the outcomes of treatment. Risk-averse people prefer gambles in which the spread of the outcomes, that is, the variance, is low to gambles with higher variance. Such preferences are consistent with an aversion to health status risks that increases with duration. The above analysis tells us that if people indeed become more averse to health status risks if duration increases, then improvements in the comorbidity will decrease optimal treatment intensity.

5. Changes in the comorbidity in the QALY model

An important model in medical decision making is the QALY model $U(H, T) = V(H)W(T)$, where V is a utility function over health status, and W a utility function over duration (Pliskin et al., 1980; Miyamoto and Eraker, 1988). A special case of this model is the linear

QALY model, in which $W(T)$ is linear. We analyze what the effects of known changes in the comorbidity are on optimal treatment selection in the QALY model.

If $U(H, T) = V(H)W(T)$, then $U_1 = V'(H)W(T)$, $U_{11} = V''(H)W(T)$, $U_{12} = V'(H)W'(T)$, and $U_{112} = V''(H)W'(T)$. Hence

$$\frac{\partial(-U_{11}/U_1)}{\partial T} = \frac{V''(H)W'(T)V'(H)W(T) - V''(H)W(T)V'(H)W'(T)}{(V'(H)W(T))^2} = 0 \quad (10)$$

and we conclude that $dn/dT = 0$, that is, changes in duration do not affect the patient's treatment decision in the QALY model.

6. Treatment decisions when the comorbidity is risky

Let us suppose now that the effects of the comorbidity are risky. Contrary to the health status risk, which the patient can control through his choice of treatment intensity, we assume that the comorbidity risk is beyond the patient's control. For ease of illustration but without loss of generality, let there be two possible outcomes of the comorbidity, T_1 and T_2 with $T_1 > T_2$. Let π denote the probability that the patient lives T_1 years. The patient's optimization problem then becomes

$$\begin{aligned} \max_n EU &= P(\pi U(nb, T_1) + (1 - \pi)U(nb, T_2)) + (1 - P)(\pi U(-nc, T_1) \\ &\quad + (1 - \pi)U(-nc, T_2)) \end{aligned} \quad (11)$$

The first-order condition is

$$\begin{aligned} \frac{\partial EU}{\partial n} &= Pb(\pi U_1(nb, T_1) + (1 - \pi)U_1(nb, T_2)) - (1 - P)c(\pi U_1(-nc, T_1) \\ &\quad + (1 - \pi)U_1(-nc, T_2)) = 0 \end{aligned} \quad (12)$$

and the second-order condition is

$$\begin{aligned} \frac{\partial^2 EU}{\partial n^2} &\equiv D = Pb^2(\pi U_{11}(nb, T_1) + (1 - \pi)U_{11}(nb, T_2)) \\ &\quad + (1 - P)c^2(\pi U_{11}(-nc, T_1) + (1 - \pi)U_{11}(-nc, T_2)) \end{aligned} \quad (13)$$

which is negative because the patient is risk averse with respect to health status ($U_{11} < 0$).

What is the effect of a risky comorbidity on the optimal treatment decision by comparison with the case of Section 3 where the effects of the comorbidity are known? Intuition may suggest that a risk-averse patient will react to the increase in risk of the comorbidity by taking less treatment risk, that is, by reducing the treatment intensity. We will show that this intuition is not generally true.

To analyze the effect of the risky comorbidity, we first simplify the two expressions in brackets in (12), which are both an expected marginal utility of health status. This simplification can be obtained through the concept of the prudence premium (Kimball, 1990), which is a concept similar to the risk premium, except that it is defined in terms of marginal utilities rather than in terms of total utilities.

Let life-expectancy be denoted by $LE = \pi T_1 + (1 - \pi)T_2$. For any health state H , let $\rho_{LE}(H)$ be the number of life-years such that $U_1(H, LE - \rho_{LE}(H)) = \pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2)$. We can then rewrite (12) as

$$PbU_1(nb, LE - \rho_{LE}(nb)) - c(1 - P)U_1(-nc, LE - \rho_{LE}(-nc)) = 0 \tag{14}$$

The parameter ρ_{LE} is a prudence premium. It indicates by how much life-expectancy has to be reduced in order to maintain the expected marginal utility of H constant. We give a formal analysis of ρ_{LE} in [Appendix A](#).

Let n^* denote optimal treatment intensity when the comorbidity is known and n^{**} optimal treatment intensity when the comorbidity is risky. The effect of the introduction of a risky comorbidity on the optimal treatment decision depends on the sign of

$$PbU_1(n^*b, LE - \rho_{LE}(n^*b)) - c(1 - P)U_1(-n^*c, LE - \rho_{LE}(-n^*c)) \tag{15}$$

If (15) is positive then the marginal benefits of treatment, measured by $PbU_1(n^*b, LE - \rho_{LE}(n^*b))$, outweigh the marginal costs of treatment, measured by $c(1 - P)U_1(-n^*c, LE - \rho_{LE}(-n^*c))$, and the patient will increase treatment intensity up to n^{**} where the marginal benefits and the marginal costs of treatment are equal. A similar line of argument shows that $n^{**} < n^*$ if (15) is negative.

It remains to determine the sign of (15). If we substitute (6) into (15) we find that

$$n^{**} \leq n^* \Leftrightarrow \frac{U_1(n^*b, LE - \rho_{LE}(n^*b))}{U_1(n^*b, LE)} \leq \frac{U_1(-n^*c, LE - \rho_{LE}(-n^*c))}{U_1(-n^*c, LE)} \tag{16}$$

We distinguish four cases based on properties of ρ_{LE} . The four cases are described in [Table 1](#). Unfortunately, it is hard to judge a priori which case is the most plausible, since, as we show in [Appendix A](#), the behavior of ρ_{LE} depends on the sign of the third and fourth derivatives of the utility function. [Table 1](#) shows, again, the crucial role of the way the individual’s aversion to health status risks (denoted by r in the table) varies with duration. Recall that we argued in [Section 4](#) that it appears plausible that the individual’s aversion to health status risks increases with duration. Formal derivations of the four cases are presented in [Appendix B](#).

7. The effect of a risky comorbidity in the QALY model

[Table 1](#) shows that we cannot make general predictions about the effect of a risky comorbidity on optimal treatment decisions. One way to draw more precise inferences is to impose restrictions on the utility function. Let us assume that the QALY model holds, that is, $U(H, T) = V(H)W(T)$. We will show that under the QALY model, the introduction of a risky comorbidity has no effect on the optimal treatment decision.

In [Appendix A](#), we derive that ρ_{LE} is positively related to $-(U_{122}/U_{12})$, which in the QALY model becomes

$$-\frac{V'(H)W''(T)}{V'(H)W'(T)} = -\frac{W''(T)}{W'(T)} \tag{17}$$

Table 1
Effect of comorbidity risk on optimal treatment decision

$\rho_{LE} = 0$	$\rho_{LE}(n^*b) = \rho_{LE}(-n^*c) = \text{constant} \neq 0$	$\rho_{LE}(n^*b) < \rho_{LE}(-n^*c)$	$\rho_{LE}(n^*b) > \rho_{LE}(-n^*c)$
$n^* = n^{**}$	if $\rho_{LE} > 0$ then $\frac{\partial r}{\partial T} \leq 0 \Rightarrow n^{**} \geq n^*$ if $\rho_{LE} < 0$ then $\frac{\partial r}{\partial T} \leq 0 \Rightarrow n^{**} \leq n^*$	if $\rho_{LE}(n^*b) > 0$ then $\frac{\partial r}{\partial T} \geq 0 \Rightarrow n^{**} > n^*$, else sign-ambiguous if $\rho_{LE}(n^*b) < 0$ then $\frac{\partial r}{\partial T} \leq 0 \Rightarrow n^{**} > n^*$, else sign-ambiguous if $\rho_{LE}(n^*b) = 0$ then $n^{**} > n^*$	if $\rho_{LE}(n^*b) > 0$ then $\frac{\partial r}{\partial T} \leq 0 \Rightarrow n^* > n^{**}$, else sign-ambiguous if $\rho_{LE}(n^*b) < 0$ then $\frac{\partial r}{\partial T} \geq 0 \Rightarrow n^* > n^{**}$, else sign-ambiguous if $\rho_{LE}(n^*b) = 0$ then $n^* > n^{**}$

Note. r denotes the individual's aversion to health status risks.

The latter is equal to the Pratt–Arrow measure of the patient’s aversion to duration risk. Hence, in the specific case of the QALY model we find that the prudence premium is equal to the risk premium and ρ_{LE} can, in the QALY model, be interpreted as the patient’s risk premium for duration risks.

It follows from (17) that the patient’s aversion to duration risk is independent of health status and, hence, that ρ_{LE} does not vary with health status. The parameter ρ_{LE} is zero if the patient is neutral to duration risk, that is, in case the linear QALY model, $U(H, T) = V(H)T$ holds. Table 1 shows that, if ρ_{LE} is zero, then there is no effect of the introduction of a risky comorbidity on treatment selection.

Table 1 also shows that if ρ_{LE} is constant but not zero then the effect of a risky comorbidity on treatment intensity depends on the way the patient’s attitude to health status risks varies with duration. We showed in Section 5 that in the QALY model the patient’s aversion to health status risks is independent of duration, that is, $\partial r/\partial T = 0$. We conclude from Table 1 that in the QALY model there is no effect of the introduction of a risky comorbidity on treatment selection.

8. Changes in the comorbidity risk

Let us finally consider the effect of changes in the comorbidity risk. Table 2 summarizes the effects of changes in one of π , T_1 , and T_2 with the other two constant. The effects of these changes are different. All changes affect life-expectancy. However, a change in π does not affect the spread of the outcomes of the comorbidity, the difference between T_1 and T_2 remains the same, whereas an increase (decrease) in T_1 increases (decreases) the spread of the outcomes of the comorbidity, and an increase (decrease) in T_2 decreases (increases) the spread of the outcomes of the comorbidity. In other words, an increase in T_1 increases the riskiness of the comorbidity, whereas an increase in T_2 reduces the riskiness of the comorbidity.

The table shows, once again, the crucial role of the way the patient’s aversion to health status risks varies with duration ($\partial r/\partial T$). Because we argued before that it seems plausible that the patient’s aversion to health status risks increases with duration we conclude that changes in the comorbidity risk that increase π or T_1 lead to reductions in optimal treatment intensity. For increases in T_2 the effect is sign-ambiguous. Derivations of the entries of Table 2 are given in Appendix C.

We derived before that in the QALY model $\partial r/\partial T = 0$. The table shows that if the QALY model holds changes in the risky comorbidity do not affect treatment intensity.

Table 2
The effect of changes in the comorbidity risk

Change in	Effect
π	$\frac{\partial r}{\partial T} \leq 0 \Leftrightarrow \frac{dn}{d\pi} \geq 0$
T_1	$\frac{\partial r}{\partial T} \leq 0 \Rightarrow \frac{dn}{dT_1} \geq 0$
T_2	$\frac{\partial r}{\partial T} = 0 \Rightarrow \frac{dn}{dT_2} = 0$, else sign-ambiguous

9. Conclusion

The main determinant of the impact of (changes in) comorbidities, whether riskless or risky, is the way in which a patient's aversion to health status risks varies with duration. We have argued that it seems plausible that the patient becomes more averse to health status risks when duration increases. However, no empirical evidence exists to date concerning the impact of duration on the patient's attitude to health status risks. Future research should fill this gap.

If the patient becomes more averse to health status risks when duration increases then improvements (worsenings) in comorbidity risk will generally lead to more (less) treatment-prone behavior. In general, comorbidities have the effect of worsening risk. Hence, our analysis seems to imply that economic evaluations and medical decision analyses that ignore comorbidities will lead to recommendations that are biased in the direction of too much treatment.

In the QALY model comorbidities have no impact on treatment decisions. This finding can be used as a diagnostic test of the validity of the QALY model. If it is observed that patients change their treatment decisions in the face of comorbidity risk then the QALY model should be discarded as a descriptive model of the behavior of these patients. Also, if patients feel that they should change their behavior on the health status dimension (e.g. make less risky choices), if the comorbidity risk changes then the QALY model should not be used as a prescriptive model of treatment selection for these patients.

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Appendix A. Analysis of ρ_{LE}

Let $\tilde{\varepsilon}$ be a random variable with mean zero and strictly positive variance $\sigma_{\tilde{\varepsilon}}^2$. Then, ρ_{LE} is defined by

$$E(U_1(H, LE + \tilde{\varepsilon})) = U_1(H, LE - \rho_{LE}) \quad (\text{A.1})$$

where E denotes the expectations operator. Approximating both the left-hand side and the right-hand side of (A.1) by a Taylor series gives

$$\begin{aligned} E(U_1(nb, LE) + \tilde{\varepsilon}U_{12}(nb, LE) + \frac{\tilde{\varepsilon}^2}{2}U_{122}(nb, LE)) \\ = U_1(nb, LE) - \rho_{LE}U_{12}(nb, LE) \end{aligned} \quad (\text{A.2})$$

Because $E(\tilde{\varepsilon}) = 0$, (A.2) gives after some rearrangement

$$\rho_{LE} = -\frac{U_{122}(nb, LE)}{U_{12}(nb, LE)} \times \frac{\sigma_{\varepsilon}^2}{2} \tag{A.3}$$

Eq. (A.3) shows that the effect of changes in health status on ρ_{LE} is determined by the sign of

$$\frac{U_{1122}U_{12} - U_{112}U_{122}}{(U_{12})^2} \tag{A.4}$$

which requires information on the fourth cross-product derivative of U .

Appendix B. Derivation of the results in Table 1

Case 1. $\rho_{LE} = 0$.

Obvious.

Case 2. $\rho_{LE}(n^*b) = \rho_{LE}(-n^*c) = \text{constant but not zero}$.

Let $z = \rho_{LE}(n^*b) = \rho_{LE}(-n^*c)$. By (16)

$$n^{**} \begin{matrix} \leq \\ > \end{matrix} n^* \Leftrightarrow \frac{\partial(U_1(H, LE - z))/(U_1(H, LE))}{\partial H} \begin{matrix} \leq \\ > \end{matrix} 0 \tag{B.1}$$

Further

$$\begin{aligned} & \frac{\partial(U_1(H, LE - z))/(U_1(H, LE))}{\partial H} \\ &= \frac{U_{11}(H, LE - z)U_1(H, LE) - U_1(H, LE - z)U_{11}(H, LE)}{(U_1(H, LE))^2} \end{aligned} \tag{B.2}$$

The sign of (B.2) depends on the sign of

$$\frac{U_{11}(H, LE - z)}{U_1(H, LE - z)} - \frac{U_{11}(H, LE)}{U_1(H, LE)} \tag{B.3}$$

The sign of (B.3) depends on $\partial(-(U_{11}/U_1))/\partial T$, i.e. on the way the patient’s aversion to health status risks changes with duration. It is easily verified that if $z > 0$ then

$$n^{**} \begin{matrix} \leq \\ > \end{matrix} n^* \Leftrightarrow \frac{\partial(-(U_{11}/U_1))}{\partial T} \begin{matrix} \leq \\ > \end{matrix} 0 \tag{B.4}$$

and that if $z < 0$ then

$$n^{**} \begin{matrix} \leq \\ > \end{matrix} n^* \Leftrightarrow \frac{\partial(-U_{11}/U_1)}{\partial T} \begin{matrix} \geq \\ < \end{matrix} 0 \tag{B.5}$$

Case 3. $\rho_{LE}(n^*b) < \rho_{LE}(-n^*c)$

Suppose that $\rho_{LE}(n^*b) > 0$. By the analysis of Case 2, if the patient’s aversion to health status risks increases or is constant with duration then

$$\frac{U_1(n^*b, LE - \rho_{LE}(n^*b))}{U_1(n^*b, LE)} \geq \frac{U_1(-n^*c, LE - \rho_{LE}(n^*b))}{U_1(-n^*c, LE)} \tag{B.6}$$

Because $\rho_{LE}(n^*b) < \rho_{LE}(-n^*c)$ and $U_{12} > 0$,

$$\frac{U_1(-n^*c, LE - \rho_{LE}(n^*b))}{U_1(-n^*c, LE)} > \frac{U_1(-n^*c, LE - \rho_{LE}(-n^*c))}{U_1(-n^*c, LE)} \tag{B.7}$$

Combining (B.6) and (B.7) gives by (16) that $n^{**} > n^*$.

If the patient’s aversion to health status risks decreases with duration then

$$\frac{U_1(n^*b, LE - \rho_{LE}(n^*b))}{U_1(n^*b, LE)} < \frac{U_1(-n^*c, LE - \rho_{LE}(n^*b))}{U_1(-n^*c, LE)} \tag{B.8}$$

Eqs. (B.7), (B.8) and (16) show that the impact of the introduction of a risky comorbidity on treatment intensity is sign-ambiguous.

Suppose next that $\rho_{LE}(n^*b) < 0$. It follows by the analysis of case 2 that if the patient’s aversion to health status risks decreases or is constant with duration then (B.6) holds. In combination with (B.7) and (16) this yields $n^{**} > n^*$. If the patient’s aversion to health status risks increases with duration then (B.8) holds, which yields in combination with (B.7) and (16) that the impact of the introduction of a risky comorbidity on treatment intensity is sign-ambiguous.

Finally, if $\rho_{LE}(n^*b) = 0$ then

$$\frac{U_1(n^*b, LE - \rho_{LE}(n^*b))}{U_1(n^*b, LE)} = \frac{U_1(-n^*c, LE - \rho_{LE}(n^*b))}{U_1(-n^*c, LE)} \tag{B.9}$$

and it follows from (B.7) and (16) that $n^{**} > n^*$.

Case 4. $\rho_{LE}(n^*b) > \rho_{LE}(-n^*c)$

Analogous to Case 3.

Appendix C. Derivation of the results in Table 2

Case 1. A change in π

Totally differentiating (12) and rearranging gives

$$\frac{dn}{d\pi} = -\frac{1}{D} (Pb(U_1(nb, T_1) - U_1(nb, T_2)) - (1 - P)c(U_1(-nc, T_1) - U_1(-nc, T_2))) \tag{C.1}$$

Because $D < 0$ we have

$$\frac{dn}{d\pi} \underset{\leq}{\geq} 0 \Leftrightarrow Pb(U_1(nb, T_1) - U_1(nb, T_2)) - (1 - P)c(U_1(-nc, T_1) - U_1(-nc, T_2)) \underset{\leq}{\geq} 0 \tag{C.2}$$

From (12) we know that

$$\frac{(1 - P)c}{Pb} = \frac{\pi U_1(nb, T_1) + (1 - \pi)U_1(nb, T_2)}{\pi U_1(-nc, T_1) + (1 - \pi)U_1(-nc, T_2)} \tag{C.3}$$

Substituting (C.3) into (C.2) gives

$$\frac{dn}{d\pi} \underset{\leq}{\geq} 0 \Leftrightarrow \frac{U_1(nb, T_1) - U_1(nb, T_2)}{\pi U_1(nb, T_1) + (1 - \pi)U_1(nb, T_2)} - \frac{U_1(-nc, T_1) - U_1(-nc, T_2)}{\pi U_1(-nc, T_1) + (1 - \pi)U_1(-nc, T_2)} \underset{\leq}{\geq} 0 \tag{C.4}$$

or

$$\frac{dn}{d\pi} \underset{\leq}{\geq} 0 \Leftrightarrow \frac{\partial(U_1(H, T_1) - U_1(H, T_2))/(\pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2))}{\partial H} \underset{\leq}{\geq} 0 \tag{C.5}$$

now

$$\frac{\partial(U_1(H, T_1) - U_1(H, T_2))/\pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2)}{\partial H} = \frac{(U_{11}(H, T_1) - U_{11}(H, T_2))B - (\pi U_{11}(H, T_1) + (1 - \pi)U_{11}(H, T_2))A}{B^2} \tag{C.6}$$

where $A = U_1(H, T_1) - U_1(H, T_2)$ and $B = \pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2)$. Some algebraic manipulation yields that the numerator of the right-hand side of (C.6) is equal to

$$U_1(H, T_2) \times U_{11}(H, T_1) - U_1(H, T_1) \times U_{11}(H, T_2) \tag{C.7}$$

and thus

$$\frac{dn}{d\pi} \underset{\leq}{\geq} 0 \Leftrightarrow \frac{-U_{11}(H, T_1)}{U_1(H, T_1)} \underset{\leq}{\geq} \frac{-U_{11}(H, T_2)}{U_1(H, T_2)} \tag{C.8}$$

Case 2. A change in T_1

Totally differentiating (12) and rearranging gives

$$\frac{dn}{dT_1} = -\frac{1}{D} (Pb\pi U_{12}(nb, T_1) - (1 - P)c\pi U_{12}(-nc, T_1)) \tag{C.9}$$

and thus

$$\frac{dn}{dT_1} \underset{\leq}{\geq} 0 \Leftrightarrow Pb\pi U_{12}(nb, T_1) - (1 - P)c\pi U_{12}(-nc, T_1) \underset{\leq}{\geq} 0 \tag{C.10}$$

A similar line of argument as in Case 1 shows that

$$\frac{dn}{dT_1} \underset{\leq}{\geq} 0 \Leftrightarrow \frac{\partial((U_{12}(H, T_1)))/(\pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2))}{\partial H} \underset{\leq}{\geq} 0 \tag{C.11}$$

and

$$\frac{\partial(U_{12}(H, T_1))/(\pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2))}{\partial H} = \frac{U_{112}(H, T_1)M - U_{12}(H, T_1)N}{M^2} \tag{C.12}$$

where $M = \pi U_1(H, T_1) + (1 - \pi)U_1(H, T_2)$ and $N = \pi U_{11}(H, T_1) + (1 - \pi)U_{11}(H, T_2)$.
 Rewriting (C.12) yields

$$\frac{dn}{dT_1} \begin{matrix} \leq \\ \geq \end{matrix} 0 \Leftrightarrow \pi(U_{112}(H, T_1) \times U_1(H, T_1) - U_{12}(H, T_1) \times U_{11}(H, T_1)) + (1 - \pi)(U_{112}(H, T_1) \times U_1(H, T_2) - U_{12}(H, T_1) \times U_{11}(H, T_2)) \begin{matrix} \leq \\ \geq \end{matrix} 0 \tag{C.13}$$

Suppose that the patient’s aversion to health status risks increases with duration. By (9)

$$U_{112}(H, T_1) \times U_1(H, T_1) - U_{12}(H, T_1) \times U_{11}(H, T_1) < 0 \tag{C.14}$$

or

$$-\frac{U_{112}(H, T_1)}{U_{12}(H, T_1)} > -\frac{U_{11}(H, T_1)}{U_1(H, T_1)} \tag{C.15}$$

Because the patient’s aversion to health status risks increases with duration, we also know that

$$-\frac{U_{11}(H, T_1)}{U_1(H, T_1)} > -\frac{U_{11}(H, T_2)}{U_1(H, T_2)} \tag{C.16}$$

Combining (C.15) and (C.16) gives

$$-\frac{U_{112}(H, T_1)}{U_{12}(H, T_1)} > -\frac{U_{11}(H, T_2)}{U_1(H, T_2)} \tag{C.17}$$

or

$$U_{112}(H, T_1) \times U_1(H, T_2) - U_{12}(H, T_1) \times U_{11}(H, T_2) < 0 \tag{C.18}$$

Substituting (C.14) and (C.18) into (C.13) gives $dn/dT_1 < 0$. By a similar line of argument we can show that if the patient’s aversion to health status risks is constant with duration then $dn/dT_1 = 0$, and if the patient’s aversion to health status risks decreases with duration then $dn/dT_1 > 0$.

Case 3. A change in T_2

The analysis is largely similar to Case 2 and we derive that

$$\frac{dn}{dT_2} \begin{matrix} \leq \\ \geq \end{matrix} 0 \Leftrightarrow \pi(U_{112}(H, T_2) \times U_1(H, T_1) - U_{12}(H, T_2) \times U_{11}(H, T_1)) + (1 - \pi)(U_{112}(H, T_2) \times U_1(H, T_2) - U_{12}(H, T_2) \times U_{11}(H, T_2)) \tag{C.19}$$

Suppose that the patient's aversion to health status risks increases with duration. Then

$$-\frac{U_{112}(H, T_2)}{U_{12}(H, T_2)} > -\frac{U_{11}(H, T_2)}{U_1(H, T_2)} \quad (\text{C.20})$$

Because the patient's aversion to health status risks increases with duration, we also know that

$$-\frac{U_{11}(H, T_1)}{U_1(H, T_1)} > -\frac{U_{11}(H, T_2)}{U_1(H, T_2)} \quad (\text{C.21})$$

Combining (C.20) and (C.21) shows that the sign of $U_{112}(H, T_2) \times U_1(H, T_1) - U_{12}(H, T_2) \times U_{11}(H, T_1)$ is ambiguous. Similarly, if the patient's aversion to health status risks decreases with duration then the sign of $U_{112}(H, T_2) \times U_1(H, T_1) - U_{12}(H, T_2) \times U_{11}(H, T_1)$ is ambiguous. If the patient's aversion to health status risks is constant then both $U_{112}(H, T_2) \times U_1(H, T_1) = U_{12}(H, T_2) \times U_{11}(H, T_1)$ and $U_{112}(H, T_2) \times U_1(H, T_2) = U_{12}(H, T_2) \times U_{11}(H, T_2)$ and $dn/dT_2 = 0$ by (C.19).

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