Cost-Effectiveness Threshold for Healthcare: Justification and Quantification

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Abstract

Every public health expenditure, including the one that saves lives or extends life expectancy of particular persons (target population), bears a cost. Although cost-effectiveness analysis (CEA) is routinely performed in health policy, ethical justification of CEA is rarely discussed. Also, there is neither consensus value nor even consensus method for determining cost-effectiveness threshold (CET) for life-extending measures. In this study, we performed ethical analysis of CEA by policy impact assessment based on connection of health and wealth (poorer people have statistically shorter life expectancies) and concluded that CEA is not only a practical but also an ethical necessity. To quantify CET, we used three independent methods: (1) literature survey of analyzing salaries in risky occupations, (2) utilizing Prospect Theory suggesting that people value their lives in monetary terms twice more than their lifetime earnings, and (3) literature survey of the U.S. current legal practice. To the best of our knowledge, nobody applied method (2) to determine CET. The three methods yielded rather similar results with CET about 1.0 ± 0.4 gross domestic product per capita (GDPpc) per quality-adjusted life-year. Therefore, a sum of not higher than 140% GDPpc is statistically sufficient to "purchase" an additional year of life—or, alternatively, to "rob" one year of life if taken away. Therefore, 140% GDP per capita per quality-adjusted life-year should be considered as the upper limit of prudent and ethically justified expenditure on life extension programs.

Highlights

What do We Already Know About This Topic?

Cost-effectiveness analysis (CEA) is routinely performed in health policy. However, very different methods for determining cost-effectiveness threshold (CET) and very different values for CET can be found in the literature. Also, ethical justification of CEA is rarely discussed.

How does your research contribute to the field?

Excessive healthcare spending claims more lives than it saves. The value of 140% of gross-domestic-product per capita per qualityadjusted life-year is the upper limit for prudent expenditure on healthcare and safety. This important side effect was mainly ignored in decisions on lockdowns targeted to save lives.

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What Are Your Research's Implications Towards Theory, Practice, or Policy?

Every program or policy with cost exceeding 140% of gross-domestic-product per capita per quality-adjusted life-year does not pass the criteria of prudent and ethically justified expenditure.

Keywords

health policy, ethics, risk management, cost-benefit analysis, willingness to pay

Introduction

Investment in healthcare, technological safety measures, safety and environment-protection regulation decrease risks and extend lives, yet increase the economic burden.¹ Thus, resource restrictions are expected, and countries will be forced to prioritize medical investments.²

Associating human life with monetary value is psychologically difficult. The opposition to a cost-effectiveness analysis (CEA) in health and safety decision-making is not unfounded,³ but CEA still unavoidable.⁴⁻⁶ CEA is routinely performed in health policy, though decisions are rarely, if ever, made based on cost-effectiveness only.⁶ Seventeen countries at least have formal cost-effectiveness thresholds (CETs).⁷ Not only health policymakers but also medical practitioners can no longer consider only benefits and side effects but should also be aware of the associated cost.⁸

The terms "cost-effectiveness analysis" and "cost-benefit analysis" are close. However, cost-benefit analysis places monetary values on health outcomes or life, and therefore raises many ethical objections.⁸

Ethical justification of CEA for life-saving and lifeextending measures is rarely discussed—it is usually stated that each dollar invested in a potentially life-saving program (e.g., cancer prevention) is not invested in another potentially life-saving program (e.g., cancer treatment). However, it does not address the frequent claim of ALARA (As Low as Reasonably Achievable) principal proponents: money spent on healthcare and safety measures (e.g., by private agents due to safety regulation) would not be invested in alternative lifeextending projects.⁹ So, the ethical justification of costeffectiveness analysis remains an open question.

Regarding value of cost-effectiveness threshold, there is neither consensus value nor even consensus method for determining the latter. Essentially, two alternative approaches welfarist and extra-welfarist—are commonly used.⁷

According to the extra-welfarist approach, in order to estimate CET, one would ideally consider all the reasonable factors—taking risk, safety of products, diet etc. The term "value of statistical life" (VSL)⁵ is in official use by the U.S. government.^{10,11} (Although the term VSL probably raises negative connotation of equating human life to some monetary value, its meaning is just that there is human life cost for any spending.) Determining CET via VSL follows the extra-welfarist approach when the government is supposed to quantitatively assess public expenditure that is worth being invested in potentially life

expectancy-extending policies and actions.¹² However, this task is formidable due to multiple uncertainties.

Alternatively, the welfarist approach is probably the most straightforward practical approach to determine CET by estimating "willingness to pay" (WTP)—how people themselves value their life and health in monetary terms.¹² In our opinion, the welfarist approach should be preferred, and the term WTP itself describes most exactly the mechanism behind the assumption that the state should not provide citizens with services (including life-extension services) that are less cost-effective than the citizens themselves are willing to pay for such services.¹³

In this paper, we address first the question of ethical justification of cost-effectiveness analysis. Then, we review the existing methods of CET determination and point on their limitations. Finally, we apply three different methods, all of them based on WTP approach, to estimate justified costeffectiveness threshold for life extension spendings.

Methods

To justify ethically the applicability of cost-effectiveness analysis to healthcare, we performed policy impact assessment based on connection of health and wealth. Since poorer people have statistically shorter life expectancies, the ALARA approach to risk has an inherent ethical problem: by statistically extending life expectancy of some target population, we statistically reduce life expectancy of the others.

For the quantification of cost-effectiveness threshold, we used three independent methods, all of them based on WTP approach, and performed literature survey of each of them: (1) analyzing salaries in risky occupations, (2) using Prospect Theory assuming that people value their lives twice more than their lifetime earnings, and (3) comparing with the U.S. current legal practice. To the best of our knowledge, nobody applied method (2) to cost-effectiveness analysis.

Results

Ethical Justification of Cost-Effectiveness Analysis for Healthcare and Safety

There is an approach that since the value of human life is the highest possible from a societal perspective, any risk should be kept "as low as reasonably achievable"—the ALARA principle,⁹ no matter the price, if it is bearable. However, the ALARA approach has an inherent ethical problem; by

statistically extending life expectancy of some target population, the society statistically reduces life expectancy of the others.

The reason is that well-being and the life expectancy of the modern industrialized society is based on its material basis. Considering an unreasonable extreme, with all resources invested in healthcare, people would just die of hunger. Another extreme—nobody suggests giving up motorized transport though it claims yearly about 35,000 lives in the U.S. alone. In general, each dollar collected as tax (even to be invested in a potentially life-saving program) makes the taxpayer poorer by one dollar. Each dollar spent by a company due to safety regulation decreases by one dollar its profit, with direct impact on the workers' salaries and shareholders' income—also making them poorer. And statistically, poorer people have shorter life expectancies.

There are many mechanisms that contribute to the correlation between socio-economic status and life expectancy. Poorer people take higher-risk jobs, they work extra hours stressing their health, they use cheaper, and consequently less safe, products, their lifestyle is less healthy, their diet is less healthy, their health insurance is less comprehensive etc. For example, it has been shown that demand for health insurance is highly elastic¹⁴—that is, people purchase health coverage plans proportionally to their income. Personal experience of one of the authors (YS) illustrates just one of multiple mechanisms leading to lower life expectancy of poorer people: Two of his neighbors lost their lives in two unrelated traffic accidents. Both drove very cheap cars because of their economic status, and both would most probably survive with minor injuries-based on the post factum analysis of the accidents-would each of their cars be just about US\$8000 more expensive. The corresponding loss of life in the two cases was 30 years (50-year-old woman) and 50 years (30year-old man)-about two hundred US\$ (!) per life-year on average.

Not every drop in income significantly affects health. If the drop is slight, the expenditures on food, medicine, and health insurance are usually not affected. The family also tries to preserve the usual vacation patterns, cutting off other spendings. Moreover, if a household/person reduces spendings that have little bearing on health or a negative bearing (e.g., purchase of alcohol, tobacco, or less healthy restaurant food), no negative effect occurs. As an anecdotal example one can remind that the food shortage during the Second World War led to considerable improvement in health of many celiac patients (and ultimately led to the understanding of the celiac mechanism).

However, such a stepwise (rather than linear) health effect of income reduction at the microlevel (households) does not mean that a small additional burden placed on the society (e.g., a tax) does not pose risks to health and life. Small changes in national income mean significant changes in the expenses of particular households.¹⁵ For example, even a small increase in company tax can bankrupt a company balancing on the brink of survival. And unemployment or a significant reduction in business income will undoubtedly force most affected households to reduce their costs, affecting their health.

It should be emphasized that healthcare costs in most developed countries are already a heavy burden on national economy¹⁶: 8–12% of GDP in OECD countries,¹⁷ almost 17% in the USA.¹⁸ Not accidentally, shifting a substantial fraction of health expenditures from the medical system to socio-economic targets has been proposed.¹⁹ It is very likely that easing safety regulations and reducing healthcare programs of questionable efficiency will save more life years than will be lost without them.

Therefore, every public expenditure, including saving lives or extending life expectancy of particular persons, has unwanted but unavoidable side effect of statistical shortening of life expectancy of other people.

The above analysis shows that a policy with costeffectiveness below some threshold claims more life than it saves. The question of decision-making is therefore whether the direct effect, or policy goal (life expectancy extension for the target population), is stronger than the side effect (life expectancy shortening for non-target population). If the side effect is stronger than the direct (policy goal), the net result of such policy is the statistical shortening of life.²⁰ Such situation has been even characterized by the term "statistical murder."²⁰ Therefore, cost-effectiveness analysis is not only practical but also ethical necessity.

Cost-Effectiveness Threshold (CET) Quantification

Analysis of the existing methods. The method of determination of CET via WTP follows the welfarist approach. The welfarist approach is probably the most straightforward practical approach to determine CET by estimating how people themselves value their lives and health in monetary terms.¹²

In our opinion, the welfarist approach should be preferred over extra-welfarist, and the term WTP itself describes most exactly the mechanism behind the assumption that the state should not provide citizens with services (including lifeextension services) that are less cost-effective than the citizens themselves are willing to pay for such services.¹³ We are going to discuss this mechanism now.

Although accepting certain (or even very probable) death for money is unacceptable, taking small risks for money is routine: every profession is associated with some risk and there are professions that are riskier than the others (firefighters, police, construction workers etc.). If on average people are ready to take risk of death with, for example, probability 1/1000 (one of a thousand) for \$1500, then WTP should be estimated as \$1.5 million. Namely, to get \$1.5 million of earnings, 1000 people on average will take the risk 1/1000 to die, and one on average will die. Though people take their risks voluntary, the net effect is that public expenditure of one WTP statistically claims one human life. The above method of valuing life was proposed by Adam Smith more than two centuries ago and has been used since then in economic analysis as well as in legal practice.²¹ Therefore, reasonable value of CET per statistical life saved should be set about the value of WTP. It is not about monetary value of life. It is about extending life population-wide.

As mentioned above, despite a growing body of empirical studies on CET, no consensus has emerged regarding the methodology. The World Health Organization (WHO) has recommended CET equaling factor 1–3 times the gross domestic product (GDP) per capita.²² Marseille et al stressed, however, that while willingness to pay for health care is related to income, this relationship maybe nonlinear, so the CET as a fraction of GDP may be too stringent in high-income countries (rejecting some efficient options) and too lax in low-income countries (accepting some inefficient options).³

British researchers²³ estimated CETs based on recent empirical estimates of opportunity costs from the UK National Health Service. The method of opportunity costs perfectly fits countries with purely-market economy. However, in all countries with reliable statistics healthcare services are heavily subsidized and strictly regulated by the state. The opportunity costs are therefore influenced by the government involvement which differs significantly in various countries, so even surveys like Shiroiwa et al²⁴ cannot provide a reliable basis for comparison.

CET Value Estimation

In light of the complexities described in the previous section, we have chosen to implement a less sophisticated and hopefully more practical approach. Our analysis is based on three independent estimations: (1) analysis of salaries in risky occupations, (2) analysis based on Prospect Theory (Nobel Prize in Economics for 2002 to Daniel Kahneman) assuming that people value their lives twice more than their lifetime earnings, and (3) comparison with the current U.S. legal practice.

1. In 1976, Thaler (later awarded the Nobel Prize in Economics for 2017) and Rosen analyzed salaries in different occupations and compared the salaries with risk (mortality). They estimated VSL to be \$200,000 \pm 60,000 in 1967 dollars.²⁵ In 2019 dollars, the above estimation corresponds to \$1.53M \pm 0.46M based on Consumer Prices Index.²⁶

In order to perform cost-effectiveness analysis of evacuation we need not only VSL, but also value of spending equivalent to statistical loss of one life-year. The latter can be obtained by dividing VSL by half of life expectancy at birth—since statistical (accidental) death can occur randomly at any time during the lifespan. For life expectancy at birth of about 80 years, typical for the developed countries, VSL should be divided by 40 years. The above estimation yields therefore CET = $$38,250 \pm 11,500$ per life-year (the accuracy of the numbers, here and below, is certainly spurious; we keep this spurious accuracy till the final averaging). 2. Thaler's estimation of VSL fits the results of Prospect Theory²⁷ that people quantify potential loss approximately twice as much as potential earning.²⁸ Namely, people quantify losing \$10, for example, as much as not gaining \$20. The conclusion of 2:1 ratio in preference between loss and gain was made based on a vast body of psychological experiments; it was verified by analysis of real-life decision-making, for example, comparing purchasing new insurance with renewing existing. According to Prospect Theory, this 2:1 rule applies not only to money but also to other goods like vacation days etc. In our case, we assume that people value their lives (that they have and can lose) in monetary terms approximately twice as much as the anticipated earnings. To the best of our knowledge, such estimation of CET has not been performed before.

Let us perform the corresponding calculation. Net yearly after-tax income of an average U.S. worker was about \$43,000 in 2019 (https://taxfoundation.org/us-tax-burden-on-labor-2020/). Doubling this sum yields CET = \$86,000 per life-year.

3. In the U.S. legal practice, the median settlement compensation for the victims of the 9–11 attack was \$1.7M (in 2017 dollars), and median death compensation awarded by jury in 2009–2013 was \$2.2M (also in 2017 dollars).²⁹ We can therefore take \$1.95M \pm 0.25M for the legal practice with corresponding CET estimation of \$48,750 \pm 6250. In 2019 US\$, CET = \$50,800 \pm 6520.

It is worth explaining why legal practice is relevant to the determining of CET. Judicial practices in a country with a respected court accumulate a large volume of practical decisions in various situations. The existing judicial practice, which does not cause condemnation or at least wide discussion, gives, therefore, a good assessment of the public acceptability of the decision from the point of view of society. Therefore, the assessment of the "value of human life" in court to determine compensation provides important guidance for CET/VLS/WTP values acceptable by the society.²¹

The CET values are summarized in Table 1. The difference between the three values is about 2-fold, which seems to us rather modest taking into account the very different estimation methods.

Rigorous statistical averaging the results of the three methods cannot be done due to many unknowns. Instead of inventing mathematical method of questionable applicability, we just take the CET value as the mean value of the three estimations, and the CET range as the range of the values from US\$ 38 250 to US\$ 86 000. Rounding the numbers to a reasonable accuracy yields:

 $CET = 60,000 \pm 25,000$ US\$ per quality-adjusted life-year. Our estimation was performed on the U.S. *data*. We can generalize by expressing the result via gross domestic product

	Method	Cost-Effectiveness Threshold (CET), US\$ per Quality-Adjusted Life-year
I	Analysis of salaries in risky occupations ²⁶	38,250 ± 11,500
2	Based on the prospect theory (people value their lives twice more than the lifetime earnings ²⁸)	86,000
3	Comparison with the current U.S. legal practice ³⁰ TOTAL	50,800 ± 6520 60,000 ± 25,000

Table 1. Independent estimations of cost-effectiveness threshold.

(GDP) per capita—US\$ 65,000 in 2019.³⁰ Rounding to reasonable accuracy yields:

CET = 1.0 ± 0.4 GDP per capita (GDPpc) per life-year.

We find therefore that in the U.S., both people as individuals and the society in general value their lives at about 1.0 \pm 0.4 GDPpc per QALY. Therefore, as discussed in the section on ethical justification, a sum of not higher than 1.4 GDPpc is statistically sufficient to "purchase" an additional quality-adjusted year of life—or, alternatively, to "rob" one year if taken away. So, 1.4×GDPpc/QALY should be considered as the upper limit of prudent expenditure on healthcare and safety: higher expenditure most probably claims more life than it saves.

The upper limit for prudent expenditure on healthcare and safety—140% GDP per capita per quality-adjusted life-year is the single most important result of this study.

Discussion

Though the value of human life is the highest value for the society, life extension by means of healthcare and safety should not become a super-goal consuming all the reasonably available resources. The reason for this is that every public expenditure, including saving lives or extending life expectancy of particular persons (target population), has unwanted but unavoidable side effect of statistical shortening of life expectancy of non-target population.

It has been stated that the impact of socio-economic factors on health is enormous compared to the power of healthcare to counteract these factors. A metaphor for the connection of socio-economic and health parameters is the "New York subway map"³¹: From Manhattan to the South Bronx, life expectancy declines by 10 years, half a year for every minute on the subway. No medical intervention, either existing or even conceivable, has the same order of magnitude of effect on health.

Our value for CET was derived by three independent methods considering different sides of economic equilibrium: (1) by analyzing salaries in risky occupations,²⁵ (2) by assuming that people value their lives twice more than the wealth they earn (Prospect Theory),²⁷ and (3) by comparing with the U.S. current legal practice.²⁹ In microeconomics terms, the former method (1) is based on demand-supply

equilibrium in the labor market. The Prospect Theory method is based on supply-side considerations determining readiness of agents (employees) to take risks. The latter method (3) is based on numbers manifesting the readiness of the society to reimburse risk posthumously.

The calculated value is in excellent correspondence with the values accepted in the field of public healthcare. It has been estimated that the U.S. national health insurance is associated with an average cost-effectiveness of about US\$ 50,000 per QALY (quality-adjusted life year) gained.¹³ It is true that values used for decision-making often have an upper limit in the \$100,000 to \$150,000/QALY or higher, as mentioned by Birch and Gafni³² or Padula et al.³³ However, Padula et al³³ note that there is a strong association between estimated ICER (incremental cost-effectiveness ratio) values and chosen CET: the regression analysis indicated that CETs have a baseline value of \$52,000 and grow by \$0.37 for each dollar increase in the estimated ICER. Therefore, higher CET values seem to be biased.

In the United Kingdom, National Institute for Health and Clinical Excellence (NICE) adopted a costeffectiveness threshold range of \$40,000 to \$60,000 per QALY.³⁴ The review of Bonis and Wong⁸ estimates healthcare CET as US\$50,000 to \$100,000 per QALY. Cameron et al estimated CETs in 17 countries and found CET/QALY values in units of GDP per capita varying widely among different countries, from as low as 0.28 (Thailand) to as high as 4.2 (Belgium).⁷ This being said, the CET values seem to be highly correlated with GDP-see Figure 4 of Cameron et al.⁷ For countries with GDPpc below about \$35K, CET/GDP is about one. For higher-income countries, CET/GDPpc varies from slightly above one (Sweden) to 4.2 (Belgium). It is important to mention that no significant correlation between CET/GDP ratio and life expectancy has been observed (Figure 3 of Cameron et al⁷). For example, Sweden with the lowest CET/GDP ratio among the high-income countries has longer health-adjusted life expectancy than Belgium with the highest CET/GDP.

Numbers very different from the calculated in this work can be found in literature; different government agencies estimate VSL (value of statistical life) to justify their policies. Their estimates should be viewed with extreme caution.

First, methodologically there are multiple sources of bias, usually towards overestimating VSL.¹¹

Second, risks of other people are often wrongly estimated, particularly when corporate employers make decisions for their employees.³⁵ The authors of the latter paper³⁵ refer to the well-known principal-agent problem, when agent may act in a way that is contrary to the best interests of the principal. Let us emphasize that the principal-agent problem seems to be at least as severe between a citizen and a governmental body.

Third and most important: let us address the question of why from about 1995 to about 2015, VSL estimates by three U.S. agencies—Department of Agriculture, Food and Drug Administration and Environmental Protection Agency— went up 3-fold from \$2-4M to \$9-10M (in 2019 dollars).²⁹ We should mention that any government agency estimating VSL faces explicit conflicts of interest: the higher the VSL, the better the outcome of cost-effectiveness analysis for any proposed policy.

Consider, for example, a policy with a price tag \$1000M (one billion dollars). If VSL is \$1.5 M, such a policy is justified if it saves about 700 people; however, if VSL is \$10M—saving 100 people (that is, being 1/7 as effective) is enough for a positive cost-effectiveness judgment. Probably not surprisingly, VSL estimations of up to US\$70 million have been cited in the literature.³⁶

Because of high volatility of VSL values reported by different government agencies, and because of the explicit conflict of interest in their VSL estimation, it seems to us prudent to use our value for the cost-effectiveness threshold (CET).

As an example, let us apply cost-effectiveness analysis to the COVID-19 crisis management in Israel. It can be estimated that the direct economic cost of the lockdowns in 2020–2021 was about US\$ 30 billion, while the Israeli population is about 9.2 million, and GDP per capita is about US\$ 45,000 (see Supplemental Appendix). Dividing 30 billion by $1.4 \times 45,000$ yields about 500,000 quality-adjusted life-years lost. The discussion of whether the above human cost was justified is beyond the scope of this paper. We shall just mention that the loss of 500,000 QALY in Israel is equal to the loss of life due to cancer (about 11,000 deaths per year,³⁷ 12 life-years per death³⁸) during 4 years.

Our analysis is not free from limitations. Several limitations stem from our estimation of CET by analyzing salaries in risky occupations.

The first limitation is that the data is more than four decades old. Unfortunately, we could not find more up-to-date research using this method which seems to us extremely important.

Next, one can reasonably ask whether individuals in jobs with a substantive risk systematically over- or under-estimate the risk. Really, personal perception can deviate from scientific assessments. The known phenomena include some underestimation of risks by young people and men as opposed to overestimation by elderly and women; overestimation of low risks and underestimation of high.³⁹ However, people usually perceive personal risks (including risk of death) rather adequately, unlike risks to other people.⁴⁰

Another limitation is that hazard pay may be more so received by individuals otherwise facing lower earnings potential. If so, the wage rate needed to entice these individuals to face the added risks is likely to be much lower than that required to entice the general population. The above assumption, while plausible, is not necessarily correct. In their estimation, Thaler and Rosen²⁵ took into account age, gender, education etc. And simply speaking, the list of high-risk occupations (Thaler and Rosen,²⁵ Table 1 at p. 288) contains not a small number of highly-paid professions demanding well-educated employees—for example, electricians, boilermakers, structural ironworkers, marshals, constables, ships' officers, and even actors.

Further, we have not used discounting in translation from VSL to CET per QALY. Proper way of discounting is an unsettled question in health economics. For example, differential discounting was used by in UK for some time,⁴¹ with 1.5% per year for life and 6% for money. This practice, however, has been terminated and substituted with equal discounting at 3% per year.⁴¹ Although discounting makes estimations much more complex and prone to bias, we anticipate that it will not affect the results in a serious manner. Let us consider discounting in the three methods we used. Professionals in risky occupations perform discounting subconsciously and automatically, so another discounting would be superfluous. The same can be said regarding CET estimation based on Prospect Theory: people discount, subconsciously and automatically, both their future earnings and their life-years potentially lost. As for the legal practice, explicit discounting of both life-years and earnings is actually performed,^{42,43} so once again, another discounting would be superfluous.

Additional limitation is connected to our use of Prospect Theory. Certainly, life is very different from other goods. Not only does the degree of importance people attach to the value of life differ from person to person, but the relationship between it and money may not be linear. However, population-wide it seems that people do treat life like other goods, which can be deduced, for example, from the analysis of purchasing insurance.²⁸ We should also mention that in health economics equal discounting is presently used for life and money,⁴¹ as discussed in the previous paragraph.

Last, our estimation was performed on the U.S. data only. However, the practice of recommending CET values as a fraction of GDP is well established and used, for example, by WHO.²² So, we believe that our estimation is generally applicable to any country with comparable institutions.

Conclusions

Every public expenditure, including saving lives or extending life expectancy of particular persons (target population), has unwanted but unavoidable side effect of statistical shortening of life expectancy of non-target population. Therefore, costeffectiveness considerations in healthcare and safety are not technical, but ethical necessity. Population-wide, a lifeextending policy with cost-effectiveness below costeffectiveness threshold (CET) claims more life than it saves.

Because of high volatility of CET values reported by different government agencies, and because of the explicit conflict of interest in their estimations, it seems to us prudent to use our value for CET, derived by three independent methods and consistent with the current health policies:

 $CET = 1.0 \pm 0.4$ GDP (gross domestic product) per capita per quality-adjusted life-year.

Therefore, 140% GDP per capita per quality-adjusted lifeyear should be considered as the upper limit of prudent expenditure on life extension.

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Author Contributions

MY and YS conceived the idea. MY, YYS and ONL performed the ethical analysis. YS performed the data analysis. MY wrote the first draft. MY, YS, YYS, ONL, AZ participated in finalizing the manuscript. AZ performed the critical revision of the manuscript. All the authors read and approved the manuscript.

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Supplemental Material

Supplemental material for this article is available online.

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