Informing a cost-effectiveness threshold for health technology assessment in China: a marginal productivity approach

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Abstract
Background Health technology assessment has been increasingly used in China, having been legally mandated in 2019, to inform reimbursement decisions and price negotiations between the National Healthcare Security Administration and pharmaceutical companies around the price of new pharmaceuticals. The criteria currently used to judge cost-effectiveness and inform pricing negotiations, 3x GDP per capita, is based on the rule of thumb previously recommended by the World Health Organization rather than an estimate based on an empirical assessment of health opportunity costs.
Objective The objective of this study was to inform a cost-effectiveness threshold for health technology assessment in China that accounts for health opportunity cost.
Methods The elasticity of health outcomes with respect to health expenditure was estimated using variations across 30 provincial-level administrative divisions in 2017 controlling for a range of other factors and using an instrumental variable approach to account for endogeneity to assess robustness of results. The estimated elasticity was then used to calculate the cost per DALY averted by variations in Chinese health expenditure at the margin.
Results The range of estimates from this study, 27,923-52,247 (2017 RMB) (central estimate 37,446) per DALY averted or 47-88% of GDP per capita (central estimate 63%), shows that a cost per DALY averted cost-effectiveness threshold that reflects health opportunity costs is below 1x GDP per capita.
Conclusion Our results suggest that the current cost-effectiveness threshold used in China is too high; continuing to use it risks decisions that reduce overall population health.

Key points for decision makers

- Health technology assessment has been increasingly used in China and the criteria currently used to judge cost-effectiveness and inform pricing negotiations does not reflect an evidence-based assessment of health opportunity costs.
- This article provides the first estimate of the marginal productivity of health expenditure in China which can be used to inform the health opportunity cost of funding a new technology.
- Our central estimate 37,446 (2017 RMB) or 63% of GDP per capita shows that a cost per DALY averted cost-effectiveness threshold that reflects health opportunity costs would be below 1x GDP per capita, suggesting that decisions made on the basis of the currently used 3x GDP per capita threshold risk resulting in net losses in overall population health.

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1 Introduction

Health technology assessment (HTA) has been increasingly used in China since its introduction in the 1990s. With the support of key decision makers from the Chinese Ministry of Health, more than 15 academic institutions conducting HTA have been established across the country. The initial version of China Guidelines for Pharmacoeconomic Evaluations was published in 2011 to guide the HTA practice [1]. The HTA Research Network was established in 2016, led by National Health Commission (NHC)'s Health Development Research Centre, and has more than 300 members from universities, hospitals, and relevant associations as well as overseas experts. In 2018, the National Centre for Evaluation of Medicines and Health Technologies was created by NHC, representing formal establishment of a national HTA agency [2–4].

HTA has since been written into Government policy documents, including the Law of the People's Republic of China on the Promotion of Basic Medical and Health care, which was approved in December 2019 [5]. Following a successful pilot in 2017 to use HTA to inform the price negotiations for 44 medicines and medical devices that were considered innovative but expensive (and therefore not yet included in the National Formulary), HTA evaluation reports are now regularly requested by the National Healthcare Security Administration (NHSA) [6]. The NHSA has also established two assessment expert panels, one responsible for undertaking cost-effectiveness analysis and other for undertaking budget impact analysis.

Whilst HTA is increasingly used in China to inform reimbursement decisions and price negotiations between the NHSA and pharmaceutical companies around the price of new pharmaceuticals, clearly defined and measurable criteria are still lacking. One such example is the threshold used to judge cost-effectiveness, which is currently set at 3x GDP per capita per disability-adjusted life year (DALY) averted [7]. This is based on historical World Health Organization (WHO) recommendations that a health technology costing less than 1x a country's GDP per capita be considered highly cost-effective while a health technology costing less than 3x GDP per capita be considered cost-effective. The WHO has since recognised the shortcomings of using a GDP-based threshold, and consequently has stopped recommending their use as cost-effectiveness thresholds [8].

It has, however, not followed this up with a recommendation of what should be used to inform cost-effectiveness thresholds in place of a GDP per capita based rule of thumb. The Disease Control Priorities Network, which aims to set out priorities for disease control across the world, in its the most recent edition applies a threshold based upon health opportunity costs to judge cost-effectiveness [9]. Some countries also explicitly consider health opportunity costs. The methods guidance for the UK's national HTA agency, the National Institute for Health and Care Excellence (NICE), states that a technology can be considered cost effective if its health benefits are greater than the opportunity costs of technologies displaced to fund it [10]. In Canada, the cost-effectiveness threshold in the draft Patented Medicines Regulations (due to come into force in July 2020) set forth by the Patented Medicine Prices Review Board, the Canadian body mandated to prevent pharmaceutical patentees from charging consumers excessive prices during the statutory monopoly period, is also based on estimates reflecting health opportunity costs [11].

Assessing whether the expected health benefits of a new technology are greater than the opportunity costs of the other health technologies that could have been funded (whether these are currently funded health technologies that are displaced or other not currently funded health technologies that could be funded) requires an evidence-based assessment of the marginal productivity of health expenditure. Research has been undertaken to estimate the marginal productivity of the healthcare system using within-country data for several countries, including the United Kingdom, Spain, Australia, the Netherlands, Sweden and South Africa [12–18]. However, such analyses are data and time intensive, and therefore not possible for all countries. The Canadian estimate is instead based on work commissioned by the PMPRB to calculate the marginal cost of a QALY in the Canadian healthcare system using evidence from cross-country data as well as within-country estimates from the United Kingdom and evidence of historical trends in cost effectiveness assessments by Canadian HTA agencies, while commissioned within-country analysis is being undertaken [11].

To date, there are only two sources available for estimates that reflect the rate at which the Chinese healthcare system currently produces health. Woods et al [19] expand upon previous work undertaken in the United Kingdom by applying data on the income elasticity of the value of health to extrapolate estimates for a wide range of countries including China. Ochalek et al [20] expand upon existing published estimates of the health effects of changes in expenditure from cross-country data to calculate a range of estimates for low- and middle-income countries (LMICs). Estimates based on within-country data are generally superior to those from cross-country data as cross-country analysis restricts the number of available variables owing to the need for international comparability. In addition, better identification strategies can typically be devised in the within-country context based on instrumental variable or natural experiment [21].

This paper follows in the footsteps of previous research undertaken to estimate the marginal productivity of the healthcare system using within-country data for specific countries, and aims to provide an estimate of the cost per DALY averted for China that reflects health opportunity costs based on an evidence-based assessment of the marginal productivity of health expenditure in China. Because an estimate of the marginal productivity of health expenditure reflects health opportunity costs, using it as a threshold to judge cost-effectiveness would ensure that decisions around whether or not to fund a health technology improve overall population health. Such an estimate can also inform how much the healthcare system can afford to pay for a new technology for it to offer a net gain in health, which may be used in negotiations around the price of new pharmaceuticals.

2 Methods

We begin by estimating the elasticity of health outcomes with respect to health expenditure per capita using variations across provincial-level administrative divisions, hereafter provinces, in mainland China in 2017[1] controlling for a range of other factors. We then conduct sensitivity analyses where we use an instrumental variable (IV) approach to account for potential endogeneity and increase the sample size by pooling data from 2011 to 2017. The data and methods used for the regression analyses are described in section 2.1.

Calculating a cost per DALY averted estimate that reflects health opportunity costs requires two steps: first, estimating the elasticity of health outcomes with respect to health expenditure; and second, calculating cost per DALY averted from the estimated elasticity. The data and methods used for this portion of the analysis are described in section 2.2.

2.1 Estimating the effect of health expenditure on health outcomes

2.1.1 Health outcomes

Our paper considers three health outcomes: DALY rate (DALYs per 100,000 population), under-5 mortality (the cumulative probability of death by age 5 given being born) and adult mortality (the cumulative probability of death by age 60 given alive at age 15). These variables reflect the kinds of health outcomes analysed in the wider literature examining their relationships with health expenditures [22]. Related studies generally tend to focus their analysis on mortality since this is widely recorded and is available for most countries. In particular, under-5 mortality is used because of international development goals that emphasise the importance of reducing avoidable mortality in this age group [23]. Some studies, however, have also considered adult working-age mortality since this is seen as an important step to achieving economic development [24]. Estimating the effect of healthcare on mortality, however, considers only part of the benefits of healthcare. An analysis by disease-area found that over half of healthcare spending in the UK was spent on disease areas for which no mortality data was recorded [25]. It is likely that this kind of healthcare spending has effects on health not through mortality, but through improvements in health-related quality of life. DALYs capture both the mortality and morbidity burden of disease that stands to be alleviated through health expenditure, and estimates of DALY burden are available for Chinese provinces from Zhou et al [26]. Analysing DALY health outcomes allows for the direct estimation of the effect of healthcare expenditure on a generic measure of health that incorporates both gains in survival and health-related quality of life.

2.1.2 Health expenditure

A key difference between this study and others is that we consider total health expenditure rather than government health expenditure only. Over 95% of the Chinese population is covered by social health insurance, where the government pays a portion of the cost of care and patients pay the remainder through deductibles and copayments

[1] Most variables considered in the study are available only up to 2017.

[27,28]. For this reason, cost-effectiveness analysis takes a broader perspective with respect to costs compared to agencies such as the National Institute for Health and Care Excellent (NICE) in the UK. For example, where a cost falls upon an individual (out of pocket) in China, this cost is included, whereas only costs falling on the National Health Service and Personal Social Services are typically included in the NICE reference case [7,10].

Studies estimating the marginal productivity of government health expenditure only are primarily useful for HTA bodies operating on behalf of primarily publicly financed health care systems and providing recommendations on the basis of improving health given a budget for health care that is exogenous to the decision. In China health care is financed through a mix of sources and so HTA necessarily operates in a different decision context. While ideally opportunity costs would be calculated separately for each component of expenditure, we combine them so that a single value for a cost-effectiveness threshold is estimated that is compatible with the approach to cost-effectiveness analysis typically undertaken in China for negotiating the price of pharmaceuticals. It could be that the health opportunity costs across different sources of financing are similar, if they are assumed to be equal then our results can be compared with estimates of marginal productivity of Chinese government health expenditure only.

2.1.3. Control variables

Our selection of control variables is informed by the literature review undertaken by Nakamura *et al.*, (2016) [29] (See Appendix D of their review). First, we obtained variables to control for the demographic profile of each province[2]: proportion of the population under age 14, proportion of population over age 65, and percentage of males in the population.[3] In addition, we obtained a number of variables that are potential determinants of the chosen health outcome variables: GDP per capita, percentage of population with at least a high school education, urbanicity rate, penetration rate of sanitary toilets, efficiency index of governance, and highway density. They are all expected to have positive association with health – i.e. fewer DALYs and lower mortality. These variables are all collected for the year 2017. Additionally, we control for regional fixed effects by categorising provinces into East, Central and West regions. Health is expected to be positively associated with the East region relative to the others [30]. To avoid issues of collinearity, variables that are too closely correlated with health expenditure per capita are excluded from the regression specification [29][4]. All the variables used in the analysis are summarised in Table 1.

[Insert Table 1 here]

[2] Our data exclude Tibet due to missing data. This leaves us with a sample size of 30.
[3] The first two are only used when the health outcome is DALY rate since the other two are already age specific.
[4] We consider 0.7 as the threshold as too high correlation.

2.1.4 Regression analysis and endogeneity problems

Analysis presented within the main paper considers the 2017 cross-section only. An additional panel analysis looking at 2011-2017 is conducted for the mortality outcomes (but not DALY, which is only available by province in 2017) and is presented in the Electronic Supplementary Material.[5]

Our base case scenario is an ordinary least square (OLS) regression using the log transformed health outcomes as dependent variables and log transformed health expenditure per capita and control variables as predictors. All the coefficient estimates can be interpreted as the elasticity of health outcomes with respect to a specific predictor. The estimates are weighted using the population size of each province and robust standard errors are used. The linear functional form assumption is tested for using 'RESET'.

There are two types of endogeneity problems that can arise when estimating the elasticity of health outcomes with respect to health expenditure. The first is reverse causality, which is evident in many western healthcare systems where healthcare budget is determined using a formula based on previous years' health outcomes [31]. By contrast, in China there is no such formula that is used to form the fiscal policy for healthcare, and reverse causality is therefore a lesser concern in our analysis [28]. Specifically, in China budget allocation is tied to capital investment and local fiscal capacity rather than the needs of facilities or the population [32]. Financial subsidies to public hospitals mainly fund capital construction and equipment acquisition, development of key disciplines, personnel training, retirees 'expenses in line with state regulations and policy-related subsidies for losses [33]. When financing major public health service projects, local governments take the main responsibility for public health services and prevention of major communicable diseases within their jurisdictions, while central government provides subsidies for cross-regional projects. Finally, different provider payment methods have been implemented whereby basic public health services are funded by financial provision per capita, while basic medical services are funded by basic medical insurance through mixed payment methods such as fee-for-service (the majority), case payment and global budget [28].

The second type of endogeneity is related to the omitted variable bias which occurs when an unobserved confounder is associated with both the health outcome and health expenditure. While controlling for a number of other determinants of health outcome reduces the likelihood of our estimates being contaminated by omitted variable bias, it may not be completely eliminated. To formally test the exogeneity of health expenditure, we adopt an IV approach and consider two IVs: the average premium fees for Basic Medical Insurance among insured people and

[5] It would be ideal to control for provincial fixed effects. Unfortunately, there is insufficient within-province variation in the expenditure variable for this approach to be viable. We therefore chose to estimate pooled OLS , which is the same type of panel analysis that is undertaken in Siverskog and Henriksson (2019) [17].

number of medical personnel per 10,000 people. The rationale for the first and our primary IV (average premium fees for Basic Medical Insurance among insured people) is that, on average, the higher fees a person pays, the more health care services the person would consume. Instrument exogeneity in this case relies upon the fee schedule by province not being related to health outcomes themselves or unobserved confounders between health expenditure and health outcomes, having controlled for a number of observable factors. Note that these fees are compulsory for employed people in urban areas. Moreover, out-of-pocket costs are typically induced for using these health care services (even if insured) which leads to higher expenditure. The rationale for the second IV is that it represents the service capacity of the healthcare system. China has a shortage of healthcare professionals [34], and so we expect that where more healthcare professionals are available to provide care, more healthcare is consumed and thus the higher health expenditure per capita is. In this case instrument exogeneity relies on the distribution of shortages across provinces being unrelated to health outcomes or unobserved confounders between health outcomes and health expenditure.

The IV regressions are implemented using the -ivreg2- Stata command. The 'gmm2s' option is chosen for a two-step feasible GMM estimation and the 'small' option for small-sample statistics. The estimates are also weighted using the population size and robust standard errors are reported. A number of tests are undertaken to check the validity of our IVs: underidentification test, weak identification test, overidentification test and endogeneity test. The linear functional form assumption is again tested for using 'RESET'.

One of the challenges of the IV approach is that one can never formally test the exclusive restriction, i.e., the IVs are not correlated with the error term in the original OLS regression, conditional on the other covariates. Obviously, our IVs are correlated to economic and social development factors that would have direct impact on health outcomes. The question is therefore whether we have sufficiently controlled for these factors in the regression. We will return to this in the discussion.

2.3 Calculating cost per DALY averted from elasticities of the health effects of expenditure

Informing an opportunity cost-based threshold requires calculating the DALYs averted from the estimated elasticities ϵ on DALYs or under-5 and adult mortality. We apply the approach taken by Ochalek et al [20], which has also been used elsewhere [21,35]. The methods for moving from an estimate of the effect of expenditure on DALYs are explained in detail in Ochalek et al [20], and we summarise them here for calculating DALYs averted from an estimate of the effect of expenditure on mortality (DALY 1 in Ochalek et al, 2018) [20] and DALYs (DALY 4 in Ochalek et al, 2018) [20].

2.3.1 Using the estimated elasticity on mortality

Calculating deaths averted

Calculating cost per DALY averted from elasticities of the effect of expenditure on under-5 and adult mortality rates requires accounting for the age and gender structure of the population and applying a series of assumptions about survival and morbidity to obtain cost per DALY averted [20]. In our base case scenario, all data are taken from the Global Burden of Disease database for year 2017 [36]. We also present results using data on deaths and population by age and gender for 2017 based on Chinese census data [37]. Deaths by age and gender are calculated from mortality rates reported by age and gender from the 2010 China census (the most recent available) in combination with the population by age and gender from 2017 assuming that the death rate by age and gender has remained the same between 2010 and 2017. DALYs are then calculated by combining data on deaths from the census with conditional life expectancy from GBD to calculate survival and using morbidity data from GBD.

The first step is to calculate the deaths estimated to be averted from a change in expenditure. Among children under 5 this is calculated as:

$$under\ 5\ deaths\ averted = 1\% * \left|\epsilon^{under\ 5\ mortality}\right| * under\ 5\ mortality$$

where under 5 mortality is the total number of deaths among children under 5 in 2017 in China.

Among adults 15-60 this is calculated by applying the elasticity on adult mortality to deaths in each 5-year age category between ages 15 and 60 (i.e., 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59):

$$adult\ deaths\ averted = 1\% * \left|\epsilon_i^{adult\ mortality}\right| * deaths^{15-19} + \cdots + 1\% * \left|\epsilon^{adult\ mortality}\right| * deaths^{55-59}$$

This assumes that the proportionate effect on adult mortality applies across age groups within the 15-60 age range.

Calculating survival effects

The survival effects of a change in expenditure are determined by applying conditional life expectancy at age of death (by 5-year age category) to the deaths averted (by 5-year age category). This gives the years of life lost (YLLs) among children under 5 and adults 15-60. While it may be the case that the same increase in healthcare expenditure would be expected to affect different age groups differently (and indeed, this is the rationale for estimating the effects on under-5s and adults separately), in the absence of good evidence to inform the extent to which the effects are likely to differ across age groups we assume that the same proportion of YLLs that are averted among these age groups are averted in the rest of the population. In other words, if the calculated YLLs averted among children under 5 and adults 15-60 represent 40% of the YLLs in those combined age categories, then we assume 40% of the YLLs in the remaining age categories are also averted.

Calculating morbidity effects

Changes in expenditure are likely to affect morbidity in both directions: increases in burden of morbidity may results from increased survival, and decreases in morbidity may result from the direct effects of expenditure (e.g., on treating existing health conditions). To account for the indirect effect, we apply the per capita YLD burden to the calculated survival effects (i.e., the YLL burden averted). To account for the direct effect, we assume that the effect of changes in expenditure on morbidity is proportional to the effect on survival by applying the ratio of YLD to YLL to estimated survival effects [38].

2.3.2 Using the estimated elasticity on DALYs

Using the estimated elasticity of the effect of expenditure on DALYs is straightforward, and DALYs averted are simply calculated as:

$$DALYs\ averted = 1\% * |\epsilon^{DALYs}| * DALY\ burden$$

Calculating DALYs averted

The DALYs averted is the sum of the survival effects (i.e., YLLs averted) and the net morbidity effects (i.e., YLD averted: the direct effect minus the indirect effect).

Calculating cost per DALY averted

We are therefore able to calculate two estimates of cost per DALY averted. The first is based upon the estimated DALYs averted calculated using the elasticity of the mortality effects of changes in expenditure. The second is based upon the estimated DALYs averted calculated using the elasticity of the DALY effects of changes in expenditure. Cost per DALY averted is calculated as:

$$cost\ per\ DALY\ averted = \frac{1\% * government\ expenditure\ on\ health}{DALYs\ averted}$$

3 Results

3.1 Estimates of elasticity

Correlation coefficient estimates among all candidate predictors are reported in Electronic Supplementary Material Table S1. Health expenditure, education, urbanicity and GDP per capita are found to be highly correlated with each other, which suggests these four variables are likely to be determined by a common factor, such as the economic and social development level. Given the high levels of correlation, the latter three are dropped from regression analyses. In addition to age and gender, the final model includes as controls three variables: government efficiency index, penetration rate of sanitary toilets and highway density. It is interesting that these three variables, in particular government efficiency index, are not strongly correlated with the aforementioned four variables. This may suggest that they are capturing the residual impact of economic and social development level on health outcomes after including health expenditure as the main predictor. Finally, to control for other forms of heterogeneity, we include regional fixed effects.

OLS estimates are presented in Table 2.[6] The estimated elasticities are statistically significant at 5% significance level in all regressions. Given a relatively small sample size, this suggests a very strong impact of health expenditure on health outcomes. Based on these estimates, spending an additional 1% on healthcare would be expected to reduce the DALY rate by 0.271%, under-5 mortality rate by 0.448%, and adult mortality by 0.677% in 2017 in China, controlling other factors.

[Insert Table 2 here]

Percentage of population under age 14 and percentage of population above age 65 both have positive impacts on DALY rate, and the latter is statistically significant. Percentage of males in the population seems to have a negative effect on all three health outcome variables but the effect is not significant. The government efficiency index has a negative and statistically significant effect on under-5 mortality, but its effect on DALYs and adult mortality is not statistically significant. As expected, the penetration rate of sanitary toilets and highway density both have negative impacts on the outcomes.[7] The regional effects included indicate a positive association with poor health, which is expected given that the reference region is East. The 'RESET' test does not reject the linear functional form of covariate.

While we are less concerned with the reverse causality, there is indeed a risk of omitted variable bias. As discussed in the previous section, we adopt an IV approach to attempt tackle this potential problem. The IV estimates are presented in Table 3 for the under-5 mortality rate outcome, Table 4 for the adult mortality rate outcome and Table 5 for the DALY rate outcome.[8] The IVs pass all three identification tests, i.e., there are no under, weak, and over identification problems. Again, the 'RESET' test does not reject the linear functional form of covariate. The endogeneity tests, however, suggest the exogeneity of health expenditure cannot be rejected based on the data. This result is not surprising given the IV estimates of elasticity are very similar to their OLS counterparts. Based on this, we use the OLS estimates to derive cost per DALY averted.

[6] Corresponding pooled OLS analysis looking at 2011-2017 for the mortality rate outcomes finds similar coefficient estimates. These results are presented in Table S2.
[7] The statistical insignificance may be caused by the relatively small sample size, e.g. large effect and large standard error at the same time.
[8] Corresponding pooled OLS IV estimates for the mortality rate outcome models are found in Tables S3 and S4, which provide very similar coefficient estimates. Again, in each case, the IVs pass all three identification tests. The endogeneity tests suggest the exogeneity of health expenditure cannot be rejected based on the data.

[Insert Tables 3, 4 and 5 here]

3.2 Cost per DALY averted

Table 6 presents the cost per DALY averted estimates calculated from the OLS model. Applying the estimated elasticities from the OLS model on under-5 and adult mortality we find that it costs 27,923 (2017 RMB) to avert a DALY in China. That is 47% of GDP per capita (4,131 2017 USD). Applying the estimated elasticities from the OLS model on DALYs results in a higher estimate of 52,247 (2017 RMB) to avert a DALY in China (88% of GDP per capita, 7,730 2017 USD). More DALYs are estimated to be averted when mortality elasticities are used than when an elasticity on DALYs is used. Although a number of assumptions are required to get from the mortality effects of expenditure to cost per DALY averted, applying the estimated elasticity on DALYs to under-5 and adult mortality would result in a very similar estimate of DALYs averted. This suggests that the assumptions employed are not unreasonable, and much of the difference in results between the two methods in our context is down to differences in the estimated elasticities.

[Insert Table 6 here]

We also present results using data on deaths and population by age and gender for 2017 where survival effects are based on Chinese census data and morbidity effects are based on GBD data. This results in higher estimates of cost per DALY averted because the census reports a lower mortality rate than GBD. Applying the same elasticity to fewer deaths results in fewer deaths averted, lower survival effects and, because of the surrogacy assumption employed, a smaller effect on morbidity.

The central estimate of cost per DALY averted is based on the average DALYs estimated to be averted using GBD data and census data based on the mortality effects of expenditure and the DALY effects of expenditure from the base case (OLS) analysis. This is 1,404,658 DALYs averted for a 1% increase in health expenditure, suggesting China currently spends 37,4446 (2017 RMB) or 63% of GDP per capita (5,540 2017 USD) to avert one DALY.[9]

4 Discussion

This paper provides the first estimate of the marginal productivity of health expenditure in China based on Chinese province-level data, which can be used to inform the health opportunity cost of funding a new technology. Our estimates are all below 1x GDP per capita, and therefore well below the 3x GDP per capita cost-effectiveness threshold widely used by scholars and policymakers in China. China has not yet disclosed the ICER threshold for

[9] Calculating using an exchange rate of 0.148 for 2017 from the World Bank https://data.worldbank.org/indicator/PA.NUS.FCRF

drug price negotiation; it is clear that decisions made on the basis of the currently used 3x GDP per capita threshold risk resulting in net losses in overall population health

The adoption of a cost-effectiveness threshold for decision-making in national medical insurance that is higher than an empirical estimate of the marginal productivity of healthcare expenditure may result in the introduction of drugs and technologies that generate less health than the health that would be generated by the same money required to fund them in the wider healthcare system, reducing total population health. This is likely to lead to suboptimal resource allocation and thus a loss of social welfare. Using a cost-effectiveness threshold that reflects the marginal productivity of the healthcare system also enables the inevitable trade-off in terms of population health forgone from approving a drug at a cost above the cost-effectiveness threshold to be made explicit, enabling greater transparency in decision-making. Nonetheless, there may be challenges to implementing a cost-effectiveness threshold that is lower than what has been used previously and pharmaceutical companies may not necessarily adjust prices to reflect the prevailing cost-effectiveness threshold. (See for example, the rejected recommendation to base the cost-effectiveness threshold for the Joint Committee on Vaccination and Immunisation in the United Kingdom on available empirical evidence [39].) Successful implementation requires strong political commitment, which China has in the Law of the People's Republic of China on the Promotion of Basic Medical and Health care [5]. It also requires institutional capacity, which exists in the National Centre for Evaluation of Medicines and Health Technologies and the wider HTA Research Network; standard methodological and process guidelines, i.e., the China Guidelines for Pharmacoeconomic Evaluations [1]; and strong enforcement [40].

HTA has become an important tool for national medical insurance coverage decisions. Applying the China specific estimate of the marginal productivity of health expenditure produced in this study as a cost-effectiveness threshold for China would have wide-ranging implications and applications. For example, the threshold may be applied to drug negotiation and pricing decisions by the NHSA. The NHSA economic evaluation team participated in the national drug negotiations of 2017 where cost effectiveness results were an important basis for the negotiations. This study provides an evidence-based estimate of cost per DALY averted that may be used as a cost-effectiveness threshold by the evaluation team, and which would ensure negotiations could be informed by estimates of the health opportunity cost of approving a drug at a given price and the expected net benefits of different potential prices.

The threshold may also benefit health resource allocation decisions at local levels. The governments of many cities in China, such as Shanghai, Beijing and Guangzhou now require HTA evidence when setting the price for new medical services. Whilst not compulsory, HTA is also increasingly used by local governments to assist their evaluation of public health interventions and medical technology disinvestments. For example, economic evaluation of colorectal cancer screening and pneumonia vaccine projects have been undertaken in many cities as an important basis for financial investment decisions.

The threshold may well have impact on hospitals' procurement decisions of medical devices as well. Since 2016, the NHC has been promoting the use of HTA in hospitals' purchase decisions. This campaign has been very successful and many hospitals across China have now included HTA evidence in their procurement of medical devices on a regular basis [41].

The range of estimates from this paper, 27,923-52,247 (2017 RMB) (central estimate 37,466) per DALY averted or 47-88% of GDP per capita (central estimate 63%), is consistent with, albeit slightly higher than, previous estimates from cross-country analyses. Woods et al [19] report a range of 1,151-4,550 (2013 USD) or 17-67% of GDP per capita per QALY gained for China based on extrapolating the UK estimate of the health effects of a change in expenditure on health outcomes using the income elasticity of the value of health to estimate ranges of cost per QALY estimates across countries. Ochalek et al [20] report a range of 3,650-5,076 (2015 USD) or 45-63% of GDP per capita per DALY averted based on expanding existing published estimates of the health effects of changes in expenditure on health outcomes and applying these to country-specific data on health expenditure, epidemiology and demography to calculate a range of cost per DALY averted estimates for low and middle-income countries.

Cost per DALY averted or QALY gained thresholds can both be used to judge estimates of cost-effectiveness where benefits are reported in QALYs or DALYs [42]. QALYs and DALYs are the two most commonly used measures of health that account for both length and quality of life. While there are methodological differences between the two, given the absence of an accepted method for translating between the two they can be used interchangeably (e.g., as in the United States [43] [44]). Published cost-effectiveness analyses in China may use either [45], but recent research has shown that differences in cost per QALY or DALY ratios for the same intervention do not materially affect comparisons of these ratios to thresholds [42].

Estimating the health opportunity costs of committing expenditure to a particular investment hinges on an empirical question linking expenditures to their estimated effects on health outcomes. While this study considers a specific approach to answering this question, there may be alternative strategies worthy of consideration for future work. The approach taken in this paper is to derive an estimate based on an elasticity estimated using a cross-sectional analysis of Chinese province-level data, which constrained our analysis to including only a small number of control variables that can measure economic and social development levels that might confound the relationship between expenditure and health. This may affect the accuracy of our elasticity estimates, but such concerns can be alleviated by our careful selection of socioeconomic control variables and the sensitivity analyses undertaken. Nevertheless, future work may consider alternative approaches to allowing for unobserved confounders such as using different instrumental variables or identifying natural experiments that lead to exogenous variations in health expenditure. It could also investigate this relationship using a more granular geographical unit of analysis so that more observations are available and there is greater ability to control for observable confounders. In addition, efforts to collect more data by province could assist estimation of elasticities of effect and their translation into a cost per DALY averted.

Once framed as an empirical question, a number of related research questions bear further consideration. Due to the vast heterogeneity among provinces in China, the effects of total health expenditure on health outcomes would be expected to vary across these if health care resources were not allocated across provinces to maximise total population health (in such a case marginal productivities should be equal). This coupled with the considerable autonomy that provinces have over decision-making in health means that establishing region-specific marginal productivity of expenditure is a research priority. Another important question concerns the appropriate mix of health care financing. If we could analyse the distribution of health opportunity costs of different types of health expenditure separately then decisions around levels of copayments to be levied could be informed.

5 Conclusion

This paper provides an estimate of cost per DALY averted that reflects health opportunity costs in the Chinese healthcare system by considering the elasticity of health outcomes with respect to health expenditure, estimated using variations between provinces in 2017 controlling for a range of other factors and using an instrumental variable approach to account for endogeneity. The estimated elasticity is used to calculate the cost per DALY of variations in Chinese health expenditure at the margin. Our estimate 37,466 (2017 RMB) or 63% of GDP per capita (5,540 2017 USD) shows that a cost per DALY averted cost-effectiveness threshold that reflects health opportunity costs would be below 1x GDP per capita, suggesting that decisions made on the basis of the currently used 3x GDP per capita threshold risk resulting in net losses in overall population health.

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Table 1. Variables and their definition and source

Variable name	Definition	Source
DALY	DALYS per 100,000 people	Zhou et al (2019) [26]
U5 mortality	Under age 5 mortality, i.e., the number of deaths by age 5 given being born per 1,000 people	Zhou et al (2019) [26]
Adult mortality	The number of deaths by age 60 given alive at age 15 per 1,000 people	Zhou et al (2019) [26]
hcepc	Health expenditure per capita (RMB)	China Health Statistical Yearbook 2018 [46]
population	Size of population (in 10,000)	China Statistical Yearbook 2018 [37]
u14	The number of people under age 14 per 100 people	China Health Statistical Yearbook 2018 [46]
a65	The number of people over age 65 per 100 people	China Health Statistical Yearbook 2018 [46]
male	The number of males in the population per 100 people	China Statistical Yearbook 2018 [37]
urban	The number of people living in urban areas per 100 people	China Statistical Yearbook 2018 [37]
edu	The number of people with at least high school education level per 100 people	Education Statistics Yearbook of China 2017 [47]
gdppc	GDP per capita (RMB)	China Statistical Yearbook 2018 [37]
toilets	Penetration rate of sanitary toilets, i.e., the accumulated number of sanitary toilets divided by the total number of households in rural area (X100)	China Health Statistical Yearbook 2018 [46]
gov	Government efficiency index, measuring efficiency of public service and social security. The former includes the degree of marketisation, the number of service facilities in urban communities, traffic accidents, fire accidents, infrastructure. The latter includes the coverage of pension for urban workers, the coverage of basic medical insurance in urban areas, and the coverage of unemployment insurance in urban areas	Zhang (2018) [48]
highway	Highway density in terms of land area (km/100 km^2)	China Transportation and Communications Yearbook 2018 [49]
medper	The number of medical personnel per 10,000 people	China Health Statistical Yearbook 2018 [46] and & China Statistical Yearbook 2018 [37]
insurfee	Average premier fees for Basic Medical Insurance (for all insured people)	China Statistical Yearbook 2018 [37]
east	East region: Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, Hainan	
central	Central region: Heilongjiang, Jilin, Shanxi, Anhui, Jiangxi, Henan, Hubei, Hunan	
west	West region: Neimenggu, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang	

Note: All the variables are for the provincial-level administrative divisions in mainland China except Tibet (so the sample size is 30).

Table 2. OLS estimates: elasticity of health outcomes with respect to health expenditure

VARIABLES	(1) U5 mortality OLS	(2) Adult mortality OLS	(3) DALY OLS
hcepc	-0.448***	-0.677***	-0.271**
	[0.142]	[0.097]	[0.097]
u14			0.039
			[0.134]
a65			0.369**
			[0.162]
male	-0.602	-1.328	-0.767
	[1.992]	[1.208]	[1.415]
gov	-0.512***	0.001	-0.052
	[0.115]	[0.141]	[0.073]
toilets	-0.129	-0.052	-0.031
	[0.280]	[0.204]	[0.161]
highway	0.002	-0.112**	-0.077
	[0.079]	[0.051]	[0.047]
central	0.113	0.019	0.009
	[0.101]	[0.077]	[0.044]
west	0.468***	0.148*	0.038
	[0.139]	[0.076]	[0.059]
Constant	11.658	15.895***	15.185**
	[8.381]	[4.694]	[6.041]
Observations	30	30	30
R-squared	0.823	0.809	0.782
RESET p-value	0.947	0.602	0.392

Note:

1. All the variables are log transformed.

2. Robust standard errors are in the bracket.

3. Statistical significance: *=10%,**=5%,***=1%.

Table 3. IV OLS estimates: elasticity of under-5 mortality with respect to health expenditure

	(1)	(2)	(3)
	U5 mortality	U5 mortality	U5 mortality
	IV	IV	IV
VARIABLES	fund income	health professionals	fund income and health professionals
hcepc	-0.399**	-0.432***	-0.428***
	[0.172]	[0.113]	[0.115]
male	-0.513	-0.572	-0.527
	[1.961]	[1.958]	[1.953]
toilets	-0.147	-0.135	-0.115
	[0.290]	[0.265]	[0.252]
gov	-0.512***	-0.512***	-0.510***
	[0.117]	[0.116]	[0.116]
highway	0.003	0.002	0.008
	[0.078]	[0.079]	[0.073]
central	0.125	0.117	0.119
	[0.098]	[0.093]	[0.094]
west	0.475***	0.471***	0.481***
	[0.134]	[0.140]	[0.131]
Constant	10.981	11.430	11.091
	[8.031]	[8.117]	[7.982]
Observations	30	30	30
K-P F statistic	75.38	37.87	136.7
Endog test p-value	0.522	0.861	0.536
IVRESET test p-value	0.333	0.738	0.433
Under id test p-value	0.0117	0.0176	0.0380
Over id test p-value			0.794

Note: 1. All the variables are log transformed. 2. Robust standard errors are in the bracket. 3. Statistical significance: *=10%,**=5%,***=1%.

Table 4. IV OLS estimates: elasticity of adult mortality with respect to health expenditure

	(1)	(2)	(3)
	Adult mortality	Adult mortality	Adult mortality
	IV	IV	IV
VARIABLES	fund income	health professionals	fund income and health professionals
hcepc	-0.697***	-0.618***	-0.685***
	[0.112]	[0.152]	[0.112]
male	-1.364	-1.221	-1.387
	[1.224]	[1.316]	[1.245]
toilets	-0.045	-0.074	-0.042
	[0.204]	[0.220]	[0.207]
gov	0.001	0.001	-0.002
	[0.141]	[0.141]	[0.141]
highway	-0.112**	-0.111**	-0.105**
	[0.052]	[0.051]	[0.050]
central	0.014	0.033	0.023
	[0.079]	[0.085]	[0.080]
west	0.145*	0.156*	0.153*
	[0.076]	[0.081]	[0.077]
Constant	16.171***	15.077**	16.130***
	[4.889]	[5.498]	[5.008]
Observations	30	30	30
K-P F statistic	75.38	37.87	136.7
Endog test p-value	0.704	0.424	0.766
IVRESET test p-value	0.629	0.253	0.546
Under id test p-value	0.0117	0.0176	0.0380
Over id test p-value			0.455

Note: 1. All the variables are log transformed. 2. Robust standard errors are in the bracket. 3. Statistical significance: *=10%,**=5%,***=1%.

Table 5. IV OLS estimates: elasticity of DALY with respect to health expenditure

	(1)	(2)	(3)
	DALY	DALY	DALY
	IV	IV	IV
VARIABLES	fund income	health professionals	fund income and health professionals
hcepc	-0.280**	-0.228	-0.260**
	[0.130]	[0.152]	[0.108]
u14	0.030	0.080	0.061
	[0.172]	[0.152]	[0.137]
a65	0.363*	0.402**	0.380**
	[0.176]	[0.192]	[0.171]
male	-0.811	-0.553	-0.759
	[1.454]	[1.682]	[1.478]
toilets	-0.025	-0.061	-0.043
	[0.176]	[0.180]	[0.167]
gov	-0.053	-0.050	-0.049
	[0.074]	[0.074]	[0.073]
highway	-0.076	-0.085*	-0.082*
	[0.053]	[0.048]	[0.047]
central	0.008	0.011	0.005
	[0.043]	[0.046]	[0.042]
west	0.040	0.030	0.031
	[0.064]	[0.058]	[0.057]
Constant	15.440**	13.944*	15.030**
	[6.416]	[7.580]	[6.415]
Observations	30	30	30
K-P F statistic	30.29	13.59	43.18
Endog test p-value	0.883	0.622	0.691
IVRESET test p-value	0.474	0.549	0.431
Under id test p-value	0.0121	0.0206	0.0373
Over id test p-value			0.703

Note: 1. All the variables are log transformed. 2. Robust standard errors are in the bracket. 3. Statistical significance: *=10%,**=5%,***=1%.

Table 6. Cost per DALY averted

Data source	Global Burden of Disease		China Census	Central estimate
Elasticity	U5 and adult mortality	DALY	U5 and adult mortality	
DALYs averted	1,883,715	1,006,725	1,323,534	1,404,658
Cost per DALY averted (2017 RMB)	27,923	52,247	39,741	37,446
Cost per DALY averted (2017 USD)	4,131	7,730	5,880	5,540
% of GDP per capita	47%	88%	67%	63%

Electronic Supplementary Material

Article Title: Informing a cost-effectiveness threshold for health technology assessment in China: a marginal productivity approach

Journal name: PharmacoEconomics

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Tables and Figures

Table S1. Correlations across candidate regressors

	hcepc	u14	a65	male	edu	urban	gdp	gov	toilets	highway
hcepc	1.000									
u14	-0.603***	1.000								
a65	0.196	-0.599***	1.000							
male	-0.081	0.128	-0.356*	1.000						
edu	0.802***	-0.702***	0.292	-0.100	1.000					
urban	0.800***	-0.744***	0.394**	0.047	0.863***	1.000				
gdp	0.794***	-0.595***	0.381**	0.046	0.777***	0.928***	1.000			
gov	0.065	-0.072	0.313*	-0.079	0.026	0.211	0.387**	1.000		
toilets	0.363**	-0.261	0.222	0.401*	0.349*	0.513**	0.553**	0.294	1.000	
highway	0.101	-0.203	0.539***	0.154	0.273	0.432**	0.463**	0.437**	0.332*	1.000

Note:

1. All the variables are log transformed
2. Statistical significance: *=10%,**=5%,***=1%

Table S2. Pooled OLS estimates: elasticity of health outcomes (two mortality rates) with respect to health expenditure

VARIABLES	(1) U5 mortality Pooled OLS	(2) Adult mortality Pooled OLS
hcepc	-0.460***	-0.637***
	[0.115]	[0.078]
male	-0.298	-1.411***
	[1.255]	[0.438]
toilets	0.010	-0.170
	[0.226]	[0.132]
gov	-0.507***	0.002
	[0.105]	[0.122]
Highway	-0.029	-0.137***
	[0.075]	[0.042]
Central	0.136	-0.003
	[0.090]	[0.055]
West	0.475***	0.068
	[0.124]	[0.057]
year2012	0.051**	0.095***
	[0.020]	[0.014]
year2013	0.106***	0.171***
	[0.037]	[0.028]
year2014	0.155***	0.234***
	[0.051]	[0.038]
year2015	0.217***	0.315***
	[0.066]	[0.049]
year2016	0.255***	0.393***
	[0.086]	[0.060]
year2017	0.259**	0.445***
	[0.100]	[0.069]
Constant	9.801*	16.102***
	[5.387]	[1.980]
Observations	210	210
R-squared	0.827	0.837
RESET p-value	0.117	0.189

Note:

1. All the variables are log transformed.
2. Robust standard errors are in the bracket.
3. Statistical significance: *=10%,**=5%,***=1%

Table S3. IV pooled OLS estimates: elasticity of under age 5 mortality with respect to health expenditure

	(1)	(2)	(3)
	U5 mortality	U5 mortality	U5 mortality
	IV	IV	IV
VARIABLES	fund income	health professionals	fund income and health professionals
hcepc	-0.399**	-0.450***	-0.440***
	[0.149]	[0.113]	[0.111]
male	-0.206	-0.282	-0.402
	[1.313]	[1.261]	[1.231]
toilets	-0.014	0.006	0.001
	[0.229]	[0.223]	[0.224]
gov	-0.506***	-0.507***	-0.515***
	[0.109]	[0.105]	[0.105]
highway	-0.026	-0.029	-0.031
	[0.075]	[0.074]	[0.074]
central	0.151	0.139	0.130
	[0.102]	[0.088]	[0.087]
west	0.485***	0.477***	0.459***
	[0.134]	[0.125]	[0.119]
year2012	0.043	0.050**	0.049**
	[0.025]	[0.020]	[0.021]
year2013	0.090*	0.103***	0.102***
	[0.048]	[0.036]	[0.036]
year2014	0.132**	0.151***	0.149***
	[0.064]	[0.049]	[0.050]
year2015	0.188**	0.212***	0.210***
	[0.085]	[0.063]	[0.064]
year2016	0.218*	0.249***	0.245***
	[0.108]	[0.085]	[0.086]
year2017	0.216*	0.252**	0.250**
	[0.127]	[0.096]	[0.097]
Constant	9.051	9.673*	10.158*
	[5.913]	[5.434]	[5.319]
Observations	210	210	210
K-P F statistic	16.39	63.81	67.28
Endog test p-value	0.490	0.876	0.610
IVRESET test p-value	0.853	0.672	0.905
Under id test p-value	0.0425	0.0139	0.0428
Over id test p-value			0.640

Note:

1. All the variables are log transformed.
2. Robust standard errors are in the bracket.
3. Statistical significance: *=10%,**=5%,***=1%

Table S4. IV pooled OLS estimates: elasticity of adult mortality with respect to health expenditure

	(1)	(2)	(3)
	Adult mortality	Adult mortality	Adult mortality
	IV	IV	IV
VARIABLES	fund income	health professionals	fund income and health professionals
hcepc	-0.654***	-0.594***	-0.629***
	[0.103]	[0.106]	[0.096]
male	-1.437***	-1.347***	-1.425***
	[0.455]	[0.483]	[0.468]
toilets	-0.163	-0.186	-0.171
	[0.139]	[0.144]	[0.140]
gov	0.001	0.003	0.006
	[0.122]	[0.122]	[0.122]
highway	-0.138***	-0.134***	-0.134***
	[0.041]	[0.042]	[0.042]
central	-0.007	0.008	0.000
	[0.057]	[0.060]	[0.058]
west	0.065	0.075	0.064
	[0.053]	[0.060]	[0.057]
year2012	0.097***	0.088***	0.092***
	[0.018]	[0.017]	[0.016]
year2013	0.176***	0.159***	0.167***
	[0.034]	[0.033]	[0.032]
year2014	0.240***	0.218***	0.230***
	[0.045]	[0.045]	[0.043]
year2015	0.324***	0.295***	0.310***
	[0.059]	[0.059]	[0.055]
year2016	0.403***	0.367***	0.386***
	[0.073]	[0.073]	[0.069]
year2017	0.458***	0.415***	0.438***
	[0.084]	[0.084]	[0.079]
Constant	16.313***	15.578***	16.066***
	[2.163]	[2.347]	[2.230]
Observations	210	210	210
K-P F statistic	16.39	63.81	67.28
Endog test p-value	0.769	0.454	0.755
IVRESET test p-value	0.270	0.736	0.664
Under id test p-value	0.0425	0.0139	0.0428
Over id test p-value			0.438

Note:

1. All the variables are log transformed.
2. Robust standard errors are in the bracket.
3. Statistical significance: *=10%,**=5%,***=1%