

## Economic consequences of better health (BMJ 2019-051258)

### Response to the editor

#### *Editors notes:*

1. *This needs to be clearer for the non-economist. Please remember when re-writing this that the BMJ's main audience are generalist healthcare physicians, not economists, so some phrasings may need to assume this. Some definitions may need spelling out at it were.*

#### Authors' response:

We have revised the manuscript to make it more accessible to BMJ's main audience of clinicians. Wherever possible we have included definitions and examples for terms that might be unfamiliar to non-economists. We also streamlined our use of economics jargon, and wherever possible, used a plain English substitute. For example, in the introduction (page 3) we included explanations for what constitute human and physical capital. See excerpt below.

#### Excerpt (from Introduction section, page 3):

Second, health promotes the accumulation of human capital (i.e. knowledge, skills, and experience) – healthier children are more likely to go to school, to learn and to develop to their full human and economic potential. Third, health promotes the accumulation of physical capital (i.e. tools of production such as buildings, machines and technology) – because greater life expectancy increases the incentives to save for retirement and these savings, in turn, will be available for investment in physical capital.

2. *In regards to the examples used, might be useful to explain in one sentence or two why they were chosen. Also order them in the chronology of the life cycle, will make it read better. I.e. birth to death.*

#### Authors' response

We included the following sentence explaining our reason for choosing these examples – “These examples were selected because they provide the strongest causal evidence yet of the link between health and future economic outcomes”.

We also reordered the examples as follows:

1. Effects of in-utero health on economic well-being in adulthood
2. Effects of child health and nutrition on economic outcomes
3. Effects of adult nutrition on productivity at work
4. Intergenerational and multigenerational effects of health on economic outcomes
5. Example of a specific medical treatment: HIV

3. *Should consider a paragraph on intergenerational benefits as well.*

We have included a section that summarizes available evidence on the intergenerational and multigenerational effects of health on economic outcomes. See excerpts below)

Excerpts (pages 6 &7)

### **Intergenerational and multigenerational effects of health on economic outcomes**

Intergenerational (e.g. from parent to children) and multi-generational (e.g. from grand-parents to grand-children) effects of health on economic outcomes have also been studied. Research in this space is relatively new, but increasing in number and quality – partly because of the growing availability of long-run data and increased sophistication of research methods. However, current evidence in support of any link is mostly associational, *not causal*. As expected, the proposed causal links between health status in one generation and economic outcomes in a future generation are complex. In separate reviews of the extant literature in economics, demography, and sociology, Janet Currie<sup>1</sup> and Alberto Palloni<sup>2</sup> conclude that early child health plays a role in the transmission of intergenerational inequalities in economic status. Plausible causal pathways run – first – from parental health status to a child’s health status, which in turn affects the child’s economic outcomes, and – second – from parental health status to parental economic outcomes, which then influences child health. While there have been few causal studies that demonstrate these pathways end-to-end, there are many that provide causal evidence for steps along the causal chain.<sup>1-4</sup>

4. *The conclusion needs to be stronger. You can assert your expert opinion here, as you have should have explained your rationale through the rest of the article so you can be stronger in your conclusions.*

### Authors’ response

We have revised our conclusion section to make it stronger and clearer to the reader what we think about the state of evidence. See excerpt below:

Excerpt (from Conclusion section, page 11):

In conclusion, there is convincing evidence on the causal effects of health on economic outcomes for a few medical domains, but for many important diseases and treatments we lack strong causal knowledge of economic effects. We see major opportunities for clinical research to contribute to filling these knowledge gaps. Clinical research could powerfully complement the existing economic literature, providing far greater precision and detail in our evidence on effects of healthcare beyond effects on health. The investments for these scientific

advances would not be very large, because past and future clinical trials and ongoing clinical cohorts could be leveraged for this research.

5. *Needs some more focus on the clinical research paragraph as well, this could do with being stronger as well. This is very important and likely of most interest to our readership.*

Authors' response

We expanded and strengthened the section on clinical research (**pages 8 – 11**). In addition, we have now included a table that describes the rationale and potential contributions for each type of study in clinical research that focuses on the economic consequences of better health (**See Table 1**). We also included potential challenges researchers should be prepared to face and examples of studies that adopted each approach.

6. *Overall the language is too dense, and needs to be more of an oversight rather than as much detail in regards to the 'jargon' or methodology of health economics.*

Authors' response

We have streamlined our use of economic jargon throughout the manuscript. Where possible, we opted for plain English language alternatives. In situations where it was necessary to use economic terms, we provided explanations and examples. **See our response to comment 1 above.**

## Reviewer(s)' Comments to Authors:

### Reviewer: 1

Name: Amrit Banstola

Job Title: Research Associate

Institution: University of the West of England

### Recommendation:

#### Comments:

*The article briefly describes the topic rather than an analysis of the topic. While some attempts have been made to present in some depth, the article is mostly descriptive. Authors have used a range of terms which will confuse readers. For example, authors have used terms such as economic consequences, economic benefit, economic outcome, economic endpoint, economic assessments, and economic return interchangeably.*

#### Authors' response

We have streamlined our use of economics jargon and where possible we include definitions to help the reader understand.

*Authors have made the introduction section unnecessary lengthy, which could be significantly reduced. The 'implications for clinical research' sections is an important part of the article but lacks reasonable argument and reasonable inferences from available information. In other words, the authors have not provided many details as needed to make a clear argument. The points and arguments are oversimplified. For example, the authors have argued that "treatment with higher economic returns should be prioritised" (page 7, line 22-24). It is not, however, clear what does economic returns means. Whatever the economic returns might be, judging the treatment based on benefit only without considering the cost involved in developing the treatment is a naive argument and largely ignore the notion of economic evaluation in healthcare.*

#### Authors' response

We thank the reviewer for this comment but we disagree that the introduction is unnecessarily lengthy. We think the length is sufficient to introduce the reader to the context, current debates, and significance of the question. We recognize that the typical BMJ reader is a clinician that would not typically be versed in the developments occurring in the non-clinical, social science literature where much of the debates have occurred to date.

We have modified the text to state "net economic returns" rather than "economic returns". **See page 4.**

*The authors have described EGMs in details but did not mention the problems, challenges and issues of EGM in clinical research. Just a general description of the EGM does not make the argument that EGM is a better method. The authors need to acknowledge the opposing view.*

Authors' response

Thanks. We have added a table that includes additional details on EGMs – details such as rationale, challenges, and examples. **See Table 1.**

*Finally, the authors have not addressed the second aim of the paper in sufficient detail i.e. "we point to a research agenda that would leverage clinical trials and routine data collection to provide, at relatively low cost, a mechanisms for expanding the range, robustness, and practical utility of the literature on the economic consequences of better health".*

Authors' response

Thanks. We have expanded and significantly updated the section on “Implications for clinical research”. **See pages 7-10.**

Other comments:

repeated text and unclear statements

**Reviewer: 2**

Name: Dr Adepoju Victor

Job Title: Project Manager

Institution: KNCV Tuberculosis Foundation

Recommendation:

Comments:

*Positive notes*

*The analysis paper is relevant to the general audience and body of researchers on economic benefits of health and treatment. The arguments are well presented in a clear, logical and coherent manner. The authors combine original ideas from multiple sources to present supporting and diametrically opposing views providing explanation for unexpected direction vis-à-vis the economic effect of specific disease and treatment which further stimulated debate and discussion for future research.*

*The 3 examples cited by the authors (HIV in sub-Saharan Africa, Spanish Flu, effect of adverse utero condition) on economic consequences of health, the suggested framework on which future researchers can explore for economic evaluation of disease and treatment and the proposed low cost approach integrating research agenda into clinical trial and routine data collection are all noteworthy. The paper is also written in sound academic language. The authors have adhered to the available guidance for articles in the analysis section: length, presentation, evidence base, contributors and sources, boxes/tables/figs, references, key message boxes*

*Please find my comments below:*

*The authors have made a case for new approach that evaluates the economic benefits of specific disease and its treatment. While this approach is promising, I am particularly worried about the omission of patient groups with co-morbidities and what would be the additive or possibly interactive effect of such multi-morbidities (e.g. HIV and Tuberculosis, HIV and diabetes, eating disorders (ED) and schizophrenia etc) on economic benefits (employment, earnings, labor productivity etc) in the long run. For instance, Samnaliev and colleagues found that individuals with eating disorders (in employment) have lower (though not significant) earnings (\$2093,  $p = 0.48$ ), compared to individuals without ED. The authors further noted that among individuals with eating disorders, the presence of mental health co morbidities was associated with lower borderline significant odds of employment (OR = 0.41, 95% CIs [0.14, 1.20]), and significantly lower earnings (\$19,374,  $p < 0.01$ ).*

Authors' response

We thank the reviewer for this comment and for drawing our attention to the potential effects of comorbidities. In our paper, whenever possible, we chose to highlight *causal* evidence over associational evidence. We did not find any studies that provided causal evidence in support of the effect of comorbidities on economic outcomes. The paper recommended by the reviewer explores statistical associations using the U.S. Medical Expenditures Panel Survey and the effect sizes were either not significant or borderline significant. We agree that it is important but do not think it adds much to our study.

*From the foregoing article, it will be interesting to see how the authors factor in the additional morbidity and the interactive effect in the analysis and the modification of the proposed framework.*

Authors' response

Again, we thank the reviewer for highlighting the issue of comorbidities, but we did not find any causal evidence in support of a link between comorbidities and economic outcomes.

*In addition, it will be good to differentiate/stratify the economic benefits of disease and treatment via-a-vis labor productivity and earnings in light of type of employment (executive/professional jobs, manual labor, business etc). We do know that higher-ordered cognitive functioning is a proxy to educational attainment hence employment at executive level. Diseases with neurocognitive sequel suffered in childhood may result in lower earnings in the long-run not necessarily because of physical disability but the neurological deficits which affect higher mental functioning and learning of such individual*

Authors' response

Thanks. We agree with the reviewer's premise but we did not find any causal evidence to support heterogeneity of the effect of health on economic outcomes across professional categories.

*With this inputs, I think the authors have done justice to the topic and the topic is useful for general readership and research audience, policy makers and also Ministries of Health and Education departments.*

Authors' response

We thank the reviewer for the comments and suggestions for improvement.

**Reviewer: 3**

Name: Yuchen Ding

Job Title: Manager, Health Economics and Outcomes Research

Institution: Novo Nordisk Inc.

Recommendation:

*Comments:*

*The study argued that RCTs and clinical records should be the "new venue" to yield evidence supporting a casual link between health and economic consequences. This topic is important and relevant to the general readers, since there is a lack of studies establishing casual relationships between health and economic outcomes.*

*Authors laid a good foundation in the background/introduction section through a comprehensive review of the prior literature on the conceptual pathways between health and economic consequences, and three examples illustrating that conflicting results may arise due to a lack of studies examining causal relationship between health and economic outcomes. Authors then proposed two solutions in the research agenda to address the aforementioned issue, however the first solution is conducting systematic literature reviews and creating evidence gap maps, which seems unrelated to the goal of getting insights on economic consequences of health using clinical data and deviating from the rest of the manuscript. The second solution is measuring economic outcomes in existing clinical trials and cohorts.*

*In terms of economic outcomes, authors gave examples such as cognitive development, educational attainment, and social functioning, which would be considered indirectly related to economic outcomes but not economic outcomes themselves. Authors need to expand their augment by including what would be considered traditional economic outcomes (i.e. direct and indirect costs), or clarify when they shouldn't be included if authors have a specific reason not to.*

Authors' response

We thank the reviewer for these comments and suggestions. In addition to cognitive development and educational attainment, our analysis also included economic outcomes like employment, earnings, and productivity.

*Moreover, I don't believe author's reasoning around IV. Authors stated that treatment is an IV for disease which means treatment can only be correlated with economic outcomes through its effect on disease per IV theory. However, this is not true, since receiving treatment or control in an RCT will not affect whether the participant has disease or not. Participants usually included in an RCT should already have the disease in the first place.*

Authors' response

Thanks. To make our point clearer, we have changed the phrase from disease occurrence and intensity to "disease persistence and intensity". Although the reviewer is correct that participants usually included in an RCT would already have the disease in the first place, it does not negate



the fact that treatment can be an IV for disease regardless of the history of disease onset. Conditional on having the disease in the first place, the only pathway for treatment to have an effect on long-term economic outcomes is through its effect on reducing the *duration* or *severity* of the disease. See excerpt below

Excerpt (from section on “Implications for clinical research” page 9)

Second, it enables the estimation of the economic effects of the disease that the treatment affects. This opportunity arises if the treatment changes the disease duration or intensity. In this case, the random variation in disease duration or intensity induced by the randomly assigned treatment could be used to estimate the causal effects of the disease on economic outcomes using instrumental-variable (IV) analyses. This approach requires that the standard assumptions of IV analyses are met, in particular the so-called exclusion restriction – the treatment may only affect the outcome through its effects on disease duration or intensity.<sup>5 6</sup> In many trials, this assumption will likely be met, e.g., in trials that randomly assign people to different medicines with few or similar side effects. may only affect the outcome through its effects on disease persistence or intensity.<sup>5 6</sup>

*In addition, it is not clear how authors propose to add economic assessments to existing or historic clinical cohort studies which were initiated many years ago. Authors may need to provide more information on this.*

Authors’ response

We have added text (**See pages 10-11**) and a table (**See Table 1**) which includes the rationale and potential contributions of adding economic assessments to existing studies, we also include potential challenges, and an example of a study that adopted that approach.

*Furthermore, authors did not acknowledge or discuss the potential opposing view, such as the challenges associated with including economic outcomes in RCTs and clinical cohorts, which left authors' claim that these investments will not be very large unfounded. In conclusion, I would suggest this manuscript to be accepted after major revisions.*

Authors’ response

We have included a table that addresses some of the challenges associated with including economic outcomes in RCTs (**See Table 1**). We list challenges such as cost, need for additional technical expertise, etc.

**Reviewer: 4**

Name: Aleksandra Jakubowski  
Job Title: Postdoctoral Fellow  
Institution: Stanford University

Recommendation:

*Comments:*

*This paper offers a good summary of existing literature about the economic consequences of improved health. The paper is well written, arguments are presented clearly, and the sub-sections with headings help reader follow along. The boxes are also helpful.*

*Below are a few questions and comments for the authors:*

- 1. HIV section (pg. 5) – Wagner et al used quasi-experimental design to evaluate impact of increased access to ART on employment in Africa. Consider including: [https://urldefense.proofpoint.com/v2/url?u=https-3A\\_www.healthaffairs.org\\_doi\\_full\\_10.1377\\_hlthaff.2014.1006&d=DwIFaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj\\_gZ4adc&r=b\\_2J4\\_4yD0J\\_ZvathxNblNFbz\\_sul2KMe5y9C48YwUE&m=g8pA8pCkxoenjp2ZR2CC6aNgbpMSFRdlyOvEALYHS7M&s=r3E-MBWOIUDCeV9jpXwuXheZSUc4E6yACRRysFy9hco&e=](https://urldefense.proofpoint.com/v2/url?u=https-3A_www.healthaffairs.org_doi_full_10.1377_hlthaff.2014.1006&d=DwIFaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=b_2J4_4yD0J_ZvathxNblNFbz_sul2KMe5y9C48YwUE&m=g8pA8pCkxoenjp2ZR2CC6aNgbpMSFRdlyOvEALYHS7M&s=r3E-MBWOIUDCeV9jpXwuXheZSUc4E6yACRRysFy9hco&e=) See also additional research by Thirumurthy about the economic functioning of people at various stages of HIV disease.*

Authors' response

Thanks. We included evidence from Thirumurthy and colleagues on employment and education outcomes following ART initiation. We also acknowledge that Wagner and colleagues used a quasi-experimental (difference-in-difference) approach, however it used country-level macroeconomic data. Our paper focused on studies that used individual-level.

- 2. In-utero section (pg. 5-6): some of the studies mentioned are classics, but others are less known (at least to this reader). I would have liked to see another sentence added about the Chernobyl and Ramadan studies that would briefly explain the main findings (e.g. what outcomes were studied).*

Authors' response

We have included a sentence to explain the findings from the Almond et. al. 2009 Chernobyl study and another to explain the findings from Almond and Mazumder's 2011 Ramadan study. See excerpt below

Excerpt (from page 5):

Almond and co-authors have investigated other natural experiments such as the exposure to Chernobyl's radioactive fallout in Sweden or temporal variation in Ramadan observance.<sup>7 8</sup> The Chernobyl study found that children exposed to radiation fallout performed worse than others in mathematics.<sup>7</sup> The Ramadan

study showed that children whose mothers observed the Ramadan fast during their pregnancy exhibited higher rates of learning disabilities.<sup>8</sup> Their results consistently confirm the hypothesis that adverse in utero conditions negatively affect adult economic outcomes.

3. *Economic effects of adult malnutrition (pg. 6) – What about the flip side of malnutrition? More and more adults around the world are eating unhealthy diets that are leading to obesity, hypertension, diabetes. What is the evidence of these conditions on productivity and economic functioning?*

Authors' response

Thanks. We have included text to explain the available evidence of a causal link between obesity and malnutrition. See excerpt below.

Excerpt (from page 6):

By contrast, there is no causal evidence that obesity – which lies at the opposite end of the spectrum of nutrition disorders – has an effect on long term economic outcomes. Several studies show statistical associations between obesity and decreased worker productivity, and earning potential,<sup>9 10</sup> but no study has as yet provided evidence of a causal link.

4. *Implications for clinical research: In several places the authors discuss that any changes in economic functioning may be lagged and that evaluation of long-run economic effects is needed. I couldn't agree more. Yet I was surprised that a stronger case for examining long-term consequences of disease on economic functioning was not made. Do the authors think that doing economic follow-ups to existing trials could be of value? What do the authors recommend in terms of the length of follow-up needed to make valid economic assessments?*

Authors' response

Thanks. We have a third recommendation to revisit old clinical trials where interventions were randomly assigned in order to assess economic outcomes. See excerpt below.

Excerpt (from pages 10-11)

A third step in the clinical research agenda on economic consequences of specific treatments is to exploit *previous* clinical RCTs. In this approach, cohorts of individuals that participated in RCTs that were concluded years (or decades) ago are traced and an assessment of their economic outcomes is conducted. This allows sufficient time for the manifestation of any long-term economic consequences that the treatment might have on the individuals who were previously randomly assigned to receive (or not receive) an intervention. A perfect example of this is the follow-up study in Guatemala to assess the

economic outcomes of adults (aged 25 to 42 years) who had received a nutritional intervention in an RCT conducted when they were children (aged 0 to 7 years).<sup>11</sup> The study found 46% higher wages, on average, in adults that received the nutrition intervention as children compared to those that did not get the intervention. Due to the long intervals between the original and follow-on studies, a potentially significant challenge with this approach is the difficulty in tracing all individuals who participated in the original study – for context, the Guatemalan study was able to reach 1,424 (60%) of the 2,392 individuals who participated in the original study. Nevertheless, this approach holds promise to generate powerful evidence to fill current gaps in the literature.

5. *In general, a discussion of multigenerational effects was missing from the piece. What do we know about the impact of improved adult health status on child schooling outcomes? More healthy and productive adults could translate to fewer children needing to care for ill individuals or substitute for lost labor. Improved life expectancies and subjective expectations could change the calculus for making human capital investments (longer horizons = more time for returns of investments). The multigenerational effects should not be overlooked.*

Authors' response

We have included a section on intergenerational and multigenerational effects of health on economic outcomes. **See pages 6-7.**

6. *Could the authors add a discussion of longer life expectancies affecting human capital investments? (Becker and Ben-Porath for theory; Delavande, Fortson, Jayachandran, Thirumurthy, Soares, Hurd etc. for empirical evidence)*

Authors' response

We thank the reviewer for this discussion. We agree that this body of work is important, but since the focus of our analysis is on person-level microeconomic data (not country-level, aggregated estimates), we decided not to include.

## Reviewer: 5

Name: Carlo Marra

Job Title: Professor and Dean

Institution: University of Otago

Recommendation:

*Comments:*

*I really enjoyed reading this paper. A couple of minor points:*

- 1. I think more description about the nuts and bolts of regression threshold analysis and instrumental variable analyses needs to be include (1-2 sentences) as some readers may not be familiar with the techniques.*

### Authors' response

We have included a brief explanation in the text and linked to relevant literature to provide detailed explanations for an interested reader.

### Excerpts (from pages 9-10)

Second, it enables the estimation of the economic effects of the disease that the treatment affects. This opportunity arises if the treatment changes the disease duration or intensity. In this case, the random variation in disease duration or intensity induced by the randomly assigned treatment could be used to estimate the causal effects of the disease on economic outcomes using instrumental-variable (IV) analyses. This approaches requires that the standard assumptions of IV analyses are met, in particular the so-called exclusion restriction – the treatment may only affect the outcome through its effects on disease duration or intensity.<sup>5 6</sup> In many trials, this assumption will likely be met, e.g., in trials that randomly assign people to different medicines with few or similar side effects.

Adding economic outcome assessments to clinical cohorts will enable the estimation of the economic effects of diseases and routine healthcare through quasi-experimental analysis. One strong quasi-experimental approach to analyzing clinical cohort data is regression discontinuity,<sup>12</sup> which exploits the fact that clinical medicine assigns many treatments by applying a threshold to continuously measured indicators, such as systolic blood pressure, low-density lipoprotein cholesterol or haemoglobin A1C.<sup>13</sup> In a small neighborhood around this threshold, regression discontinuity designs quasi-randomly assign individuals to treatment versus control conditions, because measurement error introduces randomness into the threshold-based assignment. As a result, regression discontinuity designs allow control of all unobservable confounders, similar to randomized controlled trials.<sup>14</sup>

Another quasi-experimental approach for clinical cohort studies is fixed-effects analysis, comparing individuals to themselves in different treatment states over time.<sup>15</sup> These analyses can remove confounding from two large categories of

unobservable variables, which strengthens the estimation of causal effects of diseases and treatments on economic outcomes.<sup>16</sup> Individual fixed effects allow control of all unobservable confounders that are constant over time; time fixed effects allow control of all unobservable confounders that are constant across all individuals.

2. *Adding economic outcomes to some clinical trials might be very expensive especially if long term followup is necessary. The effort and expense of maintaining the cohorts and preventing attrition need to be considered.*

Authors' response:

Thanks. We acknowledge these factors as limitations and list them as potential challenges for researchers to prepare for. **See Table 1** in manuscript and the section on “Implications for clinical research”.

*Minor point:*

1. *Extra "th" in Box 3*

## Reviewer: 6

Name: Nathorn Chaiyakunapruk

Job Title: Professor

Institution: University of Utah

Recommendation:

### Comments:

*The authors highlight the importance of the measurement economic consequences of diseases and treatment. The article is quite general. I did not clearly see the additional benefits of this work to existing knowledge on this issue.*

## References

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