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Title	Does research pay? Estimating the payoffs from cardiovascular disease research in Canada
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Reviewer 1	Chambers, JD
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General comments	Overall comments I genuinely enjoyed reading this study. It is an admirable attempt to estimate returns on medical research for CVD. While a hugely complex task I believe that the authors have done a good job at stating the study limitations and presenting their assumptions. Comparison with the Buxton paper strengthens this paper and leads to intriguing findings. The paper is timely given the challenge on funding medical research in the current economic climate and I hope that it stimulates some debate. I have a few comments and suggestions. Major/overarching comments While the reason for selecting CVD as the focus of this study is made clear in the 'Introduction' and 'Interpretation' sections, it seems a particularly complex disease area. As the authors state in the 'Limitations' section, CVD risk factors such as smoking, obesity, diabetes, etc, are likely to have a huge effect on outcomes associated with CVD. Could it be that, if decreasing returns to scale are evident in CVD treatments, that investment in reducing these risk factors provides the greatest opportunity for health gains in CVD? Abstract While the focus of the paper was to estimate the return on public/charitable-funded cardiovascular disease (CVD) I think it worthwhile to note in the abstract that estimates were also calculated for private investment. In the results section I would round the estimate of QALY gain to 2.2 million – it seems overly precise to report the exact figure. Introduction The authors state that the governments are becoming increasingly frugal. It is maybe worth adding a sentence to suggest why this is the case. Determining the return on investment is stated as "one way to ascertain the overall impact on research". What other approaches could be used? Why was this method chosen? I think this requires a little explanation. Methods The technical appendix was very useful. I think the paper would be improved if a little more explanation of the approach used was included in the main methods section. Without also reading the technical appendix the study is very difficult to follow and I think including some additional information in the main methods section would be helpful. Why did the time period of his study end in 2005? Was this year chosen for convenience or was the necessary data only available up to this point? I think it necessary to justify the time period considered. The consideration of private sector investment is important and should be accounted for in the abstract. The authors state that they performed a systematic review of the literature to obtain estimates of the QALYs gained for each intervention and the corresponding lifetime costs. While not necessary to provide complete details regarding the search, some indication of the search terms used, time period considered, etc would be useful. I note that additional information is provided in the appendix but I believe a little more detail in the body of the paper is warranted. The choice of $50,000 as a value of a QALY is justifiable but I think that its choice warrants more discussion. It seems that this valuation is integral to the study findings and some justification of this value is required. I know of one Canadian study (Rocchi et al. Value in Health 2008) that uses the $50,000 value and maybe that can be cited here. I do think it necessary to emphasize that while the $50,000 figure is accepted as a valid benchmark by health economics it is essentially arbitrary. I think that the sensitivity analysis varying this figure is useful and helps the paper. I like the "Link between Canadian CVD and health gains" section. While various assumptions were necessary for this study I think the authors do a reasonable job at laying them out clearly for the reader. The "Internal Rate of Return" section is clear and the authors justify the choice of a 12% rate. It would, however, be useful to include a citation here.

	It would be useful for the reader to include the values used in the "baseline analysis" in the "Sensitivity Analyses" section. Results In the "Health gains and costs associated with new CVD treatments" section, it would be useful to present the ICERs for the interventions for heart transplant and CABG surgery. This would allow the reader to better interpret the statement "…were among the interventions with the smallest net health gains". Interpretation I like the "Interpretation" section – It is clear and illustrates the value of the research. I do think, though, that a little more explanation is required for the final sentence, i.e., "In tandem, funds should be……". Readers will likely consider at this point how investment in obesity and diabetes has affected the results presented in this paper. Contributions Again, I like this section and think it touches on all the major points. Conclusion I would rewrite the last sentence. I think this research helps, along with the Buxton paper, to set forth an important research agenda. Considering this question from a global perspective would be very interesting and have consequences for innovation, drug prices, etc. While it certainly provides an "opportunity to collaborate" I think this somewhat underplays the potential benefits of this research agenda.
Reviewer 2	Raftery, JP
Institution	
General comments	This is an interesting attempt which relies heavily on assumptions which are neither justified not fully acknowledged as limitations in the text. If it is to be published major revisions are needed. The funder, CIHR may have been happy with the report but it could be seen as having a vested interest. The methods are opaque and would benefit from a table or a schema. The main assumptions are * that Canada's contribution to global research in cardiovascular (CVD) medicine can be measured in bibliographic references or patents. This is put at 6% for all CVD. A breakdown by intervention would be more useful - it seems unlikely that the Canadian contribution was 6% for all 47 interventions included. Smoking cessation is the biggest source of QALYs, followed by hypertension control - what was Canada's contribution to the research effort in these? Is 6% plausible? How does it compare with other work? Did other similar studies use different figures? * the public/privately funded research interface is unclear - although some figures are quoted for privately funded CVD research they are not used. Some interventions such as drugs seem more likely to be due to privately funded research, others such as smoking cessation to publicly funded research. Leaving out the privately funded sector implies assumptions which are not stated - they should be. * the way in which the health gains, QALYs were derived is unclear. We are told early in the paper that the vehicle is the modified Ontario impact model (wrongly referenced as 7 in the text. Reference 7 is the only possible CVD impact model but that is not specific to Ontario) but later is seems to be from a literature search. The literature search in turn relies almost entirely on NICE technology appraisals but also on some other published studies. One would need to know the extent to which these estimates were based on single trials or on systematic reviews. The paper does not note that these are all hypothetical gains, based on clinical trials (one or a group) and highly unlikely to be so large in practice. The method seems to be that all gains from interventions with incremental cost per QALY of less that $50k can be counted in financial terms. If so, this makes the $50k threshold a key assumption. It should be made clearer if this is what is happening. * the health/society boundary also involves major assumptions. In particular the decline in CVD mortality is assumed to be due 70% to health research, which seems to be based on a publication by Bunker which was more qualitative than quantitative. 70% is high given the other figures quoted but no justification is provided.

	The paper is unclear about key terms. 47 'interventions' are mentioned but not defined. 19 of these seem to be the same drug used in different populations. 9 'mutually exclusive treatments' are mentioned - these seem to be disease subsets within CVD. These idiosyncratic terms need to be defined and justified. The text claims to have derived QALYs gained and corresponding 'marginal life time costs'. I dont think this latter part is true - unless all the economic evaluations used life time frames, which seems unlikely. The costs need to be linked to a specific year - they seem to be in 2005 values but this is not stated. It must be. A discussion of the limitations is needed in place of the current few lines and a section is needed on the research implications of the work. Finally the references are inaccurate, so that the reader has to search. The work appears to be an update and application to Canada of work by Buxton et which is reference 6 in the text but reference 5 in the list. Many other references are wrongly numbered.
Author response	The objective of our analysis was to measure the return on public/charitable research investments in CDV; therefore, we have excluded private investments from our analysis to avoid confusion, thus addressing some of the reviewers' comments (private research expenditures were included in our sensitivity analysis only). The Ontario IMPACT model, a fundamental component of our analysis, examined the changes in CVD from 1994 to 2005, making this last year a natural end point for our analysis. Thus, all expenditures are in 2005 dollars, which we have clearly stated in the revised manuscript. In the Methods section, we have included a bit more explanation of our approach, as suggested, and provided the definition of the 47 'interventions' mentioned in our manuscript (these can be found in the Appendix). We have also clarified that QALYs were obtained from a literature search (which we provide further details on) and not the IMPACT model. We have also clearly stated that the cost per QALY ($50,000) is a key assumption in our analysis, while emphasizing that this value is accepted as valid benchmark in the field and commonly used in Canada and the US. We have also provided additional information on our main assumptions. We assumed that Canada's contribution to global research in CVD can be measured by bibliographic references or patents and that this value is 6% for all CVD categories. The reviewer's comments regarding this assumption have been explained (and thus addressed) in a companion paper that was recently published in the Canadian Journal of Cardiology. We have made reference to this paper in our revised version. In addition, we assumed that 70% of the decline in CVD mortality is due to health research; this value was criticised by one of the reviewers who found it to be too high and based on only one publication. Unfortunately, there is not much literature on the topic, which made it difficult to reach a plausible result. We selected a value based on a study from Bunker (2001), which found that 44% to 68% of the variation in Canadians' health outcomes is due medical research. We rounded 68% up to 70%; however, we can recalculate our results using 68% if necessary. While not devoid of criticism, our chosen parameter is a clear improvement over previous work (Buxton et al.), which assumed this value to be 100%. We measured the return on investment using the internal rate of return (IRR); however, there are other approaches to ascertain the overall impact of research. We have provided a brief description of those alterative methods as well as the rationale for choosing the IRR, as suggested. Furthermore, we have provided a citation for using an IRR of 12% as minimum rate of acceptability. All other comments were relatively minor (for example, changes in wording or the addition of sentences to strengthen the argument) and have been addressed in the attached revised manuscript. We have also expanded the limitations section to address the reviewers' comments; in addition, we have also included a section on the research implications of our work. Finally, all references have been checked and corrected.