See page 11 and 12 for the relevant highlighted text

SP5 – Pre-publication history for Abramson et al

Decision Letter (BMJ.2013.013300)

From: hmacdonald@bmj.com

To: johnabramsonmd@gmail.com

CC: johnabramsonmd@gmail.com, hrosenbe@yorku.ca, jmwright@interchange.ubc.ca

BCC:

Subject: BMJ - Decision on Manuscript ID BMJ.2013.013300

Body: 09-Aug-2013

Dear Dr. Abramson

BMJ.2013.013300 entitled "Should people at low risk of cardiovascular disease take a statin?"

Thank you for sending us your article, which we read with interest. Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

The reviewers' comments are at the end of this letter,a s are ours.

Please don't hesitate to contact me if you wish to discuss this further.

When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Once you have revised your manuscript, go to http://mc.manuscriptcentral.com/bmj and login to your Author Center. Click on "Manuscripts with Decisions," and then click on "Create a Resubmission" located next to the manuscript number. Then, follow the steps for resubmitting your manuscript.

You may also click the below link to start the resbumission process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

http://mc.manuscriptcentral.com/bmj?URL_MASK=4SH6THK9XsFh7X5JNCGb

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

I hope you will find the comments useful.

Yours sincerely

Helen Macdonald
hmacdonald@bmj.com

IMPORTANT INFORMATION TO INCLUDE IN A RESUBMISSION

Instead of returning a signed licence or competing interest form, we require all

authors to insert the following statements into the text version of their manuscript:

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Please see our policy and the unified Competing Interests form http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests. Please state any competing interests if they exist, or make a no competing interests declaration.

Editors comments to authors:

We were all agreed that there was something in this article. Although we would have liked to accept this, we did not think it was quite clear enough to provisionally do so, because there were some fundamental facts that needed clarifying. But if you are able to make some significant changes to convince us, improve the presentation and work with us on this, I think it is likely (although could not promise) that this could work.

1) The peg/topical angle needs to be clearer. I would start with the new guidance and what happened in 2013. And then fill immediately afterwards with the 2011 background.

2) Which people are we talking about? You repeatedly refer to low risk people or low percentage risks, but let's have a more tangible picture of who they are. In reality they are probably not just the patients but many of middle aged doctors who might be reading an article like this! I appreciate you can't define low risk comprehensively but give us some examples, some typical people who are low risk. Playing around with QRISK for example you are really talking about the under 50s. The biggest factor here isn't smoking/obesity/various other co-morbidities, it's predominantly age. I found it difficult to create a low risk person on QRISK that had a major co-morbidity. My sense is that a fuller description of who we are talking about here would strengthen your argument.

3) It is always difficult with analysis articles based on research/guidelines critique to separate out criticism of studies which feel slightly hair splitting, and might be best directed to the journal that published the paper/organisation that created the guidelines, from those articles that address wider and broader issues - this seemed wider and broader which sparked our interest. However, one of the reviewers did raise a number valid criticisms and wondered whether this should be seem by a statistician. This is not an approach we usually take with analysis articles, however with that safeguard removed, I would like you to reflect on what claims are made and be confident that they are justified and couched in appropriate language. And I would encourage you to write this and make the case to your critiques rather than those are likely to agree with you ie acknowledge what weaknesses there are with you own approach and interpretation as well as with the study and guidance you dissect.

4) In the first Cochrane review. What co-morbidities were they worried about. In low risk people there must be virtually none by definition??

5) The updtaeed Cochrane review 2013 talks about a different time frame ie 1y <1%. Why a different unit of time (everything else is ten year window)?

6) Who are cholesterol treatment trialists. Who are they? Are they just a group that got together to MA?

7) We don't get a sense of why the MA was needed? How the MA results compared to the clinical trials. What statistical/clinical uncertainty was there? What was the main RQ that the original trials answered?? Were low risk people in them? Why individual patient level data? Did they do a systematic review or was it just a pooled analysis of some kind, and why? Can they insert the absolute benefits as well as the relative risk reduction?

8) How was this odd group delineated? Was a a predefinaed analysis or a subgroup effect "those with 5-year CV risk < 10%, whose average 5-year risk is 2.6%". Or is this the main analysis and you creating a new group??

9) What heterogeneity and publication bias was tested for in the MA? Any comments on this?

10) There seems to be an issue about the time of follow up. You are pointing to the fact that only a small number of the trials had long term follow up. Be clear about what time frame the original trials ran over. On the issue of follow up we were not fully clear what you were trying to say here? That the data are unreliable?

11) On serious adverse events you say HPS and ALLHAT did not report SAEs. Do you mean there were none reported, or simply that they did not comment on it?

12) Concordance/compliance cropped up in our discussions. It popped into one of the editor's minds that compliance at a year with statins at a year was poor. Although this does not directly relate to the point that you are making it does seem relevant to whether the recommendation that they should be prescribed is "worth it" at a system level. I'm sorry we were unable to recall the reference for this fact! But perhaps as experts in the area you are more familiar with it.

13) Unless we missed it, you don't reference the CTTC meta-analysis http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60367-5/abstract

14) The paragraph on the pathological findings in statin-induced myopathy seems unnecessary thorough

15) Finally this feels slightly clunky in its presentation at present, if the detail of this can be fixed I can certainly help with this. Something that occurs to me that might help is a visual aid. Perhaps a timeline showing the trials their RQ, primary outcome and clearly labelled secondary/subgroup outcome about low risk people if they were not the focus, the guidelines could be on there too with the key sentence about what to give low risk people, and the meta-analysis, and any other event/publication of note. Aside from a timeline, I think a fact box to share with patients would also help.

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
BMJ 013300
This is an interesting and well argued piece.

I do have some major concerns.

1. Most of the data presented to support the arguments come from the Cholesterol Treatment Trialists. However, often imprecise estimates are made based on published reports. One example is the data in the table that are essentially estimates based on various assumptions. Another is the statement

that around 40% of the major vascular events in the CTT meta-analysis were revascularisations (page 5 line 28).

It is not made clear whether the authors requested the exact data they required from the CCT. Perhaps, if the CTT refuse then the estimates might be justified, but this needs to be clearly documented.

2. The results presented for myopathy are misleading. NHANES focused on ascertaining symptoms from people exposed to statins. Muscle pain is incredibly common in the general population and is thus incredibly common among people both treated and not treated with statins. In the randomised Heart Protection Study, almost one third of people in both arms (i.e. including the placebo arm) complained of muscle pain and the effect estimate was 0.99 (95% CI 0.95 to 1.03). Serious rhabdomyolysis was rare: 5 cases in the 10,269 allocated to simvastatin and 3 cases in the 10,267 allocated to placebo.

3. There seems to be a 10 fold difference in the risk ratio for diabetes comparing CTT with both observational studies and with the JUPITER trial. Some discussion of how such discrepant results could have occurred would be interesting.

Liam Smeeth LSHTM

Additional Questions:
Please enter your name: Liam Smeeth

Job Title: Professor of clinical epidemiology

Institution: LSHTM

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ Group policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
In their manuscript on statin use by persons at low risk of cardiovascular disease the authors raise an important and relevant issue. Ever since the introduction of HMGcoA-reductase inhibitors discussions on the proper indications for statin use, their cost-effectiveness in various (sub)groups of patients, the benefit-harm ratio etc. have been ongoing. The landmark paper by Wald and Law (BMJ 2003) has added to these discussions by stating that

on a population level, all people over age 55 years would benefit from a polypill, with a statin as one of the main components. The broadening of the area of indications for statins to people even at low cardiovascular risk, on the other hand, has been subject of firm debate among scientists and doctors around the world, sometimes explaining the same evidence in opposite ways. The notable twist made by the Cochrane reviewers in their 2013 update therefore is of pivotal importance and could potentially have great impact on upcoming guidelines on CV risk management worldwide, with great effects not only on health, but also on costs. The authors of the current manuscript question the underlying evidence of the Cochrane, extracted from the 2012 CTT meta-analysis. Although an obviously one-sided view on this matter, they make -to my opinion- a very reasonable case and quite an in depth overview, given the word limit and aim of the analysis-article, of all relevant aspects.
Regarding their comments on all-cause mortality I would suggest to have the Table they've reconstructed from the CTT data reviewed by a statistician as I cannot fully check the validity of the methods they used in doing so.
Their over-all conclusion that focus on facilitating transition to healthier life style habits, in stead of 'wasting time and resources' on endlessly (measuring and) discussing cholesterol numbers and statin use, very much appeals to me, especially in low risk individuals.
Opponents will certainly react with dissenting opinions, but that enhances scientific and public debate on this matter.
The authors have put together a very well written paper that deserves publication.

Wouter de Ruijter, MD PhD, general practitioner/researcher and epidemiologist
Leiden University Medical Center, Dept. of Public Health and Primary Care, Leiden, The Netherlands

Additional Questions:
Please enter your name: Wouter de Ruijter MD PhD

Job Title: senior-researcher and epidemiologist

Institution: Leiden University Medical Center, Dept. of Public Health and Primary Care

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests (please see BMJ Group policy) please declare them here:

Date Sent: 09-Aug-2013

Cover Letter: BMJ.2013.015247

Dear BMJ Editors,
We have responded to your and the peer-reviewers cogent suggestions in the uploaded document "BMJ Decision Letter 2013-09-13." We addressed each of the suggestions and questions. We have greatly reduced the confusion about risk levels at 1 year, 5 years and 10 years. However, because CTT reasonably based 5-year risk calculations on the actual frequency of events in the clinical trial control groups, there is not a direct "cross-walk" between their 5-year risk calculations and the epidemiologic-based QRISK2 and Framingham 10-year risk calculations. And we didn't want to obscure the origin of the risk data by simply converting all risks to 10-year.
After addressing the issues raised in the decision letter, the manuscript is 2135 words. If there needs to be an excision, the first thing to go would be the following 38 word paragraph:

A randomized controlled trial found that improvement in cardiorespiratory fitness over 12 weeks of exercise training was significantly attenuated in 18 overweight or obese participants treated with simvastatin 40 mg compared to 19 treated with placebo , $p<0.005$.

But this does make an important point about the potential counter-productivity of statin therapy in low-risk people.
If the 2000 word limit is firm, we can go back to work—although we would appreciate your suggestions about what might go.
Much thanks for the effort you have already put into this manuscript,
John Abramson

ecision Letter (BMJ.2013.015247)

From: hmacdonald@bmj.com

To: johnabramsonmd@gmail.com

CC: johnabramsonmd@gmail.com, hrosenbe@yorku.ca, jewell@berkeley.edu, jmwright@interchange.ubc.ca

BCC:

Subject: BMJ - Decision on Manuscript ID BMJ.2013.015247

Body: 11-Oct-2013

Dear Dr. Abramson

Thank you for letting us consider your resubmitted manuscript, which we are now happy to accept for publication as an Analysis article in the BMJ subject to a few minor changes. Thank you very much for revising it – we are very pleased to be able to publish it. There are some minor revisions that need to be made, specifically a few areas where I think the message is a little too strong for the data presented. Jackie our technical editor will be in touch with you (probably today). Subject to these minor changes this will be accepted and should be in up online and likely in print by 26/9/13.

Your paper will be now sent for editing and typesetting and you will receive a proof to check within days; please check your junk mail if you have not received your proof within this time, in case the automatic email goes there. Please return it as soon as possible, so as not to delay publication.

We shall aim to publish it within eight weeks but, because we try to group papers on similar subjects together, it may take a little longer. Meanwhile could you please check the list below to ensure that we do not need any further information from you **

All articles appear in full on bmj.com and this is the canonical version of the paper. Most, but not all papers, then appear in the print version of the BMJ. For this format the paper may need to be edited down slightly to fit the page and we often put boxes, tables and the references on the web. We do this in order to keep the paper version as short and

readable as we can. We also very often commission a cartoon or find a suitable colour illustration to go with the paper.

As soon as the paper has been edited and you have approved it that is, before it appears in print the paper will be posted on line, and this counts as definitive publication, and you will receive an email notifying you that it has been posted.

If we press release your article, we will issue the press release at the time of online publication. At that time, the bibliographic information is forwarded to PubMed and other indexing agencies, so the article can be searched for and cited (the citation format appears at the top of the online article).

If you have any questions, please contact me and jannis@bmj.com, quoting the manuscript ID.

If you have any questions, please contact me, quoting the manuscript ID.

Yours Sincerely,

Helen Macdonald
hmacdonald@bmj.com

**Do We Need Any Further Information From You?

Please ensure that the following statements have been supplied in the manuscript:

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-----Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work [or describe if any]; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years [or describe if any]; no other relationships or activities that could appear to have influenced the submitted work [or describe if any].

NB - The corresponding author must collect completed ICMJE forms from all authors and summarise their declarations as above within the manuscript. You do NOT need to send copies of the forms to the BMJ, but they must be supplied to readers on request. For further guidance see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests

Date Sent: 11-Oct-2013

NOTES

Close Message

All Notes for BMJ.2013.015247

Fast track ? (.2013.013300)
Updated By: Minns Sue - Editorial Production Assistant on 12-Jun-2013

HM first read (.2013.013300)
Updated By: Macdonald Helen - Editor on 13-Jun-2013

Tessa, I'm unsure if we are expecting this or whether it just pitched up. An update of a 2011 cochrane review on statins for people with low risk cardiovascular disease came out in 2013 and reached a very different conclusion to the first. These authors obviously agree with the first one. I think their concern is that the new one will form the basis of altered NICE etc guidance and they are concerned the benefits are slim. Here they set out what the risks and benefits are and question the conclusion of the Cochrane review, and perhaps the evidence it is based on (ie lots of industry research).

I'm not sure what to make of this. The topic is good. The study is recent. But not a really strong peg. It is of great relevance to our readers. It does seem a serious effort - not just a hair splitting account of a research paper. And some useful numbers at the end. They are really calling for a more honest discussion with patients about the risks and harms. I guess the only other thing missing is the other benefits statins might have on non CV disease factors and cerebrovascular disease?

How is myopathy defined? From real life data do people carry on taking it or stop? What about if they switch to another statin?

Info for mitochondrial dysfunction and cardio resp fitness not very clear. Where has it come from? Am I being thick… How can you have increased CV events but not admissions??

Tessa, I'd be in favour of reviewing. I don't think I'm convinced about the fast track. What are your thoughts?

second read- JS (.2013.013300)
Updated By: Smith Jane - Second Opinion on 14-Jun-2013

I'm with on both of these points - yes to ref, and no to fast track (though you could tell them that we will handle it swiftly). It takes a time for changes in Cochrane reviews to prompt changes in guidelines - and I suspect this change will be contentious.

TR note (.2013.013300)
Updated By: Richards Tessa - Editor on 13-Jul-2013

Statins in primary prevention of CVD is on the list for the Overdiagnosis/overRx series with Abramson's name as suggested author. HC should consider how a revised piece could be tailored to fit the series.

HM speeded up (.2013.013300)
Updated By: Macdonald Helen - Editor on 01-Aug-2013

We are letting this into the queue late because it was semi-fast track.

I should have two reviews by the time we met....

CM before hanging committee (.2013.013300)

Updated By: Martyn Chris - Analysis Committee on 01-Aug-2013

Obviously an important topic and I thought the authors made a good case. The trouble is that it's impossible for someone not completely familiar with the details of the many trials and meta-analyses to judge whether they've been fair and unbiased in their assessment and the one review hints that they've overestimated harms. Still, it probably doesn't matter too much. If they've got it wrong people can say so in the rapid responses.

Unless I missed it, they don't reference the CTTC meta-analysis that they're complaining about:
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60367-5/abstract

The paragraph on the pathological findings in statin-induced myopathy seems unnecessary

I think there's evidence that few people prescribed statins take them for longer than a year. Perhaps that's irrelevant to the argument here but it sort of supports the authors' conclusion that:

'... each patient/doctor partnership could focus on the most important cardiovascular intervention: providing ongoing support to facilitate transition to the healthier lifestyle habits that would most effectively optimize overall health and well-being. '

reviewer suggestions by Prof Hoes (.2013.013300)
Updated By: Janssen-Seijkens Christine - Editorial Production Assistant on 01-Aug-2013

Dear Ms Macdonald,

I would like to help you out here, but I only have two days left before my holidays and am working very hard to finalize to remaining pile of work.
Unfortunately, I do not have the time to be of service on this occasion.
Alternative reviewers (I know that prof van der Graaf is not on holiday now; I don't know about the others)

Prof Yvo Smulders, Internal Medicine, Free University Medical Center Amsterdam; Smulders, Y. (Y.Smulders@vumc.nl)
Prof Richard Hobbs, primary care, Oxford University; richard.hobbs@phc.ox.ac.uk
Prof Yolanda van der Graaf, Julius Center, UMC Utrecht; y.vandergraaf@umcutrecht.nl
Prof Frank Visseren, Internal Medicine, UMc Utrecht; F.L.J.Visseren@umcutrecht.nl

Sincerely yours,

Arno W. Hoes, MD, PhD

HM thoughts (.2013.013300)
Updated By: Macdonald Helen - Analysis Committee on 01-Aug-2013

More bits from me.

Define very early on who "low risk people" are. Would be help to attribute a QRISK and or Framingham to them as well as a clinical description. To have a 2% risk you are basically talking about being under 50yrs.

In the first Cochrane review. What co-morbidities were they worried about. In low risk people there must be virtually none by definition.
The updtaeed Cochrane review 2013 talks about a different time frame ie 1y <1%. Why a different unit of time (everything else is ten year window)?

Who are cholesterol treatment trialists. Who are they? Are they just a group that got together to MA?

I don't get a sense of why the MA was needed? How the MA results compared to the clinical trials. What statistical/clinical uncertainty was there? What was the main RQ that the original trials answered?? Were low risk people in it? What was the forest plot look like in the MA? Did they want an individual pt data MA? Did they do a systematic review or was it just a pooled analysis of some kind? Can they insert the absolute benefits as well as the relative risk reduction?

How was this odd group delineated? Was a a predefinaed analysis or a subgroup effect "those with 5-year CV risk < 10%, whose average 5-year risk is 2.6%". Or is this the main analysis and you creating a new group??
What heterogeneity and publication bias was tested for in the MA? Any comments on this?

There seems to be an issue about the time of follow up. They are pointing to the fact that only a small number of the trials had LT follow up. What are you trying to say here? That the data are unreliable? Be clear about what time frame the original trials ran over.

On serious adverse events they say HPS and ALLHAT did not report SAEs. Do they mean there was none reported, or simply that they did not comment on it? (Useful point to bring out on what is needed.

I'm unclear how we report on diabetes. Is this an association? 1 case per 1000 per year, is this constant over time or if you don't have it at a year you are unlikely to?? Is it biologically plausible?

Hang R+O (.2013.013300)
Updated By: Macdonald Helen - Editor on 09-Aug-2013

Hang HM, CM JS
Votes: yes,yes,possibly

Notes as per S1. We nearly provisionally accepted this BUT we would like them to work harder. No overdiagnosis because it is treatment.

We were all agreed that there was something in this article. Although we would have liked to accept this, we did not think it was quite clear enough to provisionally do so, because there were some fundamental facts that needed clarifying. But if you are able to make some significant changes to convince us, improve the presentation and work with us on this, I think it is likely (although could not promise) that this could work.

1) The peg/topical angle needs to be clearer. I would start with the new guidance and what happened in 2013. And then fill immediately afterwards with the 2011 background.
2) Which people are we talking about? You repeatedly refer to low risk people or low percentage risks, but let's have a more tangible picture of who they are. In reality they are probably not just the patients but many of middle aged doctors who might be reading an article like this! I appreciate you can't define low risk comprehensively but give us some examples, some typical people who are low risk. Playing around with QRISK for example you are really talking about the under 50s. The biggest factor here isn't smoking/obesity/various other co-morbidities, it's predominantly age. I found it difficult to create a low risk person on QRISK that had a major co-morbidity. My sense is that a fuller description of who we are talking about here would strengthen your argument.
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5-year CV risk < 10%, whose average 5-year risk is 2.6%". Or is this the main analysis and you creating a new group??
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13) Unless I missed it, they don't reference the CTTC meta-analysis that they're complaining about: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60367-5/abstract
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15) Finally this feels slightly clunky in its presentation at present, if the detail of this can be fixed I can certainly help with this. Something that occurs to me that might help is a visual aid. Perhaps a timeline showing the trials their RQ, primary outcome and clearly labelled secondary/subgroup outcome about low risk people if they were not the focus, the guidelines could be on there too with the key sentence about what to give low risk people, and the meta-analysis, and any other event/publication of note. Aside from a timeline, I think a fact box to share with patients would also help.

HM revision
Updated By: Macdonald Helen - Editor on 11-Oct-2013

Better but...
some overstatement of data
Tweaks needed on headings etc to make less dull
No analysis articles accepted so needed to push this through and work with it fast
Passed to straight Jackie for tec editing - I'll tweak the essentials on page
Not to go to Charlesworth

HM report from emails etc
Updated By: Macdonald Helen - Editor on 09-May-2014
pre18insertion111013.docx
post18insert151013.docx
emails around revision.docx
emails around acceptance.docx

Attached emails in lead up to revision and then acceptance. I have attached a version of the paper that existed after Jackie and I did our editing (pre18insertion). Also attached is what Abramson sent back (post 18 insertion) - I can't recall seeing this version and made no visible comments by email. This is "normal".

Also a few points of note
*There was a copy drought. This was the only analysis article in a fit state for editing onwards in mid October and so two steps ran in parallel which was my clinical second edit, in tandem with Jackie's technical edit. This happens occasionally but has certainly been more of an issue since less man power/rapid turn over of analysis team.

* This was always a strongly opinionated article. We took steps to de-sensationalise the article from an editorial point of view. And asked them to get a stats author/view to be sure their numbers were sound. We debated at the editorial meeting (as CM's pre-hang note suggests) whether we should have a pro statin voice as well. We decided very consciously that those who disagreed with the opinion could come back on rapid responses and we should not hold this article up while ?commissioning the opposing view.

* With regards to the incorrect fact. This seems to have been inserted at the final stage of editing (by the authors) in response to us pushing them for further information to quantify the statements that they were making at various points in the paper but also at others.

This has two implications firstly that the peer reviewers did not scrutinize the 18% fact in particular and they may well have picked this out as erroneous. (This is "normal" process. I can't quantify but I would estimate that a >75% have more references/slightly adjusted facts/arguments inserted after peer review (that is not re-reviewed externally) before publication.)

I can't comment on whether Abramson made an error, or a judgement, when he inserted the 18% fact. In the original Zhang paper the abstract says 18%. I wonder if pushed for time Abramson took this and did not delve into the detail he might have done.

*Once corrected should we retract. The paper is clearly labelled as debate/opinion. I don't think the error undermines the argument that some think the gains are too marginal irrespective of the adverse effects. I feel concerned Rory is not able to engage in normal academic discourse. Why bypass systems designed to address errors - ie letters? Why has no one else written in?