

09-Apr-2020

BMJ-2020-055647

Heterogeneous Trends in Burden of Heart Disease Mortality by Subtypes in the United States, 1999-2018: Observational Analysis of Vital Statistics

Dear Dr. Shah,

Thank you for sending us your paper, manuscript which we sent for external peer review and discussed at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying. We hope that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Yours sincerely,

David Ludwig
Professor David Ludwig
Associate Research Editor
The BMJ
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****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (Chair), Angela Wade (Statistician), Tiago Villanueva, Joseph Ross, Shivali Fulchand, Timothy Feeney, Wim Weber, David Ludwig, Elizabeth Loder, Mark Richards

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please pay special attention to these comments by the committee, as further clarified in the peer review:

1. Provide better rationale, and more indepth methodological detail, for the joinpoint analyses
2. Use of YPLL could provide misleading implications involving racial-sex groups with lower life-expectancy. Reconsider your treatment of this issue.
3. Even though many individual causes of mortality have increased, overall HD rates continued to decline from 2011. Admittedly, this is a worrisome attenuation of a long-term trend, especially in light of ever more powerful drugs and surgical procedures. Provide a more balanced tone and summary, making sure to avoid implying an increase in overall mortality from HD.
4. Include the 2019 data if available, or soon to be available.
5. Several editors found the acronyms hard to follow. Please use them as minimally as possible, aiming to improve accessibility to the reader.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the statistician and external peer reviewers**

Statistician comments:

More information should be given re the choice of inflexion point and the decision that there was one (and only one) over the timespan. It is unclear to what extent this came from references 10 and 11 (the latter of which only seems to consider data starting at 2011) and how much by the current data (figure 1 does not suggest any inflexion point and figure 2 could be debatable). It seems unlikely that this would be a sudden change in trend and a continuum model would be preferable.

One part of the objective is to reduce disparities and yet YPLL could be introducing these into the comparisons.

Reviewer: 1

Because of their setting, these results will be of little or no interest to the patient or general reader outside the USA. Nor, I suspect, would they detain policy-makers or cardiologists elsewhere for long. Despite the enormous field of evidence, very little in the way of future guidance emerges, with only a weak recommendation on the hypertensive case as a conclusion to the work. Presentationally, it seems to me a mistake to have reported changes in a variety of ways, for the reader becomes confused as he goes through the paper. For example, being interested in trends in HF morbidity and mortality, I was alerted by the statement, in the summary abstract, that HF deaths as a percentage of the total had grown from 8 to 13 - a 60 % increase. There is a picture of this trend in the graph of fig. 1, but when I look for more numerical information I find (Table 1) a different measuring scale in use - age-adjusted mortality rate.

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Please enter your name: John Walsh

Job Title: Lay reviewer

Institution: -

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Reviewer: 2

Thank you for asking me to review this paper. I reviewed it as a patient education advocate.

- Are the questions the paper addresses relevant and important to patients and/or carers?
I think the main audience of this paper is more the public health experts and decision makers. That being said, the lay audience does see and hear about publications like this that explain the trends in deaths in the US due to different diseases. As you know, they are often reported in the mainstream news.

This paper is less for the patient audience and that is understandable. But I think patient advocacy groups (at least for African Americans and patients with low-socioeconomic status) would be interested in this paper as it adds to the evidence base on potential differences for those groups so they can advocate for improved care/prevention.

- Are there topics or issues that are missing, or need to be highlighted more?

An issue for the patient/carer/layperson audience is the lack of clarity about how the authors are defining "hypertensive heart disease." I am not sure how the authors are defining this from the dataset they used– even after I looked up the ICD-10 code for it. It would help the audience if they added their interpretation of it and how they are differentiating it from both ischemic HD and HF.

For example, hypertensive heart disease can include heart failure (Code I11.0).

Another point may be an issue for the style guide for BMJ, but I feel compelled to note that "black Americans" is not really the favored terminology – "African-American" is typically the preferred term for a patient audience in the US.

Another issue that may need some attention is the interpretation of the results in how care of patients (secondary prevention) may or may not be influencing the results. (I noted that they mention clinical quality improvement for secondary prevention in the last paragraph – but a more detailed discussion does seem warranted and of interest to heart patients).

I wondered if the authors considered whether the results could have been influenced by better care of IHD (guideline directed therapy, as they noted) leading to longer lives but also progression to HF? Again, the overlap of diagnoses becomes confusing to the layperson.

Perhaps the authors could consider adding an additional paragraph on how guideline-directed secondary prevention may have influenced the results – to support their final statement about future research on quality of care improvements. Patients would care about both primary and secondary prevention (Relevant for a patient is this question "If I already have IHD, how can I prevent it from progressing to HF?")

- Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges?

I applaud the authors that they included racial/ethnic data in this analysis, even though the information they were able to get was limited. But it does add to the body of evidence about the disproportionate effect of cardiovascular disease on African Americans.

I think the challenge for the lay audience is understanding the limitations of this study to explain the "why" of the results. I think the conclusion in the abstract that prevention of HTN seems to be the only thing that matters feels too limited and too conclusive based on the observational nature of the study.

- Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered?

Given the observational design and epidemiological focus, the outcomes are not that important to patients. But I think that is okay given the purpose of the study.

- Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/ carers?

As I noted previously, an added brief discussion of what the results might be saying about secondary prevention would make the discussion section stronger for this patient audience. And potentially could be a motivator for the patient to adhere to guideline directed therapy. The same point applies to the primary prevention audience – as the authors noted would ideally be patients who have hypertension so the doctor could help motivate the patient if they needed additional motivation to care for themselves and hopefully prevent heart diseases.

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Reviewer: 3

Aim of manuscript was to evaluate trends in heart disease mortality using national death certificate data from 1999-2018 during which time there were 12.9 million deaths due to heart disease. Overall, my comments are fairly minor.

Abstract:

1. Greater clarity in the text of the abstract is needed.

2. Line 24. Needs to be clearer, how about "The proportion of total HD deaths attributed to IHD decreased from x to x, while the proportion of deaths attributed to HF and Hypertensive HD increased (from x to x, and x to x, respectively).
3. Line 31, "The steepest increase in HF" do you mean after 2011?
4. Line 45, "widest black-white disparities" how about "largest"
5. I think the YPLL angle of the results makes for a better summary statement of the paper and could be highlighted in the abstract. The crude number of events could be potentially removed from the text.
6. Suggested text for abstract taken from the discussion section "The results translate into approximately 3.5 million potential years of life lost in 2018 due to total HD, but this burden was borne disproportionately in different race-sex groups and attributed to different HD subtypes. YPLL increased by 80% and 31% for hypertensive heart disease and heart failure, respectively from 1999-2018."

Introduction: Text is relevant to topic. No changes recommended.

Methods:

They utilized CDC's database of death certificates and evaluated heart disease outcomes: total and by subtype (ischemic heart disease, heart failure, hypertensive heart disease, valvular heart disease, arrhythmias, pulmonary, and other). Trends were evaluated by sex and race (Blacks and Whites). Rates for other ethnic/race groups were considered to be unreliable due to incomplete reporting of race/ethnicity for these groups.

Outcomes were age adjusted mortality rates (AAMR) and years of potential life lost (YPLL) using average life expectancy during the study period as the referent. They evaluated annual percent change using jointpoint regression. The description of the methods is complete and the methods chosen were in line with epidemiological/statistical methods for this type of study.

1. The vast majority of HD patients are generally over 65. The population of 65+ is a heterogeneous group from the young old to the very old. So, why did the authors chose a cut off of ≥ 65 years? An alternative cut-off could be 65-79, and 80+. As average life expectancy is 80 years or so, then events in the 65-79 age group would represent premature events.

2. There must be regional differences in AAMR and YPLL and potentially in trends. The paper is long enough as is, but it would be worthwhile knowing whether the observations reported were consistent by region in the US. If so, this would simply require adding a sentence to the results. If there were striking differences, then perhaps a supplemental figure would be valuable.

Results: The depiction of the results in tables and figures are clear. The study identified rebound where gains made with decreasing HD rates prior to 2011 reversed where certain HD subgroups showed an increase in rates after 2011.

Figures 1 and 2 –very nice and I like the supplemental figure where YPLL are also depicted graphically.

Discussion—

1. Heart disease mortality trends reflect a combination of changes in underlying incidence of disease and survival and should be mentioned.
2. Any potential changes in heart disease diagnosis and management or in death certificate coding during the time period of 1999-2018 should be mentioned.
3. The authors mention the growing prevalence of obesity, diabetes, hypertension and mention diet quality, and physical inactivity, but what about the drug abuse epidemic? Could underlying increases in drug abuse contribute to the rebound we now see with increases in heart failure mortality in the U.S. population?
4. Page 9, line 52. "leveraging YPLL" better to state "expressed as YPLL"
5. Page 10, line 54 and later on page 11. We would anticipate that socioeconomic disparities in health care access and delivery would also relate to Black-White mortality disparities especially in the US context with a range of health care coverage.

6. Use of word "decendents" throughout manuscript. Authors should use "deaths" or "deceased".
"Number of deaths" or percent of deceased or of deaths, for example. Decendants would be offspring
and I am not familiar with the term decendents.

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Reviewer: 4

This is a very well-written manuscript investigating important public health issue about the changes in mortality of heart diseases (overall and by subtypes) throughout years. The authors showed the

increased burden of deaths from hypertensive heart diseases and heart failure despite a decreased burden of IHD which can provide a more specific picture to policy makers focusing on tackling these diseases in the US. I enjoy reading this paper and have some minor comments that authors might worth considering:

1. Can authors describe further the WONDER database, e.g. were all citizens living in the US potentially included in the database, would there be any exceptions? Would there be any potential missingness of cause of death?
2. Wondered if any changes in coding practice over the years that might potentially affect the results? Perhaps worth mentioning it in the discussion section.
3. Sorry if I had an oversight, just wondered if only main cause of death be considered in the main analysis?
4. Authors used 2000 US standard population - just wanted to know if/how the population structure changed after 2000? And by ethnicity?
5. Any chance to look at if there's any statistically significant difference in mortality rates/year potential life lost between gender and ethnicity over the years? I'm not a statistician and not sure if it's possible but it might be useful to know

Minor:

Abstract - I was a bit confused when I read "AAMR was highest from IHD, but APC from HF and HTN-HD was highest after 2011". Suggest to rephrase this sentence

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Reviewer: 5

Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

It is increasingly recognized that the long-term fall in cardiovascular mortality rates in many developed countries is now coming to a halt.

This paper is different from similar publications in focusing on specific heart diseases trends by race rather than all cardiovascular disease (Lopez AD, Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. *Int J Epidemiol.* 2019 Dec 1;48(6):1815-1823) or focusing on differences in the US by state (Global Burden of Cardiovascular Diseases Collaboration, Roth GA, et al The Burden of Cardiovascular Diseases Among US States, 1990-2016. *JAMA Cardiol.* 2018 May 1;3(5):375-389)
It would be helpful to contextualize the paper more

- Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it?

It is very important for policy makers to be aware that temporal declines in the leading cause of death have come to a halt and to appreciate that the impact is different in different groups.

- Scientific reliability

There are some issues with the conceptualization as showing differences by race in the US. Race is a somewhat loaded term that is best avoided and does not represent the full range of differences by ethnicity in the US. Please replace the categorization by race with a nuanced and appropriate categorization.

- Research Question - clearly defined and appropriately answered?

It might be better to include all cardiovascular diseases because they share several causes and one type of cardiovascular disease might be a sequelae of another, so it is difficult to interpret trends in specific cardiovascular diseases in isolation.

Please clarify the years of potential life lost (YPLL) calculation. Are the race-sex specific estimates based on current US race-sex specific life expectancy? Life expectancy is substantially shorter in "blacks" than "whites" in the US. Using race-sex specific life expectancy (https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_07-508.pdf) would mean that a "black" man dying at 65 years would be counted as losing 16.4 life years but a "white" man 18.1 life years. Is that how the calculation was done? If so, please re-consider or justify comprehensively. If not, please make the calculation completely clear. Please also make this point explicit as regards sex. US life expectancy is also shorter for men than women, so a "white" woman dying at 65 years loses 20.6 life years compared with 18.1 years for a "white" man. Using sex-specific life expectancy assumes this difference is natural rather than another disparity that could perhaps be addressed. Again, please make this point explicit with justification.

- Overall design of study - adequate ?

The authors are limited by their choice of data CDC Wonder database, is there any other source that would allow a more granular categorization, particularly to separate out Hispanics because they show different and informative patterns.

- Participants studied - adequately described and their conditions defined?

The authors might consider in more detail the validity of causes of death on death certificates.

- Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?

The methods are fairly standard

- Results - answer the research question? Credible? Well presented?

The results given are clear and well-presented, within their limitations

- Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data?

Message clear?

Several sources agree on stagnating mortality from cardiovascular disease in the US and elsewhere. Could the increasing rate of death from heart failure and hypertensive heart disease in any way be the result of fewer deaths from ischemic heart disease meaning more people are surviving a heart attack and so living on to die of heart failure or hypertensive heart disease. To put it another way are more people are dying of heart failure because more people have survived the competing risk of ischemic heart disease, or perhaps the competing risk of stroke? Please contextual the results better bearing in mind that cardiovascular diseases share causes and one may be a sequela of another.

Could lack of major new treatments for cardiovascular disease be a factor in the observed patterns?

Please reflect on the strengths and weaknesses of the methods used here compared with the Global Burden of Disease study methods

- References - up to date and relevant? Any glaring omissions?

As mentioned above

- Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?

The last sentence of the abstract conclusion is probably true but does not clearly follow from the data presented.

Summary

As regards the last point of section 1 it would be better to understand cardiovascular disease sub-types as a whole.

As regards Section 2, this study does not show that more attention should be paid to heart failure risk factors. Heart failure death could be more common because more people are surviving a heart attack to have heart failure

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Please enter your name: CM Schooling

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Reviewer: 6

The manuscript is well written. Below are my comments.

1. For clarity to the reader, include 95% CI in the abstract and throughout the text.
2. For race consider using (race, non-Hispanic Black and non-Hispanic white)
3. The authors should distinguish between annual percent change (APC) and average annual percent change (AAPC)
4. Does "mean annual percentage change (APC)" mean AAPC?
5. Since this is 20 years of trends, authors should consider reporting APC (segments) and AAPC (weighted average) ["mean annual percentage change (APC)"].

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Please enter your name: Vincent Mendy

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Reimbursement for attending a symposium?: No

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Reviewer: 7

This paper examined death rates and trends for various subtypes of heart disease mortality by age, race, and sex. I commend the authors distillation of a large volume of data and results into an understandable paper. This paper would be a valuable addition to the critical literature of the recent slowing of trends in cardiovascular disease death rates. Overall, this is a solid paper. I have a few major comments related to the methods and discussion, and the remaining comments are minor.

Major comments

1. I question the use of joinpoint regression to calculate trends, especially since the 2011 inflection point was pre-determined. Joinpoint is useful when the inflection point is unknown, but complicates the analysis when the inflection point is fixed. First, joinpoint is generally used to find and compare inflection points. However, given the vastly different rates presented in this paper, joinpoint's ability to detect those inflection points varies greatly by outcome and demographic group. For example, joinpoint would easily detect an inflection point for IHD deaths among older white men, but would be unlikely to detect an inflection point for arrhythmia among younger black men. Secondly, by inserting an inflection point into joinpoint results, an additional step is required to calculate the APC, adding additional complexity and imprecision.

A simpler approach would be to use log-linear regression (or Poisson regression to account for large differences in rate precision stemming from vastly different death counts) before and after 2011. This method would greatly simplify the analysis and, I believe, be more appropriate.

2. The authors adequately describe the differences in the racial burden of HD such that blacks have a higher burden than whites. However, this explanation does not support the findings such that whites have greater increases than blacks. What are the implications of whites have greater changes, despite having a lower burden. What factors could be changing more in whites than in blacks?

3. Additionally, the discussion does not address differences by race and gender combined. These results should be placed in context, especially given the potential implications for biologic vs. social determinants.

4. The public health implications could be strengthened by focusing more on the results of this paper. How could the observed trends be used to inform programs, policy, and interventions with respect to age, race, and sex? Since this analysis does not specifically examine drivers of these trends, it seems that the implications should focus more on the demographic groups and outcomes and less on the specific risk factors.

Minor comments

5. The first sentence needs a citation.

6. The increases mentioned on page 4, line 19 are occurring not only in some demographic groups, but also in counties across the country.

7. Do black and white race include Hispanic ethnicity? This is especially important given the very different CVD risk profile and HD mortality trends among Hispanic Americans.

8. What was the motivation behind the selection of these three age groups?

9. Note in the first sentence of the results that those deaths exclude races other than white and black.

10. "Other heart disease" and "All other heart disease" have two different meanings. In some places, this distinction becomes hard to untangle. Is there another term other than "all other heart disease" that the authors could use for the YPLL results?

11. The phrase "rate of AAMR declines" is used only on page 7, line 27. Throughout the rest of the manuscript, the authors refer to "trends in AAMR", which is a much clearer phrase.

12. On page 11, line 33, the authors state that data for non-white and non-black racial/ethnic groups are not available. These groups are available through WONDER.

13. In the tables, both the p-value and the CI do not need to be included. The p-value can be removed since the CI also indicates statistical significance.

14. For Figure 1, please indicate in the caption that there is a break in the y axis.

15. Figure 2 graphs the rates, not the trends.

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Please enter your name: Adam Vaughan

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Institution: Centers for Disease Control and Prevention

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