Author's response to reviews

Title: Projected growth of the adult congenital heart disease population in the United States to 2050: an integrative systems modeling approach

Authors:

Catherine P Benziger (cpast@uw.edu)
Karen Stout (karenst@cardiology.washington.edu)
Elisa Zaragoza-Macias (ezaragoza-macias@cardiology.washington.edu)
Amelia Bertozzi-Villa (abertozz@uw.edu)
Abraham D Flaxman (abie@uw.edu)

Version: 2
Date: 2 June 2015

Author's response to reviews: see over
Dear Editors,

Thank you for the opportunity to revise our manuscript to address the issues raised by these reviewers, and thank you to the reviewers for their work, as well. A query from Reviewer 2 about the ICD-9 causes we used to identify CHD deaths led us to reconsider all of the ICD-8, 9, and 10 causes we used, and to make some changes inspired by their query, eliminating ICD codes for congenital anomalies of the veins from our cause list that were included incorrectly. In this process, we identified an error in our mortality data processing code, which we have now corrected, which is why we removed ICD codes and now report 288,813 CHD deaths in our database, up from 279,050 in the previous draft. As testament to the robustness of our method, this does not change any of our estimates or projections substantially. For example, we now estimate that from 1968 to 2010, the size of the ACHD population increased by a factor of 2.3, a decrease from our old estimates of 2.6.

We appreciate all of the time the reviewers took to comment on our work. We will respond to the reviewers’ reports point-by-point below.

**Review 1:**

*Review: Projected growth of the adult congenital heart disease population in the United States to 2050: an integrative systems modeling approach*

*General comments: This is a creative and clever approach to tackling this problem of estimating and projecting the size of the adult CHD population in the US. Empirical surveillance data beyond birth prevalence are lacking in the US and the authors understand the seriousness of this large gap in current knowledge; the authors are correct in their assessment that a mathematical model is a reasonable approach to take. The authors do a very nice job of laying out the need for this work as well as the data inputs for the model. The paper is, in general, well-written and clear. The authors do a nice job of explaining their study’s limitations as well.*

We thank the reviewer for this positive assessment.

*Major Compulsory Revisions:*

1. *The paper would benefit from a more thorough explanation of “integrative systems modeling”. The description of the method provided is not adequate for someone unfamiliar with the approach. It was not possible for this reviewer to assess the validity of the model given its description; a reviewer with expertise in DisMod-PDE should have a chance to review this paper.*

We apologize for the lack of detail, an issue raised by other reviewers as well. We have expanded the description in the methods section and included a web appendix that goes into more mathematical detail on the model to remedy this. We have also added a reference to our currently-in-press book on the ISM approach to modeling disease progression where the term first appears in the main article.
2. Although the authors recognize that NHIS estimates of “recalled” CHD prevalence are low compared to measured birth prevalence from population-based birth defects surveillance systems, this is a major limitation of this work. The extent of the under-estimation should ideally be quantified using some kind of sensitivity analysis. For example, could the same analyses have been possible using other estimates of birth prevalence – such as those reported by the Metropolitan Atlanta Congenital Defects Program? See Reller et al. J Pediatr. 2008 Dec;153(6):807-13. Even if the authors choose to retain the NHIS data this model and not use a more realistic data input for the birth prevalence, then the results should probably be expressed as “minimal” estimates – and the results of a sensitivity analysis be reported. The fact that these are minimal estimates is mentioned on page 14 in the Discussion, but it should be more prominently demonstrated – incorporated into the abstract, and results – and possibly even the title of the paper.

We believe that recalled CHD is the most useful quantity to measure for health service provision, which we see as a primary application of our work; the number of recalled CHD cases quantifies how many people might respond to a health awareness campaign urging people with ACHD to see a specialist. However ACHD prevalence is also of great interest, and at the reviewer’s suggestion, we conducted a sensitivity analysis that extrapolated the prevalence measurements from Atlanta (Reller et al, http://www.ncbi.nlm.nih.gov/pubmed/18657826) to the entire USA.

In Reller et al, there are two relevant measurements: the overall birth prevalence of CHD of 81.4 per 10,000 and the prevalence of critical CHD of 15.6 per 10,000. It is straightforward to include either of these measurements as additional data in the DisMod-PDE ISM, and we have added a sensitivity analysis as a supplementary web appendix that includes the results of including each of these measurements separately. As you would expect, we found that including the 81.4 per 10,000 birth prevalence substantially raises our estimates, e.g. for 2010, the data raises the estimate from our baseline estimate of 251,000 ACHD cases to a high estimate of 866,000 ACHD cases, constituting a 3.5-fold increase. On the other hand, including the 15.6 per 10,000 birth prevalence of critical CHD lowers the estimate to 154,000 critical ACHD cases, a 1.6-fold decrease.

From this, we can conclude that recalled ACHD is probably capturing more than just the critical CHD cases, but is far from capturing all CHD cases, and the model is rather sensitive to the prevalence data available (the sensitivity to the prevalence data is also demonstrated by the uncertainty quantification included in the main paper).

Minor Essential Revisions:

1. The paper would also benefit from data tables – and not just figures.

We have added table 1 to highlight our main findings on the increase in the number and prevalence of ACHD cases over time.

2. NHIS is the National Health Interview Survey – not Information – see: http://www.cdc.gov/nchs/nhis.htm

We have corrected this error, thank you for identifying it.
Review 2:

Summary: The primary goal of this paper is to determine the prevalence of CHD in adults from 1970 to 2050 in USA. In order to predict the prevalence of the recalled CHD, the authors use a statistical compartmental model called DisMod-PDE in a Bayesian framework. To do this several assumptions are made: 1. The birth prevalence (i.e. incidence of CHD) was constant over time; 2. The prevalence ratio and excess mortality rate was constant across cohorts, etc. The authors estimate that there will be 480,000(95% UI: 380,000-560,000) CHD patients in 2050; 3. Recalled CHD is a reasonable proxy for CHD prevalence. The major limitation of the analysis is the accuracy of the prediction model. The conclusions of the study are therefore not supported by the data presented. As the authors indicate in the introduction, at best, they estimating recalled, ‘public knowledge of CHD’- even so there are methodological limitations.

We thank the reviewer for their time reading and commenting on this paper. We agree with the assumptions 1 and 3 identified by the reviewer, and have tried to clearly identify them in our work. However, regarding the reviewer’s assumption (2) that the prevalence ratio and excess mortality are constant across cohorts, this is importantly not a limitation of our approach, as prevalence, and excess mortality are both allowed to vary with age and time, and therefore also across cohorts. We do assume that prior to 1968 age-specific excess mortality is constant across cohorts, but this has little impact on our estimates because of the high mortality prior to modern surgical interventions. We have adjusted the language in the methods section to try to make this clearer, since we consider it an important strength of our approach.

Methodological limitations:

1. Assumptions: Can the authors indicate on what basis they believe the assumptions to be justified? I do not understand on what basis the prior distributions were determined for the Bayesian portion of the modeling since all information used is either assumed or modeled.

We have used a “weakly-informative” approach to prior distributions, which is now elaborated Section 2 of web appendix 2 to demonstrate that the result of a different set of prior beliefs would not yield a substantially different conclusion. The reviewer is not entirely correct in the claim that all information used is either assumed or modeled; we use all the measured data from the NHIS and NVSS as well. For example, as we state at the beginning of the results section, our estimates are based on 92.4 million death certificates. We have now added to this section that our estimates are also based on 180,766 NHIS interviews.

2. Validation: Can the authors at least provide information to verify their model. Even within their own data, the authors could take part of data (e.g. years from 2000-2010) as a test set and check the compartmental model’s predictive ability form 2000-2010. Thus even if this model could be used for the purposes intended, the model is not validated within their own dataset.

This hold-out cross-validation approach is an excellent idea, and we have incorporated it into the sensitivity analysis web appendix 2 as section 1, which we added in response to reviewer comments. It shows that the estimates change by 5-10% when the data from later years is held out.
3. **Bias:** A: Using recalled CHD can lead to under-estimation or over-estimation of prevalence of CHD. The numbers presented in terms of prevalence are vastly different from what is published. This is not sufficiently and comprehensively addressed. It diminishes the credibility of the findings.

In figure 4 we compare our estimates to the four existing estimates of ACHD prevalence we identified in our literature search, and as we state at the beginning of our “main findings” subsection, our estimate of ACHD prevalence of 1.4 per thousand “is lower than a recent meta-analysis, which found the adult CHD population prevalence to be around 3 per thousand, but they were limited by the large heterogeneity of the studies and did not include the US.” As we state in our “limitations” subsection, “Our results show that since 1997, there has been a birth prevalence of recalled CHD of around 3 per 1,000, which we would like to use as an estimate of moderate to severe cases of CHD. This is lower than recently published birth prevalence of 4 to 7 per 1,000.” We feel that a difference between 3 and 4 per 1,000 is hardly a vast differences, and even a difference between 3 and 7 per 1,000 is reflected by the large margin of error shown in our uncertainty quantification. However, the reviewer is correct that using recalled CHD will miss some cases that are moderate or severe CHD and will include some cases that are not. We believe that overall this will balance out to a conservative lower bound on the number of ACHD patients that the US health system could expect to seek care following a successful media campaign to raise awareness.

4. **Conclusions:** The mortality data is the most robust but these findings are not new. For the prevalence, I strongly doubt the study can predict the prevalence of CHD only depending on the covariates age and year. There are many possible covariates that were not included in the paper. The conclusion of the abstract refers to women of reproductive age. Is this a major conclusion of the study?

We hope that our addition of holdout cross-validation in response to this reviewer’s limitation 2 goes some way to convincing the reviewer that it is possible to predict prevalence of CHD based on age and time. Although many covariates such as Down syndrome, smoking, and alcohol use have been proposed to explain CHD, there is no scientific consensus around any informative predictors. In a model for neural tube defects, we could take the approach of forecasting the changes in folate deficiency to inform our model, and for future forecasting efforts on other diseases this will be an important direction for methodological innovation. In the case of CHD, however, there is nothing analogous.

For some women with ACHD, pregnancy carries high risks, and some medications for CHD, such as warfarin, are contraindicated during pregnancy. We therefore consider our estimate of the number of reproductive-aged women with ACHD a public-health relevant secondary conclusion of the study.

5. **Rational and Definitions:** Is it possible for the authors to indicate the rational for using the integrative systems model? What is the compartment $C$, $a$? What is the prevalence ratio being used; the ratio is between which two prevalence rates?

We have added details to the methods section and a web appendix with more details on the integrative systems model to address the requests from this and other reviewers. In short, the integrative systems model provides a way to bring together prevalence data from NHIS and death data from NVSS. In this regard, it is a particular type of nonlinear regression model, where the specific nonlinear function to fit...
comes from a mechanistic model of disease progression. The name comes from the pharmacokinetics/pharmacodynamics literature where this approach was pioneered.

There is one point of technical language that seems to have been a sticking point for this reviewer in particular: we used the term “prevalence ratio” to mean the number of cases divided by number of survey respondents. This is sometimes called a “prevalence rate”, but is technically not a rate, since the denominator is persons, not person-years. However, it seems that the technically incorrect use of the term “prevalence rate” will make things clearer, so we have adjusted the language in the text.

Case definitions: Do I understand correctly that the following ICD-9 codes were used for congenital heart disease? Please provide rational for using the following codes? Have these ever been validated for accurate CHD estimates?

745 Bulbus cordis anomalies and anomalies of cardiac septal closure
745.7 Cor biloculare
745.8 Other
747 Other congenital anomalies of circulatory system
747.5 Absence or hypoplasia of umbilical artery
747.6 Other anomalies of peripheral vascular system
747.8 Other specified anomalies of the circulatory system
753 Congenital anomalies of urinary system
753.9 Unspecified anomaly of urinary system

We thank the reviewer for this careful attention to detail. Except for one typographical error in our Supplementary Table 1, these are ICD-9 codes we used (753.9 should have read 759.3 [Situs inversus]). We selected these codes following the Global Burden of Disease Study categorizations (1,2), and they have been used in other work as well (3). However, inspired by the referee’s concern about the validity of these codes for capturing CHD deaths, we have carefully reviewed the ICD 8, 9, and 10 codes we are using, and identified a number of codes which we feel are better to exclude. We have therefore recalculated all of the estimates and projections in our paper excluding the following causes:

<table>
<thead>
<tr>
<th>Version</th>
<th>Cause Number and Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD 8</td>
<td>747.5 Absence or hypoplasia of umbilical artery</td>
</tr>
<tr>
<td>ICD 8</td>
<td>747.6 Other anomalies of peripheral vascular system</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.5 Absence or hypoplasia of umbilical artery</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.6 Other anomalies of peripheral vascular system</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.60 Anomaly of the peripheral vascular system, unspecified site</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.61 Gastro-intestinal vessel anomaly</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.62 Renal vessel anomaly</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.63 Upper limb vessel anomaly</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.64 Lower limb vessel anomaly</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.69 Anomalies of other specified sites of peripheral vascular system</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.8 Other specified anomalies of circulatory system</td>
</tr>
<tr>
<td>ICD 9</td>
<td>747.81 Anomalies of cerebrovascular system</td>
</tr>
</tbody>
</table>
6. Formatting: I don’t understand Figure 3(b) and Figure 4. Can explanations be provided? The formatting of the figures is poor. There are sections in the methods which should be included in the limitations.

We have modified the captions for figures 3 and 4 to make them clearer, but they seem pretty straightforward. Similarly, the formatting of the figures seems quite good to us. Recognizing that there are many differing (and strongly held) opinions on the visual display of quantitative information (4–7), however, we are, and will continue to be, open to specific suggestions about how to make the formatting and explanations of figures clearer. In this same vein of responding to the reviewer as completely as possible, we have reviewed the methods section and have removed the sensitivity to including the NHIS-measured 0-51 week old prevalence from the methods section (it is still reported in the limitations).

7. Inaccuracies: Abstract and introduction—there are published well validated estimates of adult CHD prevalence based on empirical estimates some of which are cited by the authors. Therefore there are inaccuracies in the abstract and introduction. References 4, 6 and 7 are neither ‘meta analyses’ nor are they ‘recent’ as stated in the introduction.

We have adjusted the language in the abstract and introduction to be more precise, and updated the text to refer to the correct reference (4 and 6 should not have been included, only 7). Estimates of adult CHD prevalence have indeed been published, and we have attempted to include all of them in our figure 4. None of these estimates project forward to 2050, however. Reference 7, “The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation,” by van der Bom et al, is what we referred at a meta-analysis, and perhaps the reviewer considers this use of the term imprecise. In that paper, the synthesis of evidence collected in systematic review is referred to as “an evidence-based calculation”, and we have changed the language in our text to avoid calling this calculation a meta-analysis. We feel that calling a paper published in 2012 recent is justified, however.

We wish to again that the referee for their time and for their comments, which we feel have made the paper clearer and stronger, especially their detailed checking of the ICD codes on our cause list, which we feel now better capture the CHD deaths we intended them to represent.
**Review 3:**

Reviewer’s report: In this manuscript the authors seek to develop estimates of the prevalence of CHD in the United States, with projections to 2050. Input sources are national vital statistics (mortality) and the National Health Interview Survey (NHIS, misnamed on p 6 first line of methods as ‘Information’ and also in the abstract).

We thank the reviewer for identifying this error in the abstract and methods section of our paper, and have corrected it.

**Major Compulsory Revisions:**

The authors have not incorporated data on national estimates of the prevalence of CHDs, which are available for selected defects (Parker et al. BDRA 2010), nor have they utilized information on survival with specific defects (several recent references including Hirsch et al J Pediatr 2010; Kucik et al AJP 2014; Wang et al J Pediatr 2013; BDRA 2013; J Pediatr forthcoming 2015). Given that we have specific data on prevalence and survival outcomes to early childhood among infants born with the most prevalent and serious CHDs, one would think that this information would trump data, at least for early childhood, derived solely from cause of death certification.

Ideally, the authors might revise their methodology to incorporate data from these sources. If not, at least the manuscript should reflect the existence of these sources, make a cogent argument why they were not used, and consider their potential effect on the estimates in evaluating the utility of this work in the discussion section.

We agree data from birth defect surveillance systems will be superior to death certificates in terms of both sensitivity and specificity. If our focus was on any of the specific selected defects than these papers report on (aortic valve stenosis [AVS], atrioventrical septal defect [ASD], coarctation of the aorta [CA], common truncus [CT], hypoplastic left heart syndrome [HLHS], teratology of Fallot [TOF], transposition of the great arteries [TGA]), this information would be preferred, and a strength of the integrative systems modeling approach is that data on birth prevalence and survival can be included in the model and fit simultaneously with the survey data and death certificate data.

Because we are interested in producing an estimate for all moderate and severe CHD cases, the more accurate, but more focused, information from the papers based on the National Birth Defect Prevention Network (NBDPN) data cannot be integrated directly. An comparison of the numbers is instructive: In Parker et al, estimates of the national prevalence of CT, TGA, TOF, ASD, and HLHS in 2004-06 in USA are reported separately, and summing the prevalences of each of these provides a rough estimate of the birth prevalence of CHD: 0.74 + 3.04 + 4.05 + 4.70 + 2.31 = 14.8 per 10,000. Our estimate is more double this, at 32.6 per 10,000. This corresponds closely to the crude comparison of deaths by cause in the NVSS database. In 1990, we identified 5,447 death certificates where one of the ICD-9 CHD codes appeared, and in response to this comment from the reviewer, we additionally identified the number of death certificates where a CHD code for CT, TGA, TOF, ASD, or HLHS appeared, as summarized in the following table:

<table>
<thead>
<tr>
<th>Cause</th>
<th>ICD-9 Codes</th>
<th>Death Certificates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The ratio of the sum of ASD, CT, HLSL, TGA, and TOF death certificates to the total CHD death certificates we identified is $2,696 / 7,109 = 0.418$, which is relatively close to the ratio of the sum of prevalences to our estimated prevalence, $14.9 / 32.6 = 0.454$.

It is interesting to note what causes appear in the 58% of death certificates that we include based on ICD codes other than those in the table above. The top of the list is 746.9 – Unspecified anomaly of the heart, and here are the top five:

<table>
<thead>
<tr>
<th>Underlying ICD-9 Code</th>
<th>Underlying Cause</th>
<th>Number of Death Certificates</th>
</tr>
</thead>
<tbody>
<tr>
<td>746.9</td>
<td>Unspecified anomaly of heart</td>
<td>1,665</td>
</tr>
<tr>
<td>746.8</td>
<td>Other specified anomalies of heart</td>
<td>436</td>
</tr>
<tr>
<td>745.6</td>
<td>Endocardial cushion defects</td>
<td>164</td>
</tr>
<tr>
<td>758.2</td>
<td>Edward’s syndrome</td>
<td>140</td>
</tr>
<tr>
<td>747.3</td>
<td>Anomalies of pulmonary artery</td>
<td>137</td>
</tr>
</tbody>
</table>

We have added the reference to the papers on survival methods to the introduction, and have extended the limitations section to discuss the potential relevance of surveillance data, if it matched the case definitions of other data sources. Although additional analyses bringing together birth prevalence data collected by NBDPN with more focused death certificate data from NVSS would certainly be of interest, we believe that this falls outside of the scope of our present paper.

**Minor Essential Revisions:**

1. Provide a definition of 'recalled CHD'. It would appear that this means self-report of being told by a health care professional that the interviewee has a specific CHD diagnosis. But the term 'recalled CHD' will likely be foreign to most health researchers and readers

   Excellent suggestion. We came up with this term to reflect precisely what is being measured by the question in NHIS, and have now modified the text to communicate it more clearly with others.

2. p 4, first para. The sentence describes a recent meta-analysis, but includes three references. References 4 and 6 do not apply to this sentence.

   Thank you for catching this error, which we have corrected.
3. On p 6, where ‘recalled CHD’ is discussed, although at first it appears that the term applies across the age span, later the authors discuss a question about their child. The authors should clarify whether this source is used to obtain a crude notion of population prevalence across all ages from the NHIS, or just for children.

Starting in 1997, NHIS collected this information just for children (although it was collected for all ages prior to 1997, the data shows large increases in prevalence in older ages, which likely reflects misunderstanding the question, perhaps by confusing congenital heart disease with congestive heart disease.) We use NHIS data on recalled CHD to calculate prevalence for single year age groups from age 0 to 18, but this is the input data for our integrative systems model. An output of the model is (different) age-specific estimates of recalled CHD, which are produced up to age 65 (also by single-year age groups). We have attempted to clarify this in the CHD prevalence subsection and the modeling subsection of the methods section.

4. On p 8 - give more details about DisMod-PDE - most readers will have no familiarity with this model, where it sits in the panoply of other modeling approaches, or for that matter what an integrative systems model is. Merely citing references 19 and 20 is not sufficient.

We have added some text to the methods section and also added a web appendix describing the details of DisMod-PDE in response to this and similar requests from several other reviewers.

5. Also on p 8, birth defects researchers strongly prefer to use prevalence rather than incidence (Mason et al, BDRA 2005).

Thank you for calling attention to this important detail, we have adjusted this language.

6. Somewhere, also in the methodology, consider discussing the implications of secular change in rate of termination after prenatal diagnosis - it is hard to foresee the future, but unlikely that this rate has been or will be constant over time.

We have added a web appendix of sensitivity analysis in response to other reviewer comments, and in this framework it is straightforward to include a scenario where an increased rate of termination leads to decreasing birth prevalence of a certain percent per year (starting in 2015). As would be expected, there is a “dose-response” relationship: the larger the annual decrease, the smaller the projected future population. For a 1%-per-year decrease, the projection is 3.3% lower, and for a 10%-per-year decrease it is 38% lower. We agree with the reviewer that it is hard to foresee the future, but we hope that this sensitivity analysis approach demonstrates the strength of the ISM approach and provides a range of possibilities under differing scenarios.

7. Also in methods, how do cases diagnosed in adulthood factor into the estimates?

These cases are missed, and we have added this important caveat to the limitations section of our discussion. Although we estimate the prevalence recalled CHD (and have increase our efforts to explain this concept), the reviewer correctly identifies a limitation in our approach, which is that people who are diagnosed in adulthood will meet the criteria for recalled CHD, but will not be counted in the numerator of our estimates. This is another reason to consider our work a conservative lower bound on the number of people with ACHD.
8. *p 13 in limitations. Discuss the role also of underdiagnosis or late diagnosis along with misdiagnosis*

We have added the caveats as well. Thank you to the reviewer for this careful attention to the potential pitfalls of survey-based research.

9. *Noted above are several additional references which will provide balance to the methods and argument.*

We have added these references in the now-extended discussion comparing our estimates to other measurements.

10. *The figures are not ready for production as presented. Figure 1 should show the actual values on the Y-axis rather than 10 to -3, etc., that would translate to 1000, 10000, 100000 . . . but does the graph show mortality, or survival? To this reader’s eye, it seems to show survival, with many more infants surviving in recent years.*

Thank you for this feedback about the figures. It appears that they have confused other reviewers as well, so we have edited the captions and changed their format a bit in an attempt to make them clearer. Although it is a custom to use scientific notation on semi-log plots, we have followed the reviewer’s advice and used standard notation instead, and hope that this will be appreciated by other readers as well. The plots show data and estimates of cause specific mortality rates, measures of age-specific mortality in the general population, which have decreased precipitously in the last decades. The reviewer is quite right that this decrease in mortality corresponds to an increase in survival, both in infants and in older children. However, the elevated mortality rates in 20-64 year olds have not decreased in pace with the other age groups.

11. *Figure 2b assumes a level rate for birth prevalence, which is highly unlikely. While we do not have national data, metropolitan Atlanta has data from the 1960s, and New York State from the early 1980s. NBDPN has prepared national estimates for specific CHDs for 1999-2001 and 2004-2006 (Canfield et al BDRA 2006; Parker et al BDRA 2010).*

The reviewer is quite right to question this assumption, which we have tried to state clearly in our methods section (and show clearly in Figure 2b). The NBDPN estimates from the papers cited by the reviewer show that from 2000 to 2005 there was a decrease in birth prevalence of common truncus, HLHS, and TGA, and an increase in ASD and TOF prevalence. All of these estimates have moderate-sized confidence intervals, so it is likely that some of these changes are due to chance variation. Based on this and the similarly noisy nature of the NHIS prevalence data, we feel that the assumption of constant birth prevalence is the best compromise at this point. As mentioned above, we have now added a sensitivity analysis that includes a scenario where birth prevalence decreases by a constant amount per year starting in 2015, and in the 3% per year decrease case which most closely matches the change observed in NBDPN data, our model projects 8% less people with ACHD in 2050 than in the baseline model.

12. *The discussion seems rather long in relation to the data presented.*

We have edited the discussion to remove any excess, but we feel that what remains is all worthy of inclusion.
Review 4:

Major compulsory revisions:

1. Appropriate population estimates were multiplied to the disease rate estimates to obtain a population number and UI. Do the authors need to consider the uncertainty in the population estimates for either the forecast or UI? How do the two uncertainties compound in this setting?

We generally believe the population estimates to be more precise than the prevalence estimates, but the reviewer is quite right that we have neglected to include their uncertainty. In the estimates where population numbers are based on census and inter-census surveys, the magnitude of this simplifying assumption is negligible, but in the projections into the future, the population projections clearly have substantial uncertainty of their own. This also raises the question of differential migration, based on future availability/unavailability of ACHD care, as well as its perceived value. As another reviewer noted, it is hard to foresee the future, which is an insurmountable limitation in this approach. We have taken the approach of simplicity: using the US Census Department projections of population with an assumption that the uncertainty is independent of the uncertainty in our prevalence estimates, and is a negligible addition to the already-large uncertainty in our forecast.

The US Census Department does provide alternative scenarios for population projections, which we have included in the sensitivity analysis added in response to other reviewers’ suggestions. Using the low-growth scenario reduces the 2050 population projection by 5%, and using the high-growth scenario increases it by 5%.

2. Reference DisMod-PDE when it is first stated.

Thank you for identifying this oversight, we have done so.

3. The modeling section is tough because the model is not stated explicitly so it is not clear what to do. This can be mitigated by referencing another paper or a link to a comprehensive software manual.

We have moved the references so that they appear more prominently when DisMod-PDE is first stated (in response to [2] above), as well as added more to the methods section about the model, and we have also added a web appendix with the relevant mathematical details so that readers can get the gist of the approach without referring to another paper or software manual (although both are still also referenced and available for readers who want to know the nitty-gritty details).

4. I can’t say I am ok with the statistical methods in the paper because the method is not well enough described.

We hope that the additions described above address the reviewers concerns.

Minor essential revisions:

1. Define recalled CHD.

We have added this in the methods section in response to this and similar requests from other reviewers.
2. It may be good to state the names associated the ICD codes with the numbers. Also a more detailed explanation of why these codes were used for supplemental materials. Is this choice based on past history, what do other use etc....

We have greatly extended this supplemental material, in response to this comment and similar concerns raised by reviewer 2. In short, we began with the same list that the Global Burden of Disease Study uses, but refined it based on the concerns of reviewer 2. Our new list has been reviewed by an ACHD fellow at UW Medical, and we hope that it now meets the high standards of reviewer 2, as well. As you can see from the changes to the headline estimates between this draft and the initial submission, the differences in cause list do not substantially change the estimates (although it is important that it be correct!).

References


