PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Modelling Years of Life Lost Due to Acute Type A Aortic Dissection in the German Healthcare Setting: A Predictive Study
AUTHORS	Schiele, Philipp; König, Adriana N.; Meyer, Alexander; Falk, Volkmar; Nienaber, Christoph; Kurz, Stephan

VERSION 1 – REVIEW

REVIEWER	Mylonas, Spyridon N. University of Cologne, Department of Vascular and Endovascular Surgery
REVIEW RETURNED	20-Aug-2023

GENERAL COMMENTS	The authors performed a systematic review of the literature and by combining/comparing the findings with the demographic data from the German healthcare authorities have developed a predictive model along patient pathways to estimate the burden of ATAAD through the Years of Life Lost (YLL) metric. Hereby are my comments: Please provide the inclusion and exclusion criteria applied for the literature review. Did you perform a risk of bias assessment for the eligible studies? Applying the PRISMA guidelines would increase the quality of your paper Please provide a table of the included studies.

REVIEWER	Vrsalovic, Mislav University of Zagreb Faculty of Medicine
REVIEW RETURNED	24-Aug-2023

GENERAL COMMENTS	The study primarily relied on modelling techniques and parameterization using available published data. There are some issues regarding potential biases and uncertainties associated with data quality and reliability. So, the crucial question is about statistical and epidemiological methods used in the study. It would be highly recommended firstly to include statistical editor and epidemiologist, and cardiologist/vascular medicine specialist later on in the review process. Best wishes

REVIEWER	Russo, Claudio Ospedale Niguarda Ca Granda, Cardiovascular Surgery
REVIEW RETURNED	26-Oct-2023

GENERAL COMMENTS	I congratulate the Authors for such an intersting paper, enphasizing crucial aspect in the management of AAD type A. This papere coul be very usefull in treatment of such demanding disese and in ordere to proper public resources allocation

REVIEWER	Johnson, Catherine University of Washington
REVIEW RETURNED	20-Dec-2023

GENERAL COMMENTS	This manuscript is well-written and provides an important contribution to the field of research. However, there are a few points which the authors should consider: 1) YLLs are inherently a population-level metric and should not be used to make individual-level decisions. A policy change that may increase overall survival of persons with ATAAD may negatively impact survival for a patient or subgroup of patients, thus the title is misleading as the information provided should not be used for decision-making by patients. 2) Given that the incidence of aortic dissection was obtained from autopsy studies, it would be useful to know how the population of persons who are autopsied compares with the general population. It would also be useful to know how many persons with ATAAD are captured by autopsy studies; this proportion is likely to vary by age. 3) Ultrasound screening for aortic aneurysm/dissection is quite common in high-income locations; including the impact of screening on survival/YLL burden should be included in the analysis. 4) What model is being used to determine the impact of the different scenarios? The description in the main text is insufficient with regards to the approach(es) used and the limitations due to the implementation of the chosen modeling strategy.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:

We greatly appreciate Reviewer 1's supportive comments on the systematic literature review and the use of demographic data from the German Healthcare Authorities. This approach has indeed enabled us to develop a predictive model to estimate the burden of ATAAD using the YLL metric.

Following Reviewer 1's suggestions, we have:

Inclusion and Exclusion Criteria: Added detailed inclusion and exclusion criteria for the literature review in the Methods section of our manuscript. This enhancement ensures our systematic review aligns with best practices and provides clarity on our study selection process.

PRISMA Guidelines: In alignment with the suggestion that was also raised in the editorial comment we have included a PRISMA checklist to the submission for the review aspect of the paper, which also includes a risk of bias assessment.We further point to the limitations for a potential risk of bias, but highlight that additional studies can easily be added to the model. All studies that were identified were used in the model and can thus be found in the reference list.We would like to emphasize that our study's primary focus is on the predictive model and includes the systematic search to identify relevant studies that inform the model.

Response to Reviewer 2:

Reviewer 2's observations on the use of published evidence and the methodologies employed are well-taken.We respect the Journal's Editorial Board's process in selecting reviewers and trust in their expertise and judgment.We understand the concerns about potential biases and uncertainties, which we hope are at least partially addressed by the addition of the PRISMA checklist. The uncertainty of the estimate may indeed be hard to quantify, which is why we have chosen to not only model the best and worst-case scenarios but also to make the model available via a dashboard. This allows for the exploration of different scenarios and the inclusion of additional studies as they become available.

Response to Reviewer 3:

We are heartened by Dr. Russo's recognition of the significance of our work in addressing key aspects of the management of typeA aortic dissection and its potential to inform public resource allocation.We remain committed to highlighting the critical political impact of our findings.

Response to Reviewer 4:

Dr. Johnson's acknowledgment of our manuscript's contribution is much appreciated. We wish to address her concerns thoughtfully:

YLL as a basis for individual treatment decisions: We agree that YLL is not a suitable metric for individual
treatment decisions but instead may be used on an aggregate level. As suggested by the reviewer, we have adapted the title of our manuscript to reflect this.

Autopsy Data: We agree that the age distribution in the autopsy data is not reflective of the age distribution of
Germany. However, we would like to clarify that we only used the relative incidence rates from the study, which was then mapped to the age distribution of Germany. Additionally, we provide another distribution based on the population based study by Howard and colleagues. To make this more clear, we have rephrased the corresponding paragraph in the manuscript.

Applying the relative incidence rates per age group according to this distribution (Figure 3) to the population data of Germany, we derived an annual incidence rate of 14.5 cases per 100,000 population

Ultrasound Screening: We clarify that our study does not conflate ultrasound screening for AAA with AD, as no such screening for AD exists to our knowledge in the German healthcare system. Since the study by Zaschke and colleagues also was conducted in Germany, we believe that the (mis)diagnosis rates are comparable. To address this point as a distinction between Germany and other systems, we have added the following sentence to the manuscript:

Additionally, ultrasound screening may be used to enhance the diagnosis process even further.

Model Description: The impact of the different scenarios is characterized by the difference in YLL between the best and worst-case scenarios.We have added a sentence to the manuscript to clarify this point.

Thus, the overall impact of the different scenarios amounts to 19,832 (8,750) YLL.

We hope these responses and the modifications made to our manuscript address the reviewers' comments comprehensively and enhance the quality and impact of our study.

VERSION 2 – REVIEW

REVIEWER	Mylonas, Spyridon N. University of Cologne, Department of Vascular and Endovascular Surgery
REVIEW RETURNED	19-Feb-2024

GENERAL COMMENTS	The authors have conducted a very interesting study with a unique design trying to investigate the outcome of patients with ATAAD. Although the modeling process seems reasonable and robust there are a few issues that should be addressed: “a risk of bias assessment was conducted for each selected study to ensure the reliability and validity of our analysis” Please elaborate which test for risk of bias (Cochrane , Joanna Briggs, ect) was applied. Please add the results as a supplementary figure. The model is based on several publications for each parameter. This leads to confusing interpretation of the results. For instance “All estimates are based on the incidence distribution presented in Kurz et al . 3 . [3] , with alternative results provided based on an incidence distribution presented in Howard et al . 2 . [2] in parenthesis.” The publication of Kurz et al. represents a german population, while the publication of Howard et al refers to a British population. As the YLL modeling has taken into consideration the population pyramid of Germany, one could consider to avoid citing the study by Howard et al. On the contrary, referring only to a single study would weaken the robustness of the results. Moreover, the publication of Zacke et al, which is used to define the worst and the best scenario, refers also to german population. Thus, combining the available studies in a meta-analysis and obtaining pooled results would strengthen the validity of the suggested model. An alternative could be to use only studies referring to German population. In this case this should be stated in the inclusion criteria of the eligible studies, which however is clearly stated in the limitations section “Furthermore, our study focused on the population of Germany, limiting generalizability and applicability to other regions with different healthcare systems and demographics.”

REVIEWER	Johnson, Catherine University of Washington
REVIEW RETURNED	04-Mar-2024

GENERAL COMMENTS	I appreciate the authors' careful attention to the issues raised during the review process.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewers

We sincerely thank Reviewers 1 and 4 for their insightful comments on our manuscript. Your feedback has been invaluable in refining our research.

Reviewer 1's thoughtful suggestions regarding potential biases and interpretation have been carefully considered. Below, we respond to the suggestions point-to-point.

Clafirifaction on the risk of bias assessment:

We acknowledge the importance of ensuring the robustness of our findings and will address this concern by providing a clear description of our study selection process and rationale for inclusion criteria.

Given the nature of our study, many domains typically considered in risk of bias assessments, such as bias due to randomization, deviation from intended intervention, missing data, and outcome measurement, were not applicable. Instead, our risk of bias assessment primarily addressed biases arising from differences in populations or measurements. For example, we considered biases stemming from data records collected from emergency departments, which may not capture immediate mortality cases of ATAAT, compared to studies based on full population data or autopsies. To enhance clarity on this aspect, we have revised the corresponding paragraph in our paper to not use the more narrowly defined term “risk of bias assessment”. The two sentences now read:

After removing duplicates, the remaining studies were assessed for inclusion and relevance by at least two independent reviewers using strict criteria.

and

Additionally, each study underwent careful evaluation to ensure the reliability and validity of our analysis, with a particular focus on the considered study populations and measurements.

Providing an alternative incidence distribution:

We fully agree with the reviewer that it is highly important to use parameters derived from comparable populations. To improve our exposition of the results, we have modified the introduction of the section to:

The simulation results for our predefined scenarios are outlined below. All estimates are primarily based on the incidence distribution reported in Kurz et al. [3], which reflects the German population. Alternative results are also provided, based on an incidence distribution presented in Howard et al. [2] (originating from Oxfordshire, United Kingdom) and presented in parenthesis for comparative purposes.

We believe this option is preferable over fully removing the results because of the considerable uncertainty in these parameters due to the low incidence rates. While acknowledging the limitations of comparing populations, it's worth noting that the UK and German populations share many similarities. As mentioned by the reviewer, we have duly noted this as a limitation of our study. With the modified introduction, we are confident that readers will grasp the significance of these numbers in illustrating the impact of the incidence distribution on overall years of life lost.

To Reviewer 4, we express gratitude for recognizing our efforts in addressing the issues raised during the review process. Your feedback is appreciated and serves as encouragement to further enhance the manuscript.

We also extend our thanks to the editorial team, particularly Emma Johnson and Clare Partridge, for their support and guidance throughout this process.

We have carefully reviewed all comments and made appropriate revisions. Please refer to the attached manuscript for detailed responses and corresponding revisions.

VERSION 3 – REVIEW

REVIEWER	Mylonas, Spyridon N. University of Cologne, Department of Vascular and Endovascular Surgery
REVIEW RETURNED	13-May-2024

GENERAL COMMENTS	The author's have clarified the raised issues. I have no further comments. Congratulations for your very interesting work!