Author's response to reviews

Title: Population risk factor estimates for abdominal aortic aneurysm from electronic medical records: a case control study

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Timothy Shipley, PhD
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Dear Dr. Shipley,

We would like to submit our revised manuscript entitled: “Population risk factor estimates for abdominal aortic aneurysm from electronic medical records: a case control study” by myself, G Tromp, JR Elmore, H Kuivaniemi, DP Franklin, HL Kirchner and DJ Carey, for publication in BMC Cardiovascular Disorders.

We are grateful for the two expert Reviewers for their insightful comments. Below we provide detailed responses to the specific comments.

**Reviewer 1:**

1. **Limited information is provided with regard to the relevance of the findings for AAA research. Make clear that their work focuses on incident AAA disease and not on AAA progression, which may involve different risk factors.**

   **Response:** We agree with the Reviewer that risk factors that contribute to the development and progression of AAA are likely to differ. We are looking only at incident AAA disease, using the first confirmed diagnosis of AAA for each patient. We have clarified this in the "Background" (first paragraph on page 4), and “Discussion” (page 12) sections.

2. **To what extend are the findings influence by co-morbidity? Even in a time of screening most AAAs are incidental findings. How is co-morbidity influencing the results of this study (i.e. kidney disease as a reason for an abdominal ultrasound).**

   **Response:** We agree that most AAAs are detected as incidental findings. Our vascular clinic estimates that approximately 95% of aneurysms are asymptomatic until they rupture. Of the asymptomatic aneurysms almost all are found by chance during testing for another medical condition. Aortic screening exam has rarely been used until October 2013 at Geisinger when a new Epic initiative was started. Physical exam rarely detects an aneurysm due to obesity padding the aneurysm and limiting physical exam findings. **The role of co-morbidities as causes for screening and incidental detection of AAA is not clear**
3. Are the observed associations [of co-morbidities] causative or correlative?

**Response:** The Reviewer raises an important point. Since this is a cross sectional study, we cannot determine causation. Also, we have a large number of smokers in our population (both cases and controls) which may mute the magnitude of the associated variables. We have added a sentence “Since the current study is cross-sectional, we cannot determine causation, but rather the results reveal correlations between incident AAA and various clinical variables.” in the “Discussion” (page 11) pointing this out.

4. With the exception of benign and malignant neoplasms (is smoking the co-correlate for the association between malignant neoplasm and AAA?) the authors did not identify novel risk markers for AAA disease.

**Response:** Indeed, our study identified only a few novel risk factors: benign, myelogenous and malignant neoplasms. The correlation with malignant neoplasm is weak, but could plausibly be due to increased tobacco exposure, one of the strongest risk factors for AAA. On the other hand, the negative association with benign and myelogenous neoplasms is in some ways more intriguing.

5 Relative low risk for sex (2.0), does this reflect a more masculine life style in the Geisinger cohort?

**Response:** The Reviewer correctly observes that the OR for sex is lower than that inferred from the ratio of male to female cases. We used multivariable analysis, and the risk effect from other variables may decrease the effect of any other covariable including sex. When we performed unadjusted univariate analyses in the preliminary stages of this study, the risk for sex was much higher. Also, Pennsylvania has one of the highest rates of AAA mortality as seen in the CDC data: http://wonder.cdc.gov/controller/datarequest/D91;jsessionid=480C999B1BC677993F84EC28E74B0DE0We have added a statement in the “Background” section (first paragraph on page 4): “Pennsylvania has one of the highest rates of mortality from AAA in the USA [2].”

**Reviewer 2:**

1. A reverse relation between benign neoplasms and risk for AAA is identified as a new finding. Both the epidemiological, clinical and biological significance of this finding is unclear.
Response: We agree that the significance of this finding is unclear. Further research is necessary and may provide a clue to the molecular biology of AAA. We included this in the “Discussion” section (page 11): “The protective association of benign neoplasms with AAA identified in the current study is intriguing. The most common type of neoplasm was of the skin, significantly more common in controls than cases. Neoplasms of the digestive system were more common in cases. The identified association is biologically plausible since two genes (CDKN2BAS and DABP2) with strong associations to AAA have roles in cell growth [65,66]. Further research is necessary and may provide a clue to the molecular biology of AAA.”

2. “Generalizability of the results to other populations is unknown, ...” The main concern regarding this is that few populations outside the Geisinger Health System in Pennsylvania is registered in such a comprehensive database as presented here. The quality of the input into clinical databases varies a lot. In addition, not all of the electronic medical record systems make queries, as done in this report, possible.

Response: We agree with the Reviewer that the data that can be obtained from an EMR such as the one at Geisinger is not universal. On the other hand, due to changes in USA Federal regulations involving Centers for Medicare and Medicaid Services CMS payment it is likely that in the near future almost all health systems in the USA will have an EMR and be able to easily retrieve the metrics we used. In addition, several research networks are using EMRs indicating that a number of other institutions have data comparable to that of Geisinger. To expand discussion on this topic, we have included in the “Discussion” section the following statement (pages 11-12): “Approaches to using EMR data are being investigated by a number of groups including the NIH-funded electronic Medical Record and Genomics (eMERGE) Network [68,69] and the Health Maintenance Organization Research Network (HMORN) Virtual Data Warehouse (VDW) project [70]. “

3. The population studied here is the 2.6 million inhabitants included in the Geisinger Health System. The percentage of the population in the actual area this represents is not stated.

Response: The Reviewer raises an important point. Geisinger serves a geographically large catchment area, some of which is sparsely populated. The region is divided into about 38 administrative divisions called counties. To address the reviewer’s comment, we obtained the population counts for the counties where Geisinger serves at least 10% of the population based on the US 2010 Census. In aggregate Geisinger serves about half of the two million residents in the aforementioned counties.

We have modified the description of the study population in the “Methods” (page 5) section: “GHS provides primary and specialty care to a highly stable population of 2.6 million residents in Central and Northeastern Pennsylvania. Geisinger serves a large catchment area. We restricted the region to those
regional divisions (counties) where Geisinger serves more than 10% of the county population. Among these counties Geisinger serves about half of their two million inhabitants.”

We also added H. Lester Kirchner as an additional co-author, since he assisted in the revisions and provided statistical expertise to the manuscript.

Yours Sincerely,

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Research Scientist