Appendix - Enhanced Methods and Results section

**Manuscript title:** ‘National, regional and global mortality due to alcoholic cardiomyopathy in 2015’

**Authors:** Jakob Manthey, Charlotte Probst, Margaret Rylett, Jürgen Rehm

**Abbreviations**

AAF = alcohol-attributable fraction, i.e. proportion of deaths due to alcoholic cardiomyopathy among all deaths due to cardiomyopathy

ACM = alcoholic cardiomyopathy

AUD = alcohol use disorder

CM = cardiomyopathy

GBD = Global Burden of Disease

WHO = World Health Organization

**METHODS**

The methods are largely based on a previous publication [1]. This document gives a detailed description on the modelling decisions for the current analysis.

**Mortality data**

As alcohol exposure is traditionally measured for populations 15 and older [2, 3], all mortality data was restricted to this age group.

Data on deaths due to ACM were mainly retrieved from the WHO mortality data base [4]. Where any three-digit ICD-10 I42.X code was reported, we obtained the sex- and age-specific number of ACM (ICD-10 code I42.6) deaths for the three most recent years. If no ICD-10 I42.6 death was reported, 0 ACM deaths were coded. For N=89 WHO member states, sex-specific mortality data could be obtained from this data base. For Russia and Slovenia, ACM mortality figures were obtained by government sources ([5, 6]).

For more stability in ACM mortality data, three-year moving averages were used where available (N=5 countries with data from one year, N=3 from two years, N=83 from three years). The obtained ACM mortality data were recorded between 1995 and 2016 (median = 2014). For the majority of countries (N=79), at least one source year was in the most current three-year-period of available mortality data (2013-2015), whereas for 14 countries all mortality data were recorded before 2013.

In all countries without ACM mortality data (N=102), all covariate data was based on 2015 values.

All data on deaths due to CM were sourced from the WHO [7]. These figures represent all deaths due to “Cardiomyopathy, myocarditis, endocarditis”. To allow for comparisons with ACM mortality data from the GBD study, country-specific data were obtained from the GBD Results Tool [8].
Covariate data
The most recent estimates for adult per capita consumption from 2015 or earlier were obtained from the Global Information System on Alcohol and Health [3].

The proportion of people with AUD and the proportion of current drinker was obtained from the Global Status Report on Alcohol and Health [9]. For a small number of countries without data, we assumed the same proportions of AUD and current drinker as the nearest countries with available data (Cook Islands, Marshall Islands, Niue, Nauru, Palau, Tuvalu = Federated States of Micronesia; Monaco = France; Saint Kitts and Nevis = Antigua and Barbuda; San Marino = Italy).

Population data was sourced from the United Nations World Population Prospects [10]. Regional clusters were defined as GBD sub regions [11].

Data analyses
It was aimed to model the relationship between population alcohol exposure and deaths due to alcoholic cardiomyopathy. In an extensive process, potential sex-specific candidate models were reviewed for best data fit. First, non-nested candidate models were built using APC, AUD prevalence and number of CM deaths as predictors. Poisson and negative binomial models were considered to be adequate regression techniques as the majority of countries reported very few or zero deaths [12]. Likelihood ratio tests indicated best fit of negative binomial models. Due to excess zeroes in the outcome variable, an additional zero-inflation term was considered to improve the model. Vuong tests indicated best fit for non-inflated models. Subsequently, a number of candidate models using various combinations of potential covariates (AUD, APC, proportion of drinkers, population size, number of cardiomyopathy deaths) were reviewed referring to density plots, comparison of observed and fitted values, and plausibility of predictions (e.g. fewer ACM deaths than CM deaths). Finally, for well-fitting models, likelihood ratio and Vuong tests evaluated if alternative model specifications (i.e., Poisson and/or zero-inflation) can improve data fit. In Appendix Table A1 and Appendix Table A2, model specifications of key candidate models including results from likelihood ratio and Vuong tests are presented for the female and male population, respectively.

Eventually, two negative binomial regression models were selected. In the female model, ACM deaths were predicted by APC among females (Incidence rate ratio (IRR) = 1.72, 95% confidence interval (CI): 1.20-2.62, p<.001), AUD prevalence (IRR = 1.18, 95% CI: 0.82-1.75, p=.323), the log population size (IRR = 0.66, 95% CI: 0.48-0.93, p=.001), in addition to using the log of CM deaths as offset. In the male model, ACM deaths were predicted by APC among males (IRR = 1.23, 95% CI: 1.15-1.30, p<.001) and the log of CM deaths (IRR = 2.30, 95% CI: 1.91-2.84, p<.001).

In order to evaluate the goodness of fit of the models, we looked at residuals-vs-fitted plots and density plots of predicted vs. recorded values for visual inspection. Further, we compared predicted and recorded values, where absolute differences of at least 10 deaths per 1,000,000 adults and of 5% in the AAFs were identified as relevant deviations. Systematic differences in the regional distributions (using standardized residuals larger than 1.96) were identified between countries within and beyond these thresholds.

In N=3 countries (Niue, Nauru, Tuvalu) 0 CM deaths were recorded for females and males. As this implies 0 ACM deaths counts, they were excluded from the models.
A newly computed variable contained the number of recorded ACM deaths and added predicted deaths for countries without any recorded mortality data. 95% confidence intervals were obtained from the predicted standard error for both recorded and predicted values. Thus, this variable presented the main results, denoting ACM mortality data for each country by sex. Mortality rates (expressed as number of ACM deaths per 1,000,000 adults) and AAFs were calculated from this variable.

A combination of sex-stratified results produced figures for the total population. ACM deaths were summed up over sex, the mortality rates were weighted using female and male population sizes, and the AAFs were weighted using the sex-specific number of CM deaths. Aggregation over countries was done in an analogous manner.

In the additional analysis, countries with underreporting ACM deaths were identified as countries in which the recorded number of ACM deaths was lower than the rounded lower CI of the corresponding predicted number of ACM deaths. This was done separately by sex and for the total population. As quantitative indicator for underreporting, the difference between predicted and recorded ACM deaths was summed over the identified countries. All analyses were performed with R [13].

RESULTS

See Appendix Table B for ACM deaths, mortality rates and AAFs for each country by sex.

Goodness of fit

For a comparison of recorded and predicted values for each country, see Appendix Table C. In Appendix Figure 1, density distribution of recorded and predicted deaths due to ACM are presented by sex and for the total population.

With regard to mortality rates in the total population, relevant deviations were observed in 17 countries (female population: N=10, male population: N=20). A larger number of countries showed relevant deviations between recorded and predicted AAFs (total population: N=30, female population: N=20, male population: N=34). Looking at the comparison of recorded and predicted mortality rates in the total population, a significant number of deviations were found in countries from Central Europe and Eastern Europe (female: Central Europe and Eastern Europe, male: Central Europe and Eastern Europe). Regarding AAFs, a significant number of deviations were found in countries from Central Asia, Central Europe, and Eastern Europe (female: Eastern Europe, male: Central Europe, and Eastern Europe). In other words, the majority of regions were not affected by systematic deviation between recorded and predicted values. However, some countries in Central Asia, Central Europe, and Eastern Europe could not be adequately represented by the models (see Appendix Table C).

Additional analyses

Comparing predicted and recorded ACM data results in a set of potentially underreporting countries, which are highlighted in Appendix Table C. For N=44 out of 91 countries, underreporting of ACM mortality data is probable according to the results of the prediction models.

Appendix Table D contains the vital statistics or modelled ACM mortality and estimates from the GBD study. Comparisons were feasible for 185 countries. For 13 countries highlighted in the Table, GBD estimates were below vital statistics/modelled data. For the remaining countries, GBD estimates exceeded vital statistics/modelled data by 0.1 to 26,800 deaths (mean difference: 326.0, median difference: 20.8).
References

Appendix Figure 1: Density distribution of alcoholic cardiomyopathy deaths, by sex and total population

Note. Solid lines denote recorded deaths, circles denote predicted deaths.
### Appendix Table A1. Female candidate model coefficients and selection details

<table>
<thead>
<tr>
<th>Model</th>
<th>Alcohol per capita (APC)</th>
<th>Alcohol use disorder (AUD)</th>
<th>log(population size)</th>
<th>Zero-inflation term: APC</th>
<th>Zero-inflation term: AUD</th>
<th>Akaike’s information criterion (AIC)</th>
<th>Likelihood ratio test*</th>
<th>AIC-corrected Vuong test**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative binomial model (final model)</strong></td>
<td>0.54 (0.18-0.96)</td>
<td>0.17 (-0.20-0.56)</td>
<td>-0.42 (-0.72- -0.07)</td>
<td></td>
<td></td>
<td>399.12</td>
<td>p &lt; .001</td>
<td></td>
</tr>
<tr>
<td><strong>Poisson model</strong></td>
<td>0.78 (0.70-0.86)</td>
<td>0.69 (0.66-0.72)</td>
<td>-0.11 (-0.15- -0.07)</td>
<td></td>
<td></td>
<td>2035.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zero-inflated negative binomial model</strong></td>
<td>0.11 (-0.27-0.48)</td>
<td>0.28 (-0.08-0.63)</td>
<td>-0.45 (-0.81- -0.08)</td>
<td>-2.62 (-5.09- -0.16)</td>
<td>0.39 (-0.72-1.5)</td>
<td>389.69</td>
<td>p = 0.160</td>
<td></td>
</tr>
</tbody>
</table>

**Note.**
* Likelihood ratio test evaluated superiority of negative binomial over Poisson model
** Vuong test examined superiority of zero-inflated negative binomial over non-inflated negative binomial model

### Appendix Table A2. Male candidate model coefficients and selection details

<table>
<thead>
<tr>
<th>Model</th>
<th>Alcohol per capita (APC)</th>
<th>log(number of cardiomyopathy deaths)</th>
<th>Zero-inflation term: APC</th>
<th>Akaike’s information criterion (AIC)</th>
<th>Likelihood ratio test*</th>
<th>AIC-corrected Vuong test**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative binomial model (final model)</strong></td>
<td>0.20 (0.14-0.26)</td>
<td>0.83 (0.65-1.04)</td>
<td></td>
<td>605.56</td>
<td>p &lt; .001</td>
<td></td>
</tr>
<tr>
<td><strong>Poisson model</strong></td>
<td>0.25 (0.24-0.25)</td>
<td>1.05 (1.03-1.06)</td>
<td></td>
<td>4373.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zero-inflated negative binomial model</strong></td>
<td>0.18 (0.12-0.24)</td>
<td>0.86 (0.66-1.05)</td>
<td>-38.76 (-184.41- 106.89)</td>
<td>603.14</td>
<td>p = 0.229</td>
<td></td>
</tr>
</tbody>
</table>

**Note.**
* Likelihood ratio test evaluated superiority of negative binomial over Poisson model
** Vuong test examined superiority of zero-inflated negative binomial over non-inflated negative binomial model
## Appendix Table B. Country- and sex-specific distribution of ACM deaths, mortality rates, and alcohol-attributable fractions

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of ACM deaths</th>
<th>Mortality rate</th>
<th>Alcohol-attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>2 (1-6)</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>Albania</td>
<td>12 (8-18)</td>
<td>4 (2-8)</td>
<td>8 (6-11)</td>
</tr>
<tr>
<td>Algeria</td>
<td>7 (3-19)</td>
<td>2 (1-7)</td>
<td>5 (2-12)</td>
</tr>
<tr>
<td>Andorra</td>
<td>2 (0-5)</td>
<td>1 (0-3)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Angola</td>
<td>25 (16-40)</td>
<td>7 (4-13)</td>
<td>18 (13-27)</td>
</tr>
<tr>
<td>Antigua and Barbuda</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Argentina</td>
<td>8 (0-94)</td>
<td>0 (0-30)</td>
<td>8 (0-64)</td>
</tr>
<tr>
<td>Armenia</td>
<td>1 (1-2)</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Australia</td>
<td>58 (35-96)</td>
<td>7 (0-22)</td>
<td>51 (35-73)</td>
</tr>
<tr>
<td>Austria</td>
<td>12 (0-192)</td>
<td>2 (0-141)</td>
<td>10 (0-51)</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>2 (1-4)</td>
<td>0 (0-1)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Bahamas</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Bahrain</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1 (0-3)</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Barbados</td>
<td>0 (0-3)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Belarus</td>
<td>403</td>
<td>29</td>
<td>374</td>
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</table>

Mortality rate

Alcohol-attributable fraction
<table>
<thead>
<tr>
<th>Country</th>
<th>(215-770)</th>
<th>(9-91)</th>
<th>(206-679)</th>
<th>(27-96.6)</th>
<th>(2.1-20.9)</th>
<th>(56.7-187.1)</th>
<th>(10.8-38.5%)</th>
<th>(1.9-18.4%)</th>
<th>(13.7-45.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>23</td>
<td>3</td>
<td>20</td>
<td>2.5</td>
<td>0.6</td>
<td>4.4</td>
<td>2.2%</td>
<td>0.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td>(0-76)</td>
<td>(0-33)</td>
<td>(5-42)</td>
<td>(0-8.1)</td>
<td>(0-7)</td>
<td>(1.1-9.3)</td>
<td>(0-7.3%)</td>
<td>(0-6%)</td>
<td>(1-8.8%)</td>
</tr>
<tr>
<td>Belize</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(0-1)</td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(0-3.4)</td>
<td>(0-2.7)</td>
<td>(0-4.2)</td>
<td>(0-4.5%)</td>
<td>(0-6.3%)</td>
<td>(0-3.8%)</td>
</tr>
<tr>
<td>Benin</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.6%</td>
<td>0.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>(1-4)</td>
<td>(0-2)</td>
<td>(1-2)</td>
<td>(0.2-0.7)</td>
<td>(0.1-0.6)</td>
<td>(0.2-0.7)</td>
<td>(0.3-1.1%)</td>
<td>(0.2-1%)</td>
<td>(0.4-1.3%)</td>
</tr>
<tr>
<td>Bhutan</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(0.1-0.5)</td>
<td>(0.1-0.8)</td>
<td>(0-0.3)</td>
<td>(0.2-1.9%)</td>
<td>(0.2-2.3%)</td>
<td>(0.2-1.3%)</td>
</tr>
<tr>
<td>Bolivia (Plurinational State of)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(0-5)</td>
<td>(0-3)</td>
<td>(0-2)</td>
<td>(0-0.9)</td>
<td>(0-1.1)</td>
<td>(0-0.7)</td>
<td>(0-0.7%)</td>
<td>(0-0.9%)</td>
<td>(0-0.5%)</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>51</td>
<td>26</td>
<td>24</td>
<td>15.4</td>
<td>15.8</td>
<td>15</td>
<td>1.3%</td>
<td>1.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>(29-88)</td>
<td>(14-49)</td>
<td>(15-40)</td>
<td>(8.9-26.8)</td>
<td>(8.6-29.2)</td>
<td>(9.3-24.4)</td>
<td>(0.7-2.2%)</td>
<td>(0.6-2%)</td>
<td>(0.9-2.5%)</td>
</tr>
<tr>
<td>Botswana</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>3.3</td>
<td>1.6</td>
<td>5</td>
<td>3.6%</td>
<td>1.7%</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>(3-8)</td>
<td>(1-2)</td>
<td>(2-6)</td>
<td>(2-5.4)</td>
<td>(0.8-3.2)</td>
<td>(3.2-7.7)</td>
<td>(2.2-6%)</td>
<td>(0.8-3.4%)</td>
<td>(3.7-8.8%)</td>
</tr>
<tr>
<td>Brazil</td>
<td>259</td>
<td>20</td>
<td>239</td>
<td>1.6</td>
<td>0.2</td>
<td>3.1</td>
<td>1.4%</td>
<td>0.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td></td>
<td>(112-561)</td>
<td>(2-70)</td>
<td>(111-490)</td>
<td>(0.7-3.6)</td>
<td>(0-0.9)</td>
<td>(1.4-6.4)</td>
<td>(0.6-3.1%)</td>
<td>(0-0.9%)</td>
<td>(1.4-6.4%)</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td>0.9%</td>
<td>0.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(0.1-1)</td>
<td>(0.1-1.2)</td>
<td>(0.1-0.8)</td>
<td>(0.2-1.8%)</td>
<td>(0.2-3.1%)</td>
<td>(0.2-1.1%)</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>1.3</td>
<td>0</td>
<td>2.7</td>
<td>0.3%</td>
<td>0%</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>(0-113)</td>
<td>(0-42)</td>
<td>(0-71)</td>
<td>(0-18.2)</td>
<td>(0-13.1)</td>
<td>(0-23.8)</td>
<td>(0-4.4%)</td>
<td>(0-2.9%)</td>
<td>(0-6.2%)</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>18</td>
<td>3</td>
<td>15</td>
<td>1.8</td>
<td>0.6</td>
<td>3.1</td>
<td>2.2%</td>
<td>0.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>(12-28)</td>
<td>(1-7)</td>
<td>(11-20)</td>
<td>(1.2-2.8)</td>
<td>(0.2-1.5)</td>
<td>(2.3-4.2)</td>
<td>(1.5-3.4%)</td>
<td>(0.3-1.8%)</td>
<td>(2.8-5.2%)</td>
</tr>
<tr>
<td>Burundi</td>
<td>8</td>
<td>2</td>
<td>7</td>
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<td>0.5</td>
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<td>2.3%</td>
<td>0.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>(6-12)</td>
<td>(1-3)</td>
<td>(5-10)</td>
<td>(0.9-2)</td>
<td>(0.3-0.9)</td>
<td>(1.6-3.2)</td>
<td>(1.6-3.4%)</td>
<td>(0.5-1.6%)</td>
<td>(2.5-4.9%)</td>
</tr>
<tr>
<td>Cabo Verde</td>
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<td>0</td>
<td>1</td>
<td>0.7</td>
<td>1.3</td>
<td>2.8%</td>
<td>2.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td></td>
<td>(0-1)</td>
<td>(0-0)</td>
<td>(0-0)</td>
<td>(0.4-2.3)</td>
<td>(0.3-1.8)</td>
<td>(0.6-2.8)</td>
<td>(1.2-6.5%)</td>
<td>(0.8-5.8%)</td>
<td>(1.6-7.1%)</td>
</tr>
<tr>
<td>Cambodia</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>0.7</td>
<td>0.3</td>
<td>1.1</td>
<td>1.3%</td>
<td>0.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td>(5-12)</td>
<td>(1-4)</td>
<td>(4-8)</td>
<td>(0.5-1.1)</td>
<td>(0.2-0.7)</td>
<td>(0.8-1.6)</td>
<td>(0.9-2%)</td>
<td>(0.3-1.1%)</td>
<td>(1.6-3.3%)</td>
</tr>
<tr>
<td>Cameroon</td>
<td>29</td>
<td>4</td>
<td>25</td>
<td>2.2</td>
<td>0.6</td>
<td>3.8</td>
<td>2.9%</td>
<td>1%</td>
<td>4.4%</td>
</tr>
<tr>
<td></td>
<td>(21-42)</td>
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Note.
ACM = alcoholic cardiomyopathic deaths according to ICD-10 (code I42.6).
Mortality rate = number of deaths per 1,000,000 adult population.
NA = number of CM deaths = 0, which implies no plausible predictions for these countries.
Number in bracket denote 95% confidence interval.
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### Venezuela (Bolivarian Republic of)

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**Note.**

ACM = alcoholic cardiomyopathic deaths according to ICD-10 (code I42.6).
Mortality rate = number of deaths per 1,000,000 adult population.
Alcohol-attributable fraction = proportion of ACM deaths among all deaths due to CM.
In highlighted countries, recorded ACM deaths are lower than lower CI of predicted ACM deaths.
## Appendix Table D. Comparison of ACM mortality data from vital registries/model predictions and from the GBD study.

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</table>

**Note.**

Vital registry mortality data refers to either directly sourced (indicated with an asterisk *) or model predictions, which represent the main results of this study.

In highlighted countries, ACM deaths in vital registries are larger than the GBD estimates.