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Association between alcohol consumption and abdominal aortic aneurysms: a systematic review and dose-response meta-analysis

Running title: Meta-analysis of aneurysms and alcohol

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Abstract

Background: Alcohol is a possible risk factor for Abdominal Aortic Aneurysm (AAA) but evidence from individual studies is weak and inconsistent. Existing narrative reviews suggest the possibility of nonlinear associations. We therefore aimed to formally quantify the association using a systematic literature review followed by dose-response meta-analysis of prospective studies.

Methods: MEDLINE, Embase and Web of Science were systematically searched to January 2017 for relevant prospective studies of alcohol consumption and AAA risk. Summary estimates of highest versus lowest levels of consumption, linear and nonlinear dose-response curves were quantified using random-effects models.

Results: Eleven relevant cohorts were identified presenting results from 3580 cases amongst 473092 participants. Data were extracted from 10 cohorts for meta-analyses of high versus low levels of alcohol consumption (risk ratio = 0.93, 95% CI 0.78-1.11, p=0.4, I²=47%). The linear dose-response RR could be derived from 11 cohorts (RR=1.00 per 8g alcohol/day, 95% Cl 0.97 to 1.04, p=0.9, I²=73%). Nonlinear dose-response results showed a tick-shaped curve with lower risks up to 2 units/day but increasing risks beyond that (p=0.05). The increase in risk beyond 2 units/day is stronger in men than in women.

Conclusions: Whilst the linear dose-response revealed little evidence of an association between alcohol consumption and AAA risk, a tick-shaped trend in the association was observed. This nonlinear dose-response revealed reduced risks for alcohol consumption below 2 units/day masking increasing risks beyond 2 units/day. Randomised controlled trials are unlikely, so this study may present the strongest level of evidence available.
Key Words: Abdominal aortic aneurysm; Alcohol; Meta-analysis; nonlinear dose-response.
**Introduction**

Abdominal aortic diameter is an independent predictor of survival\(^1\). The normal abdominal aorta is 19 to 22mm. Dilatation that is 25-29 mm is defined as sub-aneurysmal aorta, and \(\geq 30\text{mm}\) is defined as aneurysm (AAA). The vast majority of AAAs are asymptomatic until they expand beyond 55mm, when the risk of rupture increases substantially\(^2\). This rupture is associated with sudden onset of severe pain and collapse, and carries an overall mortality of 80\(^3\). Prevalence of AAA ranges from 2% to 8% in adults over the age of 65 years\(^4\) and so for this age group screening is recommended both by the United Kingdom National Health Service\(^5\) and the United States Preventative Task Force\(^6\). There are well established risk factors for AAA development such as increasing age, male sex and smoking status, but the role of alcohol remains uncertain\(^4,7-9\).

Alcohol consumption is common worldwide with an estimated intake of 6.2 litres of pure alcohol per capita per year worldwide\(^10\) and is a known cardiovascular disease (CVD) risk factor though it has been suggested that low levels of consumption may be beneficial, with only higher levels being detrimental\(^11-16\). Potential mechanisms include up-regulation of matrix metalloproteinases leading to aneurysm formation with higher intakes\(^17\), but it is not known whether the nonlinear associations generally seen in CVD apply to the same extent with AAA.

Determining the nature of the association between alcohol and AAA in adult men and women would be useful because it is a potentially modifiable risk factor. Given that evidence from individual studies is often weak and has been inconsistent, with only
narrative reviews conducted to date, the nature of the association between alcohol and AAA remains to be quantified. We therefore aimed to quantify the association using a systematic literature review followed by dose-response meta-analysis of prospective studies across a broad range of consumption levels, exploring potential sources of heterogeneity. In particular, we aimed to investigate whether a possible nonlinear trend, similar to that seen with CVD generally, exists in the relationship between AAAs and alcohol consumption.

Methods

Search Strategy

A literature search was conducted for all published articles up to January 2017 with the aim of retrieving all articles that reported associations between alcohol consumption and AAAs. Three electronic databases were searched: MEDLINE, Embase and Web of Science using keyword searches and exploded MESH terms based on synonyms for aspects of alcohol consumption and AAAs. The search was then restricted to studies identified as cohort studies, case-control studies, cross-sectional studies and randomised controlled trials, with the aim of identifying all prospective studies for meta-analysis. No date or language restrictions were imposed. The detailed search strategy used for the MEDLINE database can be seen in Supplemental Table 2. Reference lists of publications obtained were then hand-searched for additional relevant articles. The review protocol is published on PROSPERO, registration number CRD42017055529.

Study Selection
The titles and abstracts of retrieved publications were screened by two authors (SMS and DCG) to initially remove articles that were obviously irrelevant such as those pertaining to surgically associated risks of aneurysm repair and case reports. Of the remaining publications, the full texts were obtained in order to assess their relevance, again by two authors (SMS and DCG). Unpublished studies and abstracts were excluded. Only prospective cohort studies, including historical cohorts and case-control studies nested within a cohort were eligible for inclusion in the meta-analysis.

Studies must have been based on the assessment of alcohol consumption prior to the onset of AAAs to be included. Radiological/clinical diagnosis of an AAA, death due to a ruptured AAA, ruptured and/or surgical repair of an AAA or autopsy findings of an AAA were the outcomes included. An estimate of risk ratio (RR) must have been reported with the corresponding confidence interval (CI).

Alcohol consumption must have been measured quantitatively. If the number of drinks, glasses or units was quoted but not its alcohol content, the measurement was assumed to be a standard alcoholic drink and the associated alcohol content was determined by what is considered standard in the country/region where the research was conducted\textsuperscript{18-20}.

To conduct the linear dose-response meta-analysis, studies must have reported at least 3 categories of quantified alcohol intake or analysis of alcohol as a continuous variable together with the associated estimate of RR and CI. If more than one multivariable model was presented, the model used was the one most consistent with adjustment based on the
minimal sufficient adjustment sets from a directed acyclic graph, so that the most appropriate adjustment for confounding was made. Excluded were studies that reported episodic drinking patterns only such as binge drinking.

Data extraction and quality

The methodological quality of included studies was assessed by two authors (SMS and DCG) using the Newcastle-Ottawa scale. In the selection category, stars were awarded where adult participants were sampled from the general population and were representative of alcohol consumption in that population, if alcohol consumption was assessed by means of patient records or a structured interview or questionnaire, selection of unexposed participants from within the same population, and for demonstration that at the beginning of the study an AAA diagnosis was not present. In the comparability category, stars were awarded for adjustment for smoking, age and sex. Stars in the outcome category were awarded for AAA diagnosis made based on death or medical records as opposed to being self-reported, for follow-up till either the completion of the study, death or AAA diagnosis with at least 70% follow-up, where participants should have been followed up for at least 15 years.

The following information was extracted from identified studies: names of authors, publication year, type of study design, country where the research was conducted, follow-up duration, sample size, participants’ distribution by sex, participants’ age range or mean age, methods of assessment of alcohol intake and outcome assessment, total number of cases, number of non-cases or person-years and for each exposure category, alcohol intake
levels recorded as means, medians, midpoints or ranges for each category or unit of increment if analysed as continuous, RR estimates and CIs for the categories of alcohol consumption, covariates included in the multivariable model. Where the distribution of non-cases or person-years and cases in each category was not reported but the total was presented, it was estimated based on the definitions of quantiles. Data extraction was carried out by SMS and DCG, and checked by AJT.

Data synthesis and analysis

In the analysis of data, three methods were used. The first meta-analysis looked at the highest versus the lowest level of alcohol consumption. The second was a linear dose-response analysis and finally any possible nonlinear trend was assessed. A random effects model was used to derive a summary risk estimate of high versus low consumption with corresponding 95% CIs using the method described by Der Simonian and Laird\textsuperscript{22}. A linear dose-response trend was obtained for each study using Greenland and Longnecker’s method\textsuperscript{23}. The mean or median of the individual alcohol consumption category was used as the assigned exposure dose, or its midpoint if the mean or median were not given. Where the category was presented unbounded, and neither the mean nor median was quoted, the midpoint was calculated by assuming that its width was the same as the adjacent one. Where the reference category was not the lowest level of intake, estimates were first recalculated compared to the lowest intake, based on the method of Hamling et al\textsuperscript{24}. If a study presented results for alcohol consumption measured as a continuous exposure then this was used in preference as that study’s estimate in the linear dose-response analysis. If a difference in mean intakes between AAA cases and non-AAA controls was presented, a
linear dose-response was estimated based on the methods of Chêne and Thompson\textsuperscript{25}. A random effects model was then used to pool the dose-response risk estimate from each study.

Where separate cohorts were reported in the same publication, the results were included separately in the pooled analysis. This maintained study independence so that appropriate heterogeneity estimates would have been obtained. Where two publications contained data from the same cohort, the one with the most complete adjustment for confounding or most precise estimate was used, in that order of preference.

Examination of any possible nonlinearity between alcohol consumption and AAA was done using restricted cubic splines fitted to each study, using three knots fixed at the 10th, 50th and 90th percentiles through the distribution of category means, medians or midpoints of intake across all studies\textsuperscript{26}. Studies included in this analysis therefore required more than 3 categories of exposure to have been reported and could not have presented the risk only as a continuous measure of the exposure. These were then pooled using multivariate meta-analysis to estimate the linear and nonlinear components of the restricted cubic splines simultaneously\textsuperscript{27,28}.

Between-study heterogeneity was assessed using the range of individual study estimates observed\textsuperscript{29} and the $I^2$ statistic for the proportion of total variation explained by between-study variation\textsuperscript{30}. Subgroup analyses were performed for the main linear dose-response analysis to explore any characteristics of the study quality that could have contributed to
the heterogeneity obtained across the various studies. These included geographical location, follow-up length and adjustment for certain covariates. Additionally, any sex-specific associations were investigated for analyses of both linear non-linear trends. Sensitivity analyses were conducted by excluding one study at a time in order to assess the influence of each study on the overall estimate by observing to what extent the combined result changed. This also aided in exploring between-study heterogeneity. Potential small study effects such as publication bias were investigated using funnel plots. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and PRISMA guidelines were followed when conducting and reporting this review and analysis. All statistical analyses were performed using Stata version 14.2.

Results

From the 225 unique articles identified from the literature search, 9 relevant publications were identified presenting results from 11 separate cohort studies (see Figure 1). These cohorts included 3580 cases of AAA amongst 473092 participants. Of the 11 included cohorts, 4 were from Europe and 7 from the USA. Characteristics of these studies are presented in Supplemental Table 1.

Ten cohorts identified contributed towards the meta-analysis of highest vs lowest categories of alcohol intake. The summary risk ratio from this comparison was 0.93 (95% CI 0.78-
1.11, p = 0.4; I² = 47%) (see Figure 2). Estimates for individual studies ranged from around RR=0.5 to RR=2.0.

There was no indication of a small study effect such as publication bias, with no evidence of funnel plot asymmetry (p=0.2), though based on only 10 studies.

Eleven cohorts from all 9 publications could be included in the linear dose-response analysis. The category mean intakes ranged from 0 to approximately 80 mg/day of alcohol. The summary RR was 1.00 (95% CI 0.97 to 1.04; p = 0.9) per 1 UK unit (8g) of alcohol per day (see Figure 3). There was substantial heterogeneity between the studies (I²=73%) with estimates for individual studies ranging from around RR=0.7 to RR=1.7 per unit/day.

When restricted cubic splines were used to investigate the shape of the dose-response curve there was evidence of nonlinearity (p=0.05), with an apparent decreased risk at lower
levels of consumption up to about 10-15 mg/day then increasing thereafter, producing a

tick-shaped curve (Figure 4). The nonlinear dose-response curves were estimated on the
basis of six cohorts presenting results with sufficient information in 5
publications[30,34,35,37,38,40]. The data on the very highest intakes though, were based on just
one of the included studies[35]. Tick marks on the horizontal axis indicate the location of
category means, medians or midpoints of studies.

Risk of bias as assessed by the Newcastle-Ottawa scale was generally low for cohort studies
(Supplemental Table 3). Sensitivity analysis revealed similar estimates when each study was
excluded separately (data not shown. Differential adjustment for anthropometry (e.g. body
mass index) and for socio-economic markers (e.g. education) were significant sources of
heterogeneity, with those ignoring these covariates presenting higher estimates
(Supplemental Table 4). Similarly, studies based in Europe tended to present higher
estimates than those from the US.

Studies presenting results just for males produced higher overall estimates for the linear
dose-response estimates than studies presenting results just for females, though confidence
intervals were wide (Supplemental Table 4). The nonlinear dose-response curve for males,
however, produced a slightly more pronounced increase in risk at higher levels of alcohol
consumption (Supplemental Figure 1).
Discussion

This study is the first to quantify the association between alcohol consumption and AAAs in a meta-analysis and also the first to investigate any nonlinear associations that exist and to describe the shape of the dose-response curve. The linear dose-response analysis combined results from 11 large prospective cohort studies, including over 3500 cases identified from nearly 500000 participants, followed-up for between 5 and 34 years.

Both the high versus low and the linear dose-response demonstrated no evidence of a strong association between alcohol consumption and AAA. However, associations may have been masked by the observed nonlinear trend, where lower levels of alcohol consumption appeared were associated with lower risk until approximately 15 to 20 g/day, with an increasing risk thereafter. This produced a tick-shaped curve often observed with alcohol studies and with turning points similar to those seen in meta-analyses of alcohol with IHD and stroke\textsuperscript{11,42,43}. Results are also consistent with an earlier narrative review\textsuperscript{44} and research into alcohol and aortic diameter \textsuperscript{45}. The risk ratio estimates are quite modest, but AAA has a high prevalence rate, particularly in men. So if the associations are causal, even modest protection could reduce the number of diagnoses and any subsequent surgery for a large number of individuals.

A tick-shaped curve is consistent with people who consume alcohol “in moderation” also having other aspects of their lifestyle “in moderation” in ways that the individual studies
were unable to fully adjust for, or non-consumers being systematically different to the rest of the cohort they are members of, in a way that puts them at greater risk.

Meta-analysis of cohort studies is prone to the same potential biases as the contributing cohorts, so associations cannot be proved to be causal. There may be unknown residual confounding in some, if not all, of the studies. For example, not all studies adjusted for smoking, and that that did used self-reported smoking rather than an objective biomarker.

Between-study heterogeneity was high, despite restriction to prospective studies and different categories of exposure being combined onto the same scale. Exploration of potential sources of heterogeneity revealed significant differences between studies that adjusted for ischemic heart disease (IHD) and those that did not, and between studies that adjusted for education and those that did not. The studies that did not adjust for IHD excluded these patients instead, so it is possible that these patients were generally healthier, potentially eliminating any effect of moderate drinkers appearing to have lower risk than non-drinkers due to the poorer health status of abstainers. However, the interpretation of all such exploration of heterogeneity is limited by the relatively small number of studies in the meta-analyses.

A further limitation of observational studies is the use of self-reported alcohol consumption. This exposure estimate is therefore in part subjective and susceptible to differential measurement misclassification of intake. Additionally, studies in this meta-analysis mostly used current drinking patterns within the previous year to assess the exposure. If the
relevant exposure is longer-term intake, then current intake may not reflect this, but only
one study used an estimate of alcohol intake that was updated with each follow-up visit to
better reflect longer-term use \(^{37}\). Use of food frequency questionnaires (FFQs) also requires
averaging intake over the time period in question, such as the past year. This can lead to
difficulties taking episodic drinking into account, and may have included some people with
infrequent heavy drinking as being included in lower categories of intake. It is possible that
episodic drinking may also negate any beneficial effects of lower average consumption\(^{14}\).

The annual growth rate of AAAs less than 55mm is slow\(^{46}\) but then accelerates beyond that.
There is potential a different strength of association between alcohol consumption and
growth in these two stages or with subsequent rupture. It is also possible that alcohol
consumption may be associated with probability of success or otherwise of endovascular
aneurysm repair. These are possible areas for future research.

A lack of evidence of increased risk with high levels of alcohol consumption does not imply
evidence of no association. Confidence intervals remain relatively wide, allowing a range of
strength of association. Alcohol consumption is known to have detrimental effects both
acutely and chronically on various aspects of health such as liver cirrhosis, cancers of the
gastrointestinal tract and liver and increased risk of injury, as well as breast cancer even in
moderate amounts\(^{47,48}\). Therefore from a public health perspective, our results are
consistent with maintaining current recommendations for alcohol intake\(^{20}\).
The risk for developing an AAA is greater in men than women but the size at which the female AAA ruptures is potentially smaller than for men. Furthermore, women may benefit less from intervention than men and may have poorer longer-term survival than men. With these apparent differences between the risk profiles of men and women, it is therefore relevant that the dose-response curve in males appeared to be steeper than for women at high levels of consumption.

Whilst the tick-shaped dose-response curve observed is similar to that seen in other vascular diseases, there may be differences in pathogenesis. High levels of alcohol have been shown to up regulate aortic metalloproteases in rats, which has been regarded as a mechanism in the pathology of AAAs along with inflammatory factors, loss of aortic elasticity and media thickness. This could therefore account for an increased risk at higher consumption levels. While it is known that IHD is predominantly an atherosclerotic disease with the protective effects of alcohol consumption mainly attributed to its antioxidant properties, reduction in hyperlipidaemia and decreased plaque and thrombus formation, it has been suggested that atheroma formation leads to arterial remodelling which can subsequently stimulate the biological pathways involved aneurysmal formation. It is therefore possible that factors which reduce the risk of atherosclerosis can also decrease that of AAAs indirectly, even if not causally.

Only randomisation of exposure would provide more robust evidence than our review. One potential route forward may be through a combination of Mendelian randomisation and big data. Using a genetic variant as a randomly allocated instrument for the environmentally
modifiable exposure of alcohol intake\textsuperscript{60}, or in some cases even non-genetic instrumental
variables\textsuperscript{61}, may provide some more robust insight that the traditional observational cohorts
reviewed to date are unable to provide. Use of biomarkers for alcohol intake would also add
a degree more objectivity to the exposure assessment.

In conclusion, though results from observational studies should be interpreted cautiously,
this is the first study to quantify the dose-response curve for the association between
alcohol consumption and AAA and find it to be similar to that seen in IHD.
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Disclosure

The authors declare that there are no conflicts of interest.
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Figure legends

1. Figure 1: PRISMA Flowchart of article retrieval and screening process.

2. Figure 2: Forest Plot of highest versus lowest categories of alcohol consumption and AAA.

3. Figure 3: Forest Plot of linear dose-response analysis of alcohol consumption and AAA.

4. Figure 4: Nonlinear dose-response curve for alcohol consumption and AAA risk.