Aneurysm Global Epidemiology Study: Public Health Measures can Further Reduce Abdominal Aortic Aneurysm Mortality

Running title: Sidloff et al.; Aneurysm Global Epidemiology Study

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Abstract

Background—Contemporary data from western populations suggest steep declines in abdominal aortic aneurysm (AAA) mortality however international trends are unclear. This study aimed to investigate global AAA mortality trends and to analyse any association with common cardiovascular risk factors.

Methods and Results—AAA mortality (1994-2010) using ICD codes were extracted from the WHO mortality database and age standardised. WHO InfoBase and International Mortality and Smoking Statistics provided risk factor data. Nineteen WHO member states were included (Europe=14, Australasia=2, North America=2, Asia=1). Regression analysis of temporal trends in cardiovascular risk factors (1946-2010) were analysed independently for correlations to AAA mortality trends. Global AAA mortality trends show substantial heterogeneity with the USA and UK recording the greatest national decline, whilst internationally males and those under 75 demonstrated the greatest reductions. AAA mortality has increased in Hungary, Romania, Austria and Denmark therefore the mortality decline is not universal. A positive linear relationship exists between global trends in systolic blood pressure (P=<0.03), cholesterol (P=<0.03) and smoking prevalence (P=<0.02) in males and females. BMI demonstrated a negative linear association with AAA mortality (P=<0.007) whilst fasting blood glucose showed no association.

Conclusions—AAA mortality has not declined globally and this study reveals that differences between nations can be explained by variations in traditional cardiovascular risk factors. Declines in smoking prevalence correlate most closely with declines in AAA mortality and a novel ‘obesity paradox’ has been identified which requires further investigation. Public health measures could therefore further reduce global AAA mortality, with greatest benefits in the younger age group.

Key words: aneurysm, aorta, aortic disease, aortic surgery, epidemiology
Introduction

Abdominal aortic aneurysm (AAA) can be defined as an aortic diameter greater than 1.5 times its normal calibre and is a significant burden on healthcare globally. In the 20th century, AAA was a disease on the rise, with evidence of a steady increase in aneurysm incidence and mortality in the United Kingdom (UK) and the United States of America (USA). This triggered randomised trials of ultrasound screening of AAA in an effort to address the AAA epidemic, which revealed the benefit of screening in reducing deaths from AAA related mortality. However, contemporary data from western populations have reported a reversal in AAA epidemiology, with steep declines in AAA incidence and mortality during the 21st Century. It is possible that these observations are secondary to changes in population trends of known cardiovascular risk factors such as cigarette smoking and blood pressure however no large population based evidence of this currently exists.

Although several risk factors for AAA have been identified, smoking is the only modifiable risk factor that has been associated with the development, expansion and rupture of AAA with a causative link recently being revealed in vivo within a mouse model. A decline in smoking is likely to have contributed significantly to the current reversal of the AAA epidemic however this trend is not the same across the world where recent decades have seen a massive expansion in tobacco use and accelerating growth in smoking among women in the developed world. Global trends in AAA mortality are currently unclear and variations in these trends will provide a valuable opportunity to determine underlying factors associated with the disease. This study aims to examine global trends in AAA mortality and investigate the link between smoking and other common cardiovascular risk factors with AAA mortality.
Methods

Identification of AAA mortality rates

Institutional review board approval was obtained for this study. Age, gender and cause specific mortality are made available by the World Health Organisation who classify cause of death according to the International Classification of Diseases, 10th Revision (ICD-10). Information relating to the ICD-10 codes I71.3, I71.4, I71.5, I71.6, I71.8, and I71.9 which represent abdominal and thoracoabdominal aortic aneurysms, ruptured or otherwise, and aortic aneurysms of unspecified site (ruptured or otherwise) were extracted on 01/08/2012. Thoracoabdominal aortic aneurysms and aneurysms of unspecified site were included within this analysis to ensure that all lesions involving AAA were captured in the analyses. No age restrictions were placed and all available data was extracted for analysis. The availability of mortality data for each year varied between countries (range 1994-2010) however the WHO mortality database is the largest validated international mortality dataset and these differences have been taken into account within the analysis.

ICD-10 codes are generated through civil registration systems which are a major source of cause of death data recorded by the World Health Organisation (WHO)\(^7\) and only WHO member states with a data completeness rate of 50-100% were included into the study\(^{13}\). Completeness of statistics on cause of death was defined as the ratio of number of deaths for which cause of death is registered to the civil registration system to the estimated total number of deaths in the population. Mortality data was converted into deaths per 100,000 of the population after which age-standardized rates of mortality (ASM) were calculated by use of the United Nations, department of economic and social affairs, world population prospects (2010) standard ‘more developed regions’ population\(^{14}\). This standard population reflects the average male and
female age structure of regions including Europe, Northern America, Australia/New Zealand and Japan expected from 1950-2010.

**Smoking Data**

Smoking data was extracted from the International Mortality and Smoking Statistics database (IMASS Version 4.09)\(^1\)\(^5\) which made estimates from data presented in international smoking statistics (ISS3)\(^1\)\(^6\) for standardised age groups averaged by gender, 5 year period and 5 year age group. The data included into this study were gender specific prevalence of smoking (the percentage of the population who currently smoke cigarettes or any tobacco products). The definition of smokers used included those who smoke either cigarettes only or cigarettes and other products (pipe, cigars, etc.). No attempt was made to include data on smokers of hand-rolled cigarettes only or by type of manufactured cigarette (e.g. filter/plain, high/low tar, dark/blond tobacco).

This data was survey-based being derived from studies in which subjects are asked about their current smoking habits and were obtained from a variety of sources including nationally representative surveys or sources providing international comparisons. These estimates commonly start around the 1950’s (range 1946-2010) and assume that there were no smokers below the age of 15. Estimates were presented to the nearest whole number and only countries where gender specific data on smoking prevalence was available were included into this study. The availability of smoking prevalence data for each year varied between countries however ISS3 is the largest validated international smoking statistics dataset available and these differences have been taken into account within the analysis.

**Risk factor data**

Risk factor data was extracted from the World Health Organisation (WHO) infobase\(^1\)\(^4\). The
WHO InfoBase reports country derived data from; Ministry of Health national estimates; National Health Surveys; Demographic and Health Surveys (DHS); Household surveys from other UN organizations; WHO-sponsored survey instruments and external research. In order to make the data internationally comparable, adjustments are made for differences between surveys for risk factor definitions; age groups; reporting year; national representativeness of the survey data and population age-distribution.

Data on mean total cholesterol (mmol/l), mean fasting blood glucose (mmol/l), mean body mass index (Kg/m²) were extracted for the years 1980-2010 whilst data on mean systolic blood pressure (mmHg) were extracted for the years 1995-2010 from the WHO InfoBase on 01/09/2012. Each risk factor was presented as an age standardised estimate in each defined population in both males and females. Systolic blood pressure (SBP) was analysed, rather than diastolic blood pressure (DBP), because prospective studies strongly suggest that SBP is a better predictor of cardiovascular disease risk\(^1\), especially in older adults (\(\geq 55\) years), in whom most deaths from cardiovascular disease occur.

**Countries included**

After exclusion of countries based on completeness of statistics and availability of risk factor data the following 19 countries were included into this study: Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, Iceland, Israel, Japan, Netherlands, New Zealand, Norway, Romania, Spain, Sweden, UK and USA.

**Statistics**

Men and women were analysed separately. Risk factor data including mean total cholesterol; mean fasting blood glucose; mean body mass index; mean systolic blood pressure and prevalence of smoking were plotted over all available time points from which slopes of the
regression lines of the variable against time were calculated with robust standard errors.

Similarly ASM was plotted over all available time points from which slopes of the regression lines against time were calculated with robust standard errors.

The data were analysed by a linear errors-in-variables regression (Supplemental file 1), a model which allows for uncertainty in both the response and explanatory variables namely; AAA mortality and the risk factors respectively. In contrast, standard regression models assume that those regressors have been observed without error therefore, account only for errors in the dependent variables, or responses. The standard errors of variables such as the rate of change in smoking prevalence with time were calculated separately from the data for each country and then those standard errors were treated as known when fitting the regression model, as previously published by Deming. The models were fitted by maximum likelihood using the ml command in Stata12 (StataCorp, TX, USA). Significance was assessed using likelihood ratio tests. A delayed deaths analysis was performed for each country. Total unadjusted (male and female) AAA deaths per year were compared between two age groups for each country included in the analysis (deaths due to AAA in individuals under 75 years of age and deaths due to AAA in those 75 years of age and over). The proportion of deaths in the two age groups and the change in these proportions over time was calculated for each individual country.

Results

Trends in AAA mortality

This study reveals substantial heterogeneity in AAA ASM trends globally although male and female AAA mortality appears to be declining in most populations (Fig 1a and b). The USA, UK and Australia appear to have the fastest declining male AAA ASM at 6.7%, 6.2% and 6.2%
per year respectively. The largest reductions in female AAA mortality were seen in the UK and USA at 4% and 3.9% per year respectively therefore, it appears that the rate of decline in female AAA mortality is less than for male. Importantly AAA mortality is not declining globally as evidenced by an increase in male AAA ASM in Hungary (2.7%) and Romania (1.7%) and in female AAA ASM in Hungary (3.5%), Romania (1%), Denmark (2.2%) and Austria (0.5%). Some countries appear to have a declining AAA mortality in males and an increasing AAA mortality in females for example Denmark and Austria.

Although mortality is decreasing in both the over and under 75 age groups, the percentage decrease appears to be greatest in the under 75 age group. In the UK <75 mortality decreased from 30% in 2001 to 24% in 2009 (-0.8% per year) however the largest decline was seen in Japan (-0.9% per year). In total 14/19 countries had a decrease in <75 mortality while 16/19 countries saw increases in mortality in the >75 age group. Only the Netherlands appeared to have an increasing mortality trend in the <75 age group from 36% in 2001 to 43% in 2009 (1.3% increase per year).

**Trends in risk factors**

Temporal trends in the common cardiovascular risk factors show a significant amount of heterogeneity across the countries studied. Male trends in BMI (1980-2008) ranged from +0.1 Kg/m²/year observed in the USA to +0.02 Kg/m²/year in Romania whilst female BMI trends ranged from 0.12 Kg/m²/year to -0.01 Kg/m²/year again with the largest increase seen in the USA and the smallest change observed in Romania. Trends in male mean total cholesterol (1980-2008) ranged from +0.02mmol/l/year in Japan to -0.03mmol/l/year seen in Finland while trends in female total cholesterol ranged from +0.01mmol/l/year to -0.04mmol/l/year in Japan and Sweden respectively.
Trends in mean fasting blood glucose (FBG) varied significantly between countries, ranging in males from +0.02mmol/l/year in Spain to -0.003mmol/l/year in the Netherlands while female mean FBG ranged from 0.02mmol/l/year to -0.01mmol/l/year again in Spain and the Netherlands respectively. Trends in male mean systolic blood pressure (1995-2008) ranged from -0.41mmHg/year seen in the UK to -0.02mmHg/year in Spain whilst mean female systolic blood pressure ranged from -0.57mmHg/year again in the UK to -0.14mmHg/year seen in Romania. Smoking prevalence varied considerably between countries and gender with male smoking prevalence declining in most countries whilst female smoking prevalence was increasing in 6 out of 19 the countries reviewed. The largest reduction in male smoking prevalence was seen in the Canada (-4.1% per year) and Spain (-3.4% per year) whilst the smallest reduction was seen in Hungary (-1.3% per year). Only one country was seen to have an increasing male smoking trend (Romania, +0.6% per year). The largest increases in female smoking prevalence were seen in Spain and Romania at +1.4% and +1.5 per year each whilst the largest decline was seen in Iceland (-3.5% per year).

The association of trends in AAA mortality to trends in risk factors

Regression analysis suggests that trends in systolic blood pressure (Fig 2a, P=0.028), cholesterol (Fig 3a, P=0.0082) and smoking prevalence (Fig 4a, P=0.017) are positively and significantly associated with changes in male AAA mortality while trends in BMI (Fig 5a, P=0.0072) are negatively and significantly associated with changes in male AAA mortality. Similarly in females, trends in systolic blood pressure (Fig 2b, P=0.024), cholesterol (Fig 3b, P=0.024) and smoking prevalence (Fig 4b, P=0.00021) were positively and significantly associated with AAA mortality whilst trends in BMI were negatively and significantly associated with AAA mortality (Fig 5b, P=0.0039). The direction of the AAA mortality trend was in both males and females.
most similar to trends in smoking prevalence. AAA mortality was not found to be significantly associated with trends in mean FBG in males (Supplemental figure 1a, P= 0.306) or females (Supplemental figure 1b, P= 0.9).

Discussion

Between 1951 and 1995 epidemiological studies revealed that AAA was a disease on the rise, with a steady increase in aneurysm incidence and mortality in the UK\(^2\) and USA\(^3\). However, more recently, evidence from a number of countries suggests that\(^6,20\) during the 21\(^{\text{st}}\) century a reversal in AAA epidemiology has occurred, with steep declines in AAA incidence and mortality. This study represents the largest population based analysis of AAA mortality to date and confirms that AAA mortality is declining in most developed economies; however that decline is not equal between countries, gender or age groups. In addition this is the first large population based study to demonstrate a relationship between global variations in common cardiovascular risk factors and AAA mortality suggesting that public health measures to reduce the incidence of hypertension, high cholesterol and smoking could reduce global AAA mortality further.

Male and female AAA mortality is generally declining however the rate of decline is not equal with the UK and USA appearing to show the steepest drop in AAA mortality (male and female) whilst Romania and Hungary both show increases in AAA mortality across both genders. Male AAA mortality appears to be declining more sharply than female although in some countries an increasing trend in female AAA mortality has been seen with the reverse in males. This finding may reflect differences in risk factor exposure for example smoking trends are not the same across the world where recent decades have seen a general decline in male
tobacco use with an accelerating growth of smoking among women in the developed world\textsuperscript{12}.

Tobacco use is the single most important preventable health risk in the developed world, with well-established links to the development, expansion and rupture of AAA\textsuperscript{7-9} likely orchestrated by nicotine as evidenced by the findings of recent \textit{in vivo} mouse model studies\textsuperscript{10}. This study demonstrates a strongly linear relationship between temporal trends in smoking prevalence and AAA mortality.

It is known that sexual dimorphism exists amongst a number of cardiovascular diseases\textsuperscript{21}, therefore it is possible that the pathophysiology of AAA development is different in females who have been noted to have a fourfold higher rupture rate\textsuperscript{22} compared to males. In addition to the observed differences between genders, the percentage decline in AAA mortality appears to be more profound in the under 75 age group. This finding has previously been shown in the UK\textsuperscript{20} which in addition to an observed increase in the number of elective admissions for AAA in the > 75 age group may suggest that improvements in public health do not prevent AAA but instead slow down the development of AAA in genetically predisposed individuals.

The finding that an elevated BMI may be associated with a decrease in AAA mortality is novel however needs to be interpreted with caution. The association between traditional cardiovascular risk factors and an improvement in clinical outcomes has been observed in those with heart failure and chronic obstructive lung disease\textsuperscript{23-25} with this association referred to as ‘reverse epidemiology’ or more recently the ‘obesity paradox’ however whether a raised BMI actually confers any survival advantage on patients with AAA remains to be proven. Sweeting \textit{et al}\textsuperscript{22} revealed that an increased BMI was associated with a slower rate of AAA growth however that this affect was lost after adjustment for demographics including medical history and drug history. A recent population-based cohort study\textsuperscript{26} revealed waist circumference was positively
associated with the risk of AAA however BMI was not. BMI is thought to reflect total adiposity, whereas waist circumference is an approximate index of intra-abdominal fat mass, which corresponds well to visceral adiposity therefore it may be that visceral adiposity rather than total adiposity is important in the development of AAA. Smoking cessation has long been linked with weight gain\(^\text{27}\) therefore one possible explanation for the obesity paradox is that countries with the greatest reduction in smoking prevalence may have increases in obesity but a decline in AAA mortality.

Whilst the association between obesity and AAA is unclear, epidemiological studies have demonstrated obesity as an independent risk factor for type II diabetes\(^\text{28}\) and studies thus far appear to suggest a protective role for diabetes on the development of AAA\(^\text{22, 29}\) which may explain this observation. This study found no significant association between global trends in fasting glucose concentrations and AAA mortality which may suggest that the protective effect of diabetes is not secondary to changes in fasting glucose concentrations however this requires further investigation. One explanation for the lack of any association between AAA mortality and fasting glucose may be counteraction, with an increased mortality post AAA repair in diabetics\(^\text{30}\) concealing any benefit gained from slower AAA development however, whether diabetes confers any survival disadvantage on patients post AAA repair is currently unclear\(^\text{31}\).

Obesity is more common in economically developed countries therefore economical factors such as health expenditure could account for some of the differences observed in this study and it is of interest to note that the UK spent 9.3% of its gross domestic product on health expenditure in 2011 whilst the USA, Romania and Hungary spent 17.9%, 5.8% and 7.7% respectively\(^\text{32}\).

Our results do not exclude the possibility of other factors influencing population trends in AAA mortality for example the exponential increase in prescriptions of antihypertensive and
lipid lowering medication or the epidemic of type II diabetes effecting most developed economies however these effects are taken into account in that they effect population distributions of each relevant risk factor. Changes in the treatment of AAA have occurred during the study period as since the introduction of endovascular aneurysm repair (EVAR), it has become established as the treatment of choice for most suitable patients in many vascular centres. However a recent meta-analysis\textsuperscript{33} revealed no long-term survival benefit for patients undergoing EVAR compared to open surgery suggesting that this paradigm shift should not influence overall mortality trends. Other limitations of this study include the use of civil registration system mortality information from which completeness of data varies between countries and that AAA mortality has over time risen and fallen\textsuperscript{20,34-36} (not behaved linearly) however, the time points included into this study occur within the mortality decline for many of the countries included and the analysis performed takes into account both of these limitations. Mortality from aortic rupture can be missed unless autopsy is carried out therefore it is possible that AAA mortality is underestimated however this should affect all included countries equally.

**Conclusion**

This study provides robust evidence that AAA mortality is not declining globally and that a linear relationship appears to exist with worldwide trends in systolic blood pressure, cholesterol, smoking prevalence and BMI. The importance of this finding is that public health measures to address these common cardiovascular risk factors could be applied in countries with an increasing AAA trend. The delay that risk factor modification appears to have on age at AAA mortality may represent a delay in the presentation of clinically relevant AAA which would have implications for the future of AAA screening.
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**Conflict of Interest Disclosures:** None.

**References:**


**Figure Legends:**

**Figure 1.** Trends in male (a) and female (b) age standardised AAA mortality. Key: Australia – Aus; Austria – Aut; Canada – Can; Denmark – Den; Finland – Fin; France – Fra; Germany – Ger; Hungary – Hun; Iceland – Ice; Israel – Isr; Japan – Jap; Netherlands – Net; New Zealand – NZ; Norway – Nor; Romania – Rom; Spain – Spa; Sweden – Swe; United Kingdom – UK; United States of America – USA
Figure 2. Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean systolic blood pressure and AAA mortality.

Figure 3. Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean total cholesterol and AAA mortality.

Figure 4. Linear regression revealing the positive association between temporal trends in male (a) and female (b) smoking prevalence and AAA mortality.

Figure 5. Linear regression revealing the negative association between temporal trends in male (a) and female (b) mean body mass index and AAA mortality.
Figure 1a - Male

AAA mortality percentage change per year

Country

Figure 1b - Female
Figure 2a - Male

Figure 2b - Female

Trends in systolic blood pressure by country for males (Figure 2a) and females (Figure 2b).
Figure 3a - Male

Figure 3b - Female

Trends in cholesterol mortality

Trends in cholesterol
Figure 4a - Male

Figure 4b - Female

Trends in smoking prevalence

Trends in AAA mortality
Figure 5a - Male

Trends in body mass index

Figure 5b - Female

Trends in body mass index
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SUPPLEMENTAL MATERIAL

Errors in Variables Regression

A simple regression model of $y$ on $x$ can be expressed as,

$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$$

where $\varepsilon_i$ is a normally distributed random error with constant variance that represents all of the unmeasured sources of variation that make $y$ deviate from its trend line. It is implicit in this model that $x$ is measured without error.

In our analysis both $x$ and $y$ represent quantities estimated from annual data reported by each country. For example, $x$ might be the annual increase or decrease in average blood pressure over a given time interval. These quantities are estimated with error and for each country we have both an estimate of $x$ and of its standard error and similarly we have an estimate of $y$ and its standard error. If $\mu_x$ and $\mu_y$ represent the true values of the quantities that are being estimated then we assume that

$$\mu_{yi} = \beta_0 + \beta_1 \mu_{xi}$$

So it is the true levels of the quantities that are linearly related. Further we assume that the estimated value of $x \sim N(\mu_x, \sigma_x)$ where $\sigma_x$ is the standard error and is assumed known.

Similarly $y \sim N(\mu_y, \sigma_y)$. We then assume that the estimates of $x$ and $y$ are independent since they come from different surveys. Finally we assume that the variation about the trend line, in excess of the measurement error in $y$, has a constant variance. This model is similar to that used by Pocock et al.\textsuperscript{1} (1981) and is an example of an error in variables model in which the variances of the errors in $x$ and $y$ are assumed known.
The model was fitted by maximum likelihood in Stata12 (StataCorp, TX) using the \texttt{ml} command. For the examples considered in this paper convergence of the Newton-Raphson algorithm was very quick. The significance of a particular $x$ was tested by fitting the model described above and then fitting the same model but with $\beta_1=0$. The models were compared in a likelihood ratio test.
Supplemental figure 1a - Linear Regression revealing the association between trends in FBG and trends in male AAA mortality ($P = 0.306$).

Supplemental figure 1b - Linear regression revealing the association between trends in FBG and trends in female AAA mortality ($p = 0.958$).
References