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

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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 analyze any association with common cardiovascular risk factors.

Methods and Results—AAA mortality (1994–2010) using International Classification of Diseases codes were extracted from the World Health Organization mortality database and age standardized. The World Health Organization InfoBase and International Mortality and Smoking Statistics provided risk factor data. Nineteen World Health Organization member states were included (Europe, 14; Australasia, 2; North America, 2; Asia, 1). Regression analysis of temporal trends in cardiovascular risk factors (1946–2010) was done independently for correlations to AAA mortality trends. Global AAA mortality trends show substantial heterogeneity, with the United States and United Kingdom recording the greatest national decline, whereas internationally, male individuals and those <75 years of age 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 ($P \leq 0.03$), cholesterol ($P \leq 0.03$), and smoking prevalence ($P \leq 0.02$) in males and females. Body mass index demonstrated a negative linear association with AAA mortality ($P \leq 0.007$), whereas 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 that requires further investigation. Public health measures could therefore further reduce global AAA mortality, with greatest benefits in the younger age group. (Circulation. 2014;129:747-753.)

Key Words: aneurysm ■ aorta ■ epidemiology ■ mortality

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Abdominal aortic aneurysm (AAA), defined as having an aortic diameter >1.5 times its normal caliber, 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 and the United States. This triggered randomized trials of ultrasound screening of AAA in an effort to address the AAA epidemic, which revealed the benefit of screening in reducing 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.

Clinical Perspective on p 753

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 in 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. Recent decades have seen a massive expansion in tobacco use and accelerated 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 to investigate the link between smoking and other common cardiovascular risk factors and AAA mortality.

Methods

Identification of AAA Mortality Rates

Institutional review board approval was obtained for this study. Age, sex, and cause-specific mortality are made available by the World Health Organization (WHO), which classifies cause of death according to the International Classification of Diseases, 10th Revision. Information relating to the International Classification of Diseases, 10th Revision 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), was extracted on January 8, 2013. Thoracoabdominal aortic aneurysms and aneurysms of unspecified site were included in this analysis to ensure that all lesions involving AAAs were captured in the analyses. No age restrictions were placed, and all available data were 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 data set, and these differences have been taken into account in the analysis.

International Classification of Diseases, 10th Revision codes are generated through civil registration systems, which are a major source of cause-of-death data recorded by the WHO.11 Only WHO member states with a data completeness rate of 50% to 100% were included in the study.12 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 were converted into deaths per 100,000 population, after which age-standardized rates of mortality (ASMs) were calculated by use of the United Nations Population Division’s standard world population projections (2010). 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 to 2010.

Smoking Data

Smoking data were extracted from the International Mortality and Smoking Statistics database (version 4.09),13 which made estimates from data presented in international smoking statistics14 for standardized age groups averaged by sex, 5-year period, and 5-year age group. The data included in this study were sex-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 (eg, filter/plain, high/low tar, dark/blond tobacco).

These data were survey based, that is, derived from studies in which subjects were 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 1950s (range, 1946–2010) and assume that there were no smokers <15 years of age. Estimates were presented to the nearest whole number, and only countries where sex-specific data on smoking prevalence were available were included into this study. The availability of smoking prevalence data for each year varied between countries; however, international smoking statistics is the largest validated international smoking statistics data set available, and these differences have been taken into account in the analysis.

Risk Factor Data

Risk factor data were extracted from the WHO InfoBase.15 The WHO InfoBase reports country-derived data from Ministry of Health national estimates, national health surveys, demographic and health surveys, household surveys from other United Nations organizations, WHO-sponsored survey instruments, and external research. 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), and mean body mass index (BMI; kg/m²) were extracted for the years 1980 to 2010; data on mean systolic blood pressure (mm Hg) were extracted for the years 1995 to 2010 from the WHO InfoBase on January 9, 2013. Each risk factor was presented as an age-standardized estimate in each defined population in both males and females. Systolic blood pressure rather than diastolic blood pressure was analyzed because prospective studies strongly suggest that systolic blood pressure is a better predictor of cardiovascular disease risk,16 especially in older adults (>65 years of age), in whom most deaths resulting from cardiovascular disease occur.

Countries Included

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

Statistics

Men and women were analyzed separately. Risk factor data, including mean total cholesterol, mean fasting blood glucose, mean BMI, 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 analyzed by a linear errors-in-variables regression (see the online-only Data Supplement), a model that allows for uncertainty in both the response and explanatory variables, namely AAA mortality and risk factors, respectively. In contrast, standard regression models assume that those repressors have been observed without error and therefore account only for errors in the dependent variables, or responses.17 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.18 The models were fitted by maximum likelihood using the ml command in Stata12 (StataCorp, College Station, TX). Significance was assessed with likelihood ratio tests. A delayed-deaths analysis was performed for each country. Total unadjusted (male and female) AAA deaths per year were compared between 2 age groups for each country included in the analysis (deaths resulting from AAA in individuals ≤75 years of age and deaths resulting from AAA in those >75 years of age). The proportion of deaths in the 2 age groups and the change in these proportions over time were 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 (Figure 1A and 1B). The United States, the United Kingdom, 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 United Kingdom and United States at 4% and 3.9% per year, respectively; therefore, it appears that the rate of decline in female AAA mortality is less than the rate of decline in male AAA mortality. 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, for example, Denmark and Austria, appear to have a declining AAA mortality in males and an increasing AAA mortality in females.

Although mortality is decreasing in both the >75-year and <75-year age groups, the percentage decrease appears to be greatest in the <75-year age group. In the United Kingdom, mortality in those <75 years of age decreased from 30% in 2001 to 24% in 2009 (−0.8%/y); however, the largest decline was seen in Japan (−0.9%/y). In total, 14 of the 19 countries had a decrease in mortality in those <75 years of age, whereas 16 of the 19 countries saw increases in mortality in those >75 years of age. Only The Netherlands appeared to have an increasing mortality trend in those <75 years of age 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 per year observed in the United States to 0.02 kg/m² per year in Romania, whereas female BMI trends ranged from 0.12 to −0.01 kg/m² per year, again with the largest increase seen in the United States and the smallest change observed in Romania. Trends in male mean total cholesterol (1980–2008) ranged from 0.02 mmol/L per year in Japan to −0.03 mmol/L per year seen in Finland, whereas trends in female total cholesterol ranged from 0.01 to −0.04 mmol/L per year in Japan and Sweden, respectively.

Trends in mean fasting blood glucose varied significantly between countries, ranging in males from 0.02 mmol/L per year in Spain to −0.003 mmol/L per year in The Netherlands, whereas female mean fasting blood glucose ranged from 0.02 to −0.01 mmol/L per year again in Spain and The Netherlands, respectively. Trends in male mean systolic blood pressure (1995–2008) ranged from −0.41 mm Hg/y seen in the United Kingdom to −0.02 mm Hg/y in Spain, whereas mean female systolic blood pressure ranged from −0.57 mm Hg/y again in the United Kingdom to −0.14 mm Hg/y seen in Romania. Smoking prevalence varied considerably between countries and sexes, with male smoking prevalence declining in most countries and female smoking prevalence increasing in 6 of the 19 countries reviewed. The largest reduction in male smoking prevalence was seen in the Canada (−4.1%/y) and Spain (−3.4%/y), whereas the smallest reduction was seen in Hungary (−1.3%/y). Only 1 country was seen to have an increasing male smoking trend (Romania; 0.6%/y). The largest increases in female smoking prevalence were seen in Spain and Romania at 1.4%/y and 1.5%/y, respectively, whereas the largest decline was seen in Iceland (−3.5%/y).

Association of Trends in AAA Mortality With Trends in Risk Factors

Regression analysis suggests that trends in systolic blood pressure ($P=0.028$; Figure 2A), cholesterol ($P=0.0082$; Figure 3A), and smoking prevalence ($P=0.017$; Figure 4A) are positively and significantly associated with changes in male AAA mortality, whereas trends in BMI ($P=0.0072$; Figure 5A) are negatively and significantly associated with changes in male AAA mortality. Similarly in females, trends in systolic blood pressure ($P=0.024$; Figure 2B), cholesterol ($P=0.024$; Figure 3B), and smoking prevalence ($P=0.00021$; Figure 4B) were positively and significantly associated with AAA mortality, whereas trends in BMI were negatively and significantly associated with AAA mortality ($P=0.0039$; Figure 5B). In both males and females, the direction of the AAA mortality trend was most similar to trends in smoking prevalence. AAA mortality was not found to be significantly associated with trends in mean fasting blood glucose in males ($P=0.306$; Figure IA in the online-only Data Supplement) or females ($P=0.9$; Figure IB in the online-only Data Supplement).
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 United Kingdom and the United States. However, more recently, evidence from a number of countries suggests that during the 21st 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, sexes, 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, but the rate of decline is not equal, with the United Kingdom and the United States appearing to show the steepest drop in AAA mortality (male and female) and Romania and Hungary showing increases in AAA mortality across both sexes. Male AAA mortality appears to be declining more sharply than female AAA mortality, 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. Recent decades have seen a general decline in male tobacco use with an accelerated growth of smoking among women in the developed world. 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 likely orchestrated by nicotine, as evidenced by the findings of recent in vivo mouse model studies. This study demonstrates a strongly linear relationship between temporal trends in smoking prevalence and AAA mortality.

It is known that sexual dimorphism exists among a number of cardiovascular diseases; therefore, it is possible that the pathophysiology of AAA development is different in females.
who have been noted to have a 4-fold higher rupture rate\textsuperscript{22} compared with males. In addition to the observed differences between the sexes, the percentage decline in AAA mortality appears to be more profound in those <75 years of age. This finding has previously been shown in the United Kingdom,\textsuperscript{20} which, in addition to an observed increase in the number of elective admissions for AAA in those >75 years of age, may suggest that improvements in public health do not prevent AAA but instead slow 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 but 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 an elevated BMI actually confers any survival advantage in patients with AAA remains to be proven. Sweeting et al\textsuperscript{22} revealed that an increased BMI was associated with a slower rate of AAA growth but that this effect was lost after adjustment for demographics such as medical history and drug history. A recent population-based cohort study\textsuperscript{26} revealed that waist circumference was positively associated with the risk of AAA but 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 to weight gain.\textsuperscript{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.

Although the association between obesity and AAA is unclear, epidemiological studies have demonstrated obesity as an independent risk factor for type II diabetes mellitus,\textsuperscript{28} and studies thus far appear to suggest a protective role for diabetes mellitus on the development of AAA,\textsuperscript{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 mellitus is not secondary to changes in fasting glucose concentrations, but 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 after AAA repair in diabetics, concealing any benefit gained from slower AAA development. However, whether diabetes mellitus confers any survival disadvantage on patients after AAA repair is currently unclear. Obesity is more common in economically developed countries; therefore, economic 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 United Kingdom spent 9.3% of its gross domestic product on health expenditure in 2011, whereas the United States, Romania, and Hungary spent 17.9%, 5.8%, and 7.1%, respectively.

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 mellitus affecting most developed economies. However, these effects are taken into account in that they affect population distributions of each relevant risk factor. Changes in the treatment of AAA have occurred during the study period in that, since its introduction, endovascular aneurysm repair has become established as the treatment of choice for most suitable patients in many vascular centers. However, a recent meta-analysis revealed no long-term survival benefit for patients undergoing endovascular aneurysm repair compared with 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 the fact that AAA mortality has risen and fallen over time (ie, 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 both of these limitations into account. Mortality from aortic rupture can be missed unless autopsy is carried out. Therefore, it is possible that AAA mortality is underestimated, but 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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Disclosures
None.

References

CLINICAL PERSPECTIVE

This study provides robust evidence that abdominal aortic aneurysm mortality is not declining globally as has previously been suggested and that a linear relationship exists between trends in abdominal aortic aneurysm mortality and trends in systolic blood pressure, cholesterol, smoking prevalence, and body mass index. A novel obesity paradox has been identified that suggests a survival benefit for abdominal aortic aneurysm patients with an elevated body mass index; however, this requires further investigation. The importance of these findings is that public health measures to address common cardiovascular risk factors could further reduce abdominal aortic aneurysm mortality globally, and these benefits appear to be greatest in the younger age group.
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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\(^1\) (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 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