Mortality From Thoracic Aortic Diseases and Associations With Cardiovascular Risk Factors

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**Background**—Temporal trends in mortality from thoracic aortic disease are unclear. This study examined trends in mortality from thoracic aortic aneurysm (TAA) and aortic dissection (AD) with the aim of identifying associations with trends in established cardiovascular risk factors.

**Methods and Results**—TAA and AD mortality (1994–2010) using International Classification of Diseases codes was extracted from the World Health Organization mortality database and age standardized. World Health Organization InfoBase and International Mortality and Smoking Statistics provided risk factor data. Eighteen World Health Organization member states were included (Europe=13, Australasia=2, North America=2, Asia=1). Ecological regression was performed of temporal trends in cardiovascular risk factors (1946–2010) and independent correlations to mortality trends. TAA and AD mortality trends show substantial heterogeneity but are generally declining. TAA mortality has increased in Hungary, Romania, Japan, and Denmark, and AD mortality has increased in Romania and Japan; therefore, the mortality decline is not universal. A linear relationship exists between trends in systolic blood pressure, cholesterol, and body mass index and mortality from TAA. Body mass index demonstrated a negative linear association with female AD mortality, whereas trends in systolic blood pressure demonstrated a positive linear relationship with male AD mortality. Trends in smoking prevalence were not associated with TAA or AD mortality trends.

**Conclusions**—This population-level ecological regression provides evidence that mortality secondary to TAA and mortality secondary to AD are both in decline. Differences between countries could be explained by population-level changes in common cardiovascular risk factors. Public health measures could further reduce mortality from TAA and AD. *(Circulation. 2014;130:2287-2294.)*

**Key Words:** aneurysm ■ aorta ■ dissection ■ epidemiology ■ mortality ■ thorax

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Thoracic aortic aneurysm (TAA) may be defined as a localized or diffuse dilatation of the aorta to at least 1.5 times its normal caliber and may affect the aortic root, ascending aorta, aortic arch, or descending aorta. In aortic dissection (AD), blood is diverted from its usual location within the lumen of the aorta into a false lumen within the media through a tear in the intima. Together, these pathologies represent the principal thoracic aortic diseases, but little is currently known about their respective burden on healthcare systems globally, for example, trends in mortality.

Recent reports have suggested an increase in the prevalence of thoracic aortic disease in Europe, as measured by hospital admissions and operative repairs. Olsson et al° analyzed the Swedish national healthcare registers (1987–2002), revealing that the prevalence and incidence of thoracic aortic disease were higher than previously reported and increasing. Similarly, von Allmen and colleagues° demonstrated that hospital admissions in the United Kingdom (1999–2010) for thoracic aortic disease had increased. Despite this, total mortality from thoracic aortic disease in the United Kingdom had declined in the same time period, and this decline has not been reported elsewhere. Dias et al° found that mortality from thoracic aortic disease in São Paulo State has steadily increased (1998–2007).

Differences in mortality from thoracic aortic diseases are likely to exist between nations; however, current knowledge is limited to a few isolated reports from individual countries. As with abdominal aortic aneurysms, these differences in mortality may be secondary to variations in traditional cardiovascular risk factors.°° This study examined trends in mortality from AD and TAA and aimed to identify any associations with trends in established cardiovascular risk factors.

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Methods

Identification of 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 causes of death according to the International Classification of Diseases, 10th Revision (ICD-10). Information relating to the ICD-10 codes I71.0, I71.1, I71.2, I71.8, and I71.9, which represent dissection of aorta (any part), TAAs, ruptured or otherwise, and aortic aneurysms of unspecified site (ruptured or otherwise), was extracted on July 11, 2013. Aneurysms of unspecified site were included within this analysis to ensure that all lesions involving TAA 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. The methods used for conversion of deaths in age-standardized mortality (ASM) rates have previously been published. This standard population reflects the average male and female age structure of regions including Europe, Northern America, Australia/New Zealand, and Japan from 1950 to 2010.

Risk Factor Data

Risk factor data were extracted from the International Mortality and Smoking Statistics database (IMASS version 4.09) and the WHO InfoBase, the sources and limitations of which have previously been described. IMASS is a regularly updated (last update, November 14, 2013) online tool that publishes smoking prevalence data for standardized age groups averaged by sex, 5-year period, and 5-year age group (range, 1946–2010). The data included into 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.). Estimates were presented to the nearest whole number, and only countries in which sex-specific data on smoking prevalence were available were included into this study. Data on mean total cholesterol, mean fasting blood glucose, and mean body mass index were extracted for the years 1980 to 2010, and data on mean systolic blood pressure were extracted for the years 1995 to 2010 from the WHO InfoBase on January 9, 2012. Each risk factor was presented as an age-standardized estimate in each defined population in both males and females.

Countries Included

Only WHO member states with a national data completeness rate of 70% to 100% were included in the study (Figure 1 in the online-only Data Supplement). Those countries with adequate data completeness were then analyzed to ensure that they specifically had adequate data (>90% completeness) relating to the ICD-10 codes I71.0, I71.1, I71.2, I71.8, and I71.9 for each year. The IMASS database and the WHO InfoBase were then interrogated to ensure the availability of appropriate risk factor data for each country with adequate national and ICD-10171 data. With the use of these criteria, 18 countries were included in this study: Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, 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 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, age-standardized rate of mortality was plotted over all available time points from which slopes of the regression lines against time were calculated with robust standard errors. The logit of ASM rate trends was used to represent the percentage change in mortality per year.

The data were analyzed by a linear errors-in-variables regression (online-only Data Supplement). 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. The models were fitted by maximum likelihood using the ml command in Stata12 (StataCorp, College Station, TX). Significance was assessed with likelihood ratio tests. Age-standardized total (male and female) deaths per year were calculated for each country for both TAA and AD. The peak age at which mortality occurred was calculated for the years 2001 and 2009 and compared. The proportion of ASM occurring in individuals >75 years of age was compared between years.

Results

Trends in Risk Factors

Temporal trends in mean total cholesterol, mean fasting blood glucose, mean body mass index, mean systolic blood pressure, and smoking prevalence have previously been published and demonstrate a significant amount of heterogeneity across the countries studied. Male trends in body mass index (1980–2008) were highest in the United States in both men and women, with the smallest change seen in Romania. Trends in mean total cholesterol (1980–2008) were highest in Japan in both men and women, whereas trends in mean fasting blood glucose were highest in Spain (in men and women). Trends in mean male systolic blood pressure (1995–2008) were lowest in the United Kingdom. Smoking prevalence varied considerably between countries and sexes but was declining in most countries. The largest reduction in male smoking prevalence was seen in Canada, and the smallest reduction was seen in Hungary. Romania was seen to have an increasing male smoking trend, whereas in women, smoking prevalence was increasing in Spain and Romania.

Trends in Mortality From TAA

This study demonstrates a substantial amount of variability in ASM from TAA in both men and women (Figure 1). Mortality appears to be generally declining in both men and women, with the sharpest declines observed in Canada (9.5%) and the Netherlands (9.7%) in men and in Australia (7.0%) and the United Kingdom (5.5%) in women. Mortality is, however, not on the decline globally, as evidenced by increases in age-standardized TAA mortality in Denmark (2.4%), Hungary (2.1%), Japan (0.5%), and Romania (1.3%) in men and in Austria in women. In Austria, a decline was noted in male ASM with an increase in women, suggesting that differences exist between the sexes in some countries but that in general men and women demonstrated trends in the same direction.

The most common age range (Table 1) at which mortality from TAA occurred was 75 to 79 years in 2001, although variation existed, for example, in Japan (80–84 years) and Romania (60–64 years). In 2009, the most common age range at which mortality from TAA occurred remained at 75 to 79 years, but 13 of 18 countries demonstrated an increase in the proportion of age-standardized deaths occurring after 75 years of age, suggesting a delay in age at death from TAA.
Trends in Mortality From AD
ASM from AD also demonstrates variability but is declining in most countries (Figure 2). The sharpest declines in male mortality were observed in Austria (6.5%) and New Zealand (4.8%), with increases seen in Japan (4.2%) and Romania (0.8%). Mortality from AD demonstrates more heterogeneity in women compared with men, with the largest declines seen in Israel (10.4%) and Austria (5.7), whereas increases were observed in Japan (5.3%), the Netherlands (2.5%), Romania (1.1%), and Spain (1.1%).

The most common age range (Table 2) at which mortality occurred from AD in 2001 was 65 to 69 years, but variation existed. In the United Kingdom and Canada, peak age at mortality was >80 years, whereas in Hungary, it was 65 to 69 years. By 2009, the most common age range at which mortality occurred had increased to 70 to 74 years. Eleven of the countries included demonstrated an increase in the proportion of age-standardized deaths occurring after 75 years of age.

Association of Trends in TAA Mortality With Trends in Risk Factors
Regression analysis suggests that trends in systolic blood pressure ($P=0.016$; Figure 3A) and blood cholesterol ($P=0.012$; Figure 4A) are positively and significantly associated with trends in male age-standardized TAA mortality. Trends in body mass index ($P=0.021$; Figure 5A) demonstrate negative significant associations with TAA mortality, whereas trends in smoking prevalence ($P=0.282$; Figure 6A) and fasting blood glucose ($P=0.394$; Figure IIa in the online-only Data Supplement) are not significantly associated with male TAA mortality. Similarly, in women, regression analysis of trends in systolic blood pressure ($P=0.013$; Figure 3B) and blood cholesterol ($P=0.033$; Figure 4B) demonstrate positive and significant associations with trends in age-standardized TAA mortality. Body mass index demonstrates negative significant associations with TAA mortality ($P=0.024$; Figure 5B), and no association was demonstrated with trends in smoking prevalence ($P=0.069$; Figure 6B) or fasting blood glucose ($P=0.681$; Figure IIb in the online-only Data Supplement). This suggests that those countries with declining cholesterol levels also have a reduction in mortality from TAA, with a similar picture seen for systolic blood pressure.

Association of Trends in AD Mortality With Trends in Risk Factors
Regression analysis suggests that trends in systolic blood pressure ($P=0.048$; Figure 7A) are positively and significantly associated with trends in male ASM from AD. No association was

Table 1. Age Range at Peak ASM for 2001 and 2009 (TAA)

<table>
<thead>
<tr>
<th>Country</th>
<th>2001, y</th>
<th>2009, y</th>
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<tbody>
<tr>
<td>Hun</td>
<td>75–79</td>
<td>75–79</td>
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<td>Isr</td>
<td>75–79</td>
<td>75–79</td>
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<td>Jap</td>
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<td>Rom</td>
<td>80–84</td>
<td>75–79</td>
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<td>Swe</td>
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<td>75–79</td>
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<tr>
<td>Den</td>
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<td>Ger</td>
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<td>Net</td>
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<tr>
<td>Nor</td>
<td>75–79</td>
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<td>Spa</td>
<td>75–79</td>
<td>85–89</td>
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<td>Fra</td>
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<tr>
<td>UK</td>
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<tr>
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<td>Aust</td>
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<td>Can</td>
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<td>Fin</td>
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</table>

ASM indicates age-standardized mortality; Aus, Austria; Aust, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; TAA, thoracic aortic aneurysm; UK, United Kingdom; and USA, United States.

*Canada did not submit data for 2009.
demonstrated with cholesterol levels ($P=0.086$; Figure IIIa in the online-only Data Supplement), body mass index ($P=0.054$; Figure 8A), smoking prevalence ($P=0.85$; Figure IVa in the online-only Data Supplement), or fasting blood glucose ($P=0.54$; Figure Va in the online-only Data Supplement). In women, trends in body mass index ($P=0.03$; Figure 8B) were negatively and significantly associated with mortality from AD. No association was demonstrated with trends in cholesterol ($P=0.84$; Figure IIIb in the online-only Data Supplement), systolic blood pressure ($P=0.28$; Figure 7B), smoking prevalence ($P=0.72$; Figure IVb in the online-only Data Supplement), or fasting blood glucose ($P=0.59$; Figure Vb in the online-only Data Supplement). Unlike for TAA, no clear picture was demonstrated with trends in population risk factors with mortality from AD.

**Discussion**

This ecological regression represents the largest population-level analysis of mortality from TAA and AD and confirms that mortality secondary to these pathologies is generally on the decline. This decline was, however, not equal between countries, sexes, or age groups, and some countries demonstrate increases in mortality. Analysis of variations in common cardiovascular risk factors suggests that the heterogeneity in mortality between countries may be secondary to trends in population blood cholesterol levels, systolic blood pressure, and body mass index. The epidemiology of TAA and the epidemiology of AD differ, as do their respective associations with cardiovascular risk factors, suggesting that a combined analysis of thoracic aortic disease, as has been conducted previously, may be inaccurate. The lack of any significant association of TAA or AD with trends in smoking prevalence may suggest a difference in etiology compared with abdominal aortic aneurysms.

Male and female mortality from TAA is generally on the decline, but large differences are noted. Japan, Romania, Denmark, and Hungary demonstrate increasing mortality in both men and women, whereas the sharpest declines were seen in Canada and the United Kingdom (in men and women). Furthermore, within-country variations were observed between men and women. For AD, mortality is generally on the decline; however, although increases were seen in only 2 countries in men, increases were seen in 5 countries for women.

These differences may reflect differences in risk factor exposure, for example, differences in serum cholesterol concentrations across populations and over time. A recent population-based systematic analysis of worldwide mean total cholesterol levels highlighted differences in cholesterol levels between the sexes and demonstrated opposite trends in Australasia, North America, and Europe, where serum total cholesterol decreased from high concentrations, compared with East and Southeast Asia and the Pacific, where it rose from low

<table>
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<tr>
<th>Age at peak ASM, 2001, y</th>
<th>Hun</th>
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<th>Aust</th>
<th>Can</th>
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AD indicates aortic dissection; Aus, Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.

*Canada did not submit data for 2009.
concentrations. It may be expected that geopolitically close countries, for example, Denmark and Sweden, would demonstrate similar trends in mortality, but this was not the case. The results of this study suggest that these differences may be secondary to risk factor exposure. For example, the most recent WHO Report on the Global Tobacco Epidemic (2013) suggests that Denmark has a current smoking prevalence of 20%, whereas the smoking prevalence in Sweden is 11%. Current mean total cholesterol levels are 5.5 and 5.4 mmol in men and women, respectively, in Denmark and 5.2 and 5.0 mmol, respectively, in Sweden. Thus, real differences appear to exist.

In this study, Japan demonstrated increases in both TAA and AD mortality. Another population-based analysis of health examination and epidemiological studies revealed that in high-income regions, men and women in Western Europe had the highest mean systolic blood pressures and that differences existed between the sexes. Although these geographical and sex differences in risk factor exposure correlate with trends in TAA and AD mortality, it is also known that sexual dimorphism exists among a number of cardiovascular diseases. Therefore, the differences observed in this study could be partly explained by differences in the pathophysiology of TAA and ADs between men and women.

The lack of any association between trends in smoking prevalence and mortality from TAA adds to evidence that the aorta is a heterogeneous structure with varying influences above and below the diaphragm. Smoking is the main modifiable risk factor that has been associated with the development, expansion, and rupture of abdominal aortic aneurysms; however, no such association has been proven for TAA. Atherosclerosis has been shown to affect the aorta differently above and below the diaphragm, with the thoracic aorta appearing more resistant to plaque formation compared

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**Figure 3.** Linear regression revealing the positive association between temporal trends in male (A) and female (B) mean systolic blood pressure and thoracic aortic aneurysm (TAA) mortality. Those countries with a reducing population systolic blood pressure also have a declining TAA mortality. Aus indicates Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.

**Figure 4.** Linear regression revealing the positive association between temporal trends in male (A) and female (B) mean total cholesterol and thoracic aortic aneurysm (TAA) mortality. Those countries with a reducing population cholesterol level also have a declining TAA mortality. Aus indicates Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.
with the abdominal aorta. Some have attributed these observations to differences in flow and shear stress; however, differences have also been noted in the level of proteases and immune mediators. Therefore, genetic differences may exist.

The association of these mortalities with changes in body mass index is similar to that demonstrated previously for abdominal aortic aneurysms but should be interpreted with caution.

These results do not exclude the possibility of extrinsic factors, for example, antihypertensive and lipid-lowering medication, influencing population trends in mortality. However, these medications would affect population distributions of each relevant risk factor. In addition to lowering cholesterol levels, statins may reduce TAA growth rate and the proportion of TAA progressing to dissection, rupture, or death. Changes in the treatment of TAA have occurred over time; however, current evidence suggests that thoracic endovascular aortic repair has long-term results similar to those of open thoracic aortic repair. Therefore, these changes should not affect mortality trends. Analyzing the impact on mortality of an increased application of thoracic endovascular aneurysm repair for AD and TAAs is not possible in the global setting because such data are not collected globally. However, von Allmen and colleagues demonstrated that in the United Kingdom there was no association between an increasing use of thoracic endovascular aneurysm repair and a decline in mortality.

One limitation of this study is the use of civil registration system mortality information, for which completeness of data varies between countries, although we excluded countries with inadequate completeness of statistics or unavailable risk factor data. Furthermore, mortality from TAA and AD can be underestimated because undiagnosed or misdiagnosed cases causing sudden adult death may be missed unless autopsy is carried out. Another limitation of this approach is the use of population-level trends because individual patient data would be more

Figure 5. Linear regression revealing the negative association between temporal trends in male (A) and female (B) mean body mass index (BMI) and thoracic aortic aneurysm (TAA) mortality. Those countries with a increasing population BMI also have a declining TAA mortality. Aus indicates Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.

Figure 6. Linear regression revealing no clear association between temporal trends in male (A) and female (B) smoking prevalence and thoracic aortic aneurysm mortality. Aus indicates Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.
accurate and informative. Population trends in mortality may be affected by a number of confounding variables, and there is no way to correct for this with these types of data. The regression of aggregate, country-level data is a well-established method known as ecological regression, the main limitation of which is that it assumes that findings from a group (or country) apply to an individual within that group, which may not always be the case. This is called the ecological fallacy. Because individual patient-level data are not currently available, ecological regression may be useful to make as much sense as possible of the available data. Another limitation of this model is that sensitivity analyses to check the stability of this analysis across age bands are not possible because, although mortality data are available by age group, risk factor data are not. Some $P$ values obtained through these analyses were close to significance, and it is possible that, with an improvement in data gathering over time and therefore the possible inclusion of more countries, these results could be refined.

ICD-10 classifies both Stanford type A AD (involving the proximal ascending aorta) and Stanford type B AD (involving the descending aorta distal to the left subclavian artery) together (ICD-10 I71.0), but they are not the same. Untreated, type A dissections are associated with a 90% mortality, falling to a 16.9% to 20.2% 30-day mortality with appropriate surgical management. Comparatively, 25% of patients who present with acute type B dissection are complicated at admission with malperfusion syndrome or hemodynamic instability. Pooled early mortality with best medical therapy has been shown to be ≈6.4%, with up to 89% surviving to 5 years. These mortality-based data are therefore likely to represent a greater number of type A dissections. There are several heritable disorders that affect the thoracic aorta, predisposing patients to both TAA and thoracic AD. However, ICD-10 does not differentiate these from those secondary to atherosclerosis. The most common of these disorders are Marfan syndrome, which has a prevalence of 2 to 3 per 10000 individuals, and Ehlers-Danlos syndrome, which affects

Figure 7. Linear regression revealing the association between temporal trends in male (A) and female (B) mean systolic blood pressure and mortality from aortic dissection. Aus indicates Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.

Figure 8. Linear regression revealing the negative association between temporal trends in male (A) and female (B) mean body mass index and mortality from aortic dissection. Aus indicates Austria; Aut, Australia; Can, Canada; Den, Denmark; Fin, Finland; Fra, France; Ger, Germany; Hun, Hungary; Isr, Israel; Jap, Japan; Net, the Netherlands; Nor, Norway; NZ, New Zealand; Rom, Romania; Spa, Spain; Swe, Sweden; UK, United Kingdom; and USA, United States.
Conclusions
This study provides evidence that mortality secondary to TAA and AD is generally on the decline. This decline is, however, not equal between countries, sexes, or age groups, and this heterogeneity could be explained by population changes in blood cholesterol, systolic blood pressure, and body mass index. Public health measures could further reduce mortality from TAA and AD; however, smoking cessation may not play a role similar to that seen in other aneurysmal diseases.

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Disclosures
None.

References

Conclusions
This population-level ecological regression provides evidence that mortality from thoracic aortic aneurysm and aortic dissection is generally in decline; however, differences exist between countries, sexes, and age groups. A positive linear relationship appears to exist between trends in systolic blood pressure, cholesterol, and mortality from thoracic aneurysms, suggesting that public health measures to reduce the prevalence of hypertension and high cholesterol may further reduce mortality from this disease. Trends in smoking prevalence demonstrated no associations with mortality from thoracic aortic aneurysm or dissection, which adds to growing evidence that the aorta is a heterogeneous structure with varying influences above and below the diaphragm.
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Supplemental Figure legends

Supplemental figure 1 - Flow Diagram of included countries

Supplemental figure 2 – The association between mean fasting blood glucose and TAA mortality

Supplemental figure 3 - The association between trends in cholesterol levels and mortality from aortic dissection.

Supplemental figure 4 - The association between trends smoking prevalence and mortality from aortic dissection.

Supplemental figure 5 - The association between trends mean fasting blood glucose and mortality from aortic dissection.
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. (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 1 – Flow Diagram of included countries

- **USA, Japan, Mexico, UK, Canada, Venezuela, Uzbekistan, Romania, Australia, Chile, Cuba, Hungary, Sweden, Austria, Israel, Slovakia, Finland, Costa Rica, Singapore, Ireland, New Zealand, Moldova, Lithuania, Kuwait, Latvia, Estonia, Trinidad and Tobago, Malta, Bahamas, Iceland, Saint Vincent and the Grenadines, Philippines, Germany, Italy, South Korea, Colombia, Spain, Netherlands, Belgium, Czech Republic, Switzerland, Denmark, Kyrgyzstan, Norway, Croatia, Georgia, Panama, Former, Yugoslav Republic of Macedonia, Slovenia, Mauritius, Barbados, Belize, Antigua and Barbuda, Dominica, Niue.

- **Australia, Austria, Hungary, Belgium, Iceland, Romania, Ireland, Spain, Canada, Israel, Sweden, Czechoslovakia, Italy, Switzerland, Denmark, Japan, UK, Finland, Netherlands, USA, France, New Zealand, Germany, Norway, Yugoslavia.

- ***Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, Israel, Japan, The Netherlands, New Zealand, Norway, Romania, Spain, Sweden, UK and USA**
Supplemental Figure 2

Left: Male - P=0.394

Right: Female - P=0.681

Graphs showing trends in fasting blood glucose versus mortality per year for different countries.
Supplemental Figure 4

(a) Male - P=0.85

(b) Female - P=0.72
Figure Key

- Australia – Aus
- Austria – Aut
- Canada – Can
- Denmark – Den
- Finland – Fin
- France – Fra
- Germany – Ger
- Hungary – hun
- 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