Mortality From Thoracic Aortic Diseases and Associations With Cardiovascular Risk Factors

Running title: Sidloff et al.; Aneurysm Epidemiology Study

David Sidloff, MRCS, MBBS, BSc (Hon); Edward Choke, PhD, FRCS, MBBS;

Philip Stather, MRCS, MBChB, MRCS; Matthew Bown, MD, FRCS, PG Cert (Bioinformatics);

John Thompson, PhD; Robert Sayers, MBChB (Hons), FRCS (Ed), FRCS (Eng), MD

1Dept of Cardiovascular Sciences, University of Leicester and the NIHR Leicester Cardiovascular Biomedical Research Unit, Leicester, United Kingdom; 2Dept of Health Sciences, University of Leicester, Leicester, United Kingdom

Address for Correspondence:
David Sidloff, MRCS, MBBS, MBBS
Department of Cardiovascular Sciences
University of Leicester
Infirmary Road
Leicester, LE2 7LX
United Kingdom
Tel: +447736833606
Fax: +44(0)116 252 3251
E-mail: ds343@le.ac.uk

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Abstract

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 ICD codes were extracted from the WHO mortality database and age-standardised. WHO InfoBase and International Mortality and Smoking Statistics provided risk factor data. Eighteen WHO 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, however, are generally declining. TAA mortality has increased in Hungary, Romania, Japan and Denmark whilst aortic dissection 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. BMI demonstrated a negative linear association with female AD mortality whilst 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 thoracic aortic aneurysm and aortic dissection 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 thoracic aortic aneurysm and aortic dissection.

Key words: aneurysm, mortality rate, epidemiology, dissection
Introduction

Thoracic aortic aneurysm (TAA) may be defined as a localized or diffuse dilatation of the aorta to at least 1.5 times its normal calibre and may affect the aortic root, ascending aorta, aortic arch or descending aorta. In aortic dissection, 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 principle thoracic aortic diseases however 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\(^1\) analysed the Swedish national healthcare registers (1987 to 2002) revealing that the prevalence and incidence of thoracic aortic disease were higher than previously reported and increasing. Similarly Von Allmen and colleagues\(^2\) demonstrated that hospital admissions in the UK (1999 to 2010) for thoracic aortic disease had increased. Despite this, total mortality from thoracic aortic disease in the UK had declined in the same time period and this decline has not been reported elsewhere. Dias et al\(^3\) found that mortality from thoracic aortic disease in São Paulo State has steadily increased (1998 to 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 (AAA), these differences in mortality may be secondary to variations in traditional cardiovascular risk factors\(^4\). This study examined trends in mortality from AD and TAA and aimed to identify any associations with trends in established cardiovascular risk factors.
Methods

Identification of 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) who classify cause 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), thoracic aortic aneurysms, ruptured or otherwise, and aortic aneurysms of unspecified site (ruptured or otherwise) were extracted on 07/11/2013. 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 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. The methods used for conversion of deaths in age-standardized rates of mortality (ASM) have been previously published\(^4\). This standard population reflects the average male and female age structure of regions including Europe, Northern America, Australia/New Zealand and Japan from 1950-2010.

Risk Factor Data

Risk factor data was extracted from the International Mortality and Smoking Statistics database (IMASS Version 4.09)\(^5\) and the World Health Organisation (WHO) infobase\(^6\) the sources and limitations of which have been previously described. IMASS\(^7\) is a regularly updated (Last update: 14th November 2013) online tool which publishes smoking prevalence data for standardised age groups averaged by gender, 5 year period and 5 year age group (range 1946-2010). 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.). 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. 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 InfoBase⁶ on 01/09/2012. Each risk factor was presented as an age standardised estimate in each defined population in both males and females.

Countries included

Only WHO member states with a national data completeness rate of 70-100% were included into the study⁸ (Supplemental Figure 1). Those countries with adequate data completeness were then analysed to ensure that they specifically had adequate data (More than 90% completeness) relating to the ICD 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 availability of appropriate risk factor data for each country with adequate national and ICD 171 data. Utilising these criteria, eighteen countries were included into this study: Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, Israel, Japan, The 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 log\(^{10}\) of ASM trends was used to represent the percentage change in mortality per year.

The data were analysed by a linear errors-in-variables regression (Supplemental file 1). 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, TX, USA). Significance was assessed using likelihood ratio tests. Age standardised total (male and female) deaths per year were calculated for each country in both TAA and AD. The peak age at which mortality occurred was calculated for the years 2001 and 2009 and compared. The proportion of age standardised mortality occurring over the age of 75 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 been previously published\(^4\) and demonstrate a significant amount of heterogeneity across the countries studied. Male trends in BMI (1980-2008) were highest in the USA in both males and females with the smallest change seen in Romania. Trends in mean total cholesterol (1980-2008) were highest in Japan in both males and females whilst trends in mean fasting blood glucose (FBG) were highest in Spain (male and female). Trends in male mean systolic blood pressure (1995-2008) were lowest in the
UK. Smoking prevalence varied considerably between countries and gender, however, was declining in most countries. The largest reduction in male smoking prevalence was seen in the Canada whilst the smallest reduction was seen in Hungary. Romania was seen to have an increasing male smoking trend whilst in females, smoking prevalence were increasing in Spain and Romania.

**Trends in mortality from TAA**

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

The most common age range (Table 1) at which mortality from TAA occurred was 75-79 years in 2001 although variation existed for example between Japan (80-84 years) and Romania (60-64 years). In 2009 the most common age range at which mortality from TAA occurred remained at 75-79 years however 13/18 countries demonstrated an increase in the proportion of age standardised deaths occurring above the age of 75 suggestive of a delay in age at death from TAA.

**Trends in mortality from aortic dissection**

Age standardised mortality from aortic dissection also demonstrates variability however 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 aortic dissection demonstrates more heterogeneity in females compared to males, with the largest declines seen in Israel (10.4%) and Austria (5.7), whilst increases were observed in Japan (5.3%), Netherlands (2.5%), Romania (1.1%) and Spain (1.1%).

The most common age range (Table 2) at which mortality occurred from aortic dissection in 2001 was 65-69 years however variation existed. In the UK and Canada, peak age at mortality was above 80 years whilst in Hungary it was 65-69. By 2009 the most common age range at which mortality occurred had increased to 70-74. Eleven of the countries included demonstrated an increase in the proportion of age standardised deaths occurring above the age of 75.

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

Regression analysis suggests that trends in systolic blood pressure (Figure 3a, P = 0.016) and blood cholesterol (Figure 4a, P = 0.012) are positively and significantly associated with trends in male age standardised TAA mortality. Trends in body mass index (Figure 5a, P = 0.021) demonstrate negative, significant associations with TAA mortality whilst trends in smoking prevalence (Figure 6a, P = 0.282) and fasting blood glucose (Supplemental Figure 2a, P=0.394) are not significantly associated with male TAA mortality. Similarly in females, regression analysis of trends in systolic blood pressure (Figure 3b, P=0.013) and blood cholesterol (Figure 4b, P=0.033) demonstrate positive and significant associations with trends in age standardised TAA mortality. Body mass index demonstrates negative, significant associations with TAA mortality (Figure 5b, P=0.024) and no association was demonstrated with trends in smoking prevalence (Figure 6b, P=0.069) or fasting blood glucose (Supplemental Figure 2b, P=0.681). 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.

The association of trends in aortic dissection mortality to trends in risk factors
Regression analysis suggests that trends in systolic blood pressure (Figure 7a, P=0.048) are positively and significantly associated with trends in male age standardised mortality from AD. No association was demonstrated with cholesterol levels (Supplemental Figure 3a, P=0.086), body mass index (Figure 8a, P=0.054), smoking prevalence (Supplemental Figure 4a, P=0.85) or fasting blood glucose (Supplemental Figure 5a, P=0.54). In females, trends body mass index (Figure 8b, P=0.03) were negatively and significantly associated with mortality from AD. No association was demonstrated with trends in cholesterol (Supplemental Figure 3b, P=0.84) systolic blood pressure (Figure 7b, P=0.28), smoking prevalence (Supplemental Figure 4b, P=0.72) or fasting blood glucose (Supplemental Figure 5b, P=0.59). Unlike for TAA, no clear picture was demonstrated with trends in population risk factors with mortality from TAD.

Discussion
This ecological regression represents the largest population level analysis of mortality from TAA and AD and confirms that mortality secondary to these pathologies are generally on the decline. This decline was however, not equal between countries, gender 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 aortic dissection differ as do their respective associations with
cardiovascular risk factors suggesting that a combined analysis of thoracic aortic disease as has
been conducted previously\(^1\) may be inaccurate. The lack of any significant association of TAA or
aortic dissection with trends in smoking prevalence may suggest a difference in aetiology
compared to AAA.

Male and female mortality from TAA is generally on the decline however large
differences are noted. Japan, Romania, Denmark and Hungary demonstrate increasing mortality
in both males and females whilst the sharpest declines were seen in Canada and the UK (male
and female). Furthermore, within country variations were observed between males and females.
For aortic dissection, mortality is generally on the decline however whilst increases were only
seen in two countries in males, they were seen in five countries for females.

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\(^9\) highlighted differences in
cholesterol levels between genders and demonstrated opposite trends in Australasia, North
America, and Europe, where serum total cholesterol decreased from high concentrations,
compared to East and Southeast Asia and the Pacific, where it rose from low concentrations. It
may be expected that geopolitically close countries for examples Denmark and Sweden would
demonstrate similar trends in mortality however 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)\(^10\) suggests that Denmark has a
current smoking prevalence of 20% whilst Sweden’s smoking prevalence is 11%. Current mean
total cholesterol levels\(^6\) are 5.5 and 5.4mmol in men and women respectively in Denmark and
5.2mmol, 5.0mmol respectively in Sweden therefore real differences appear to exist.
In this study Japan demonstrated increases in both TAA and AD mortality. Another population based analysis\textsuperscript{11} of health examination and epidemiological studies revealed that in high income regions, males and females in Western Europe had the highest mean systolic blood pressures and that differences existed between genders. Although these geographical and gender differences in risk factor exposure correlate with trends in TAA and AD mortality, it is also known that sexual dimorphism exists amongst a number of cardiovascular diseases\textsuperscript{12} therefore the differences observed in this study could be partly explained by differences in the pathophysiology of TAA and aortic dissections between males and females.

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\textsuperscript{13}. Smoking is the main modifiable risk factor that has been associated with the development, expansion\textsuperscript{14,15} and rupture of AAA\textsuperscript{16} 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 to the abdominal aorta. Some have attributed these observations to differences in flow and shear stress\textsuperscript{17} however differences have also been noted in the level of proteases and immune mediators\textsuperscript{13} therefore genetic differences may exist. The association of these mortalities with changes in body mass index is similar to that demonstrated previously for AAA however should be interpreted with caution.

These results do not exclude the possibility of extrinsic factors influencing population trends in mortality for example antihypertensive and lipid lowering medication, however, these medications would affect population distributions of each relevant risk factor. In addition to lowering cholesterol levels Statins may reduce TAA growth rate\textsuperscript{18} and the proportion of TAA
progressing to dissection, rupture, or death\textsuperscript{19}. Changes in the treatment of TAA have occurred over time, however, current evidence suggests that thoracic endovascular aortic repair has similar long-term results as open thoracic aortic repair\textsuperscript{20} therefore these changes should not affect mortality trends. Analysing the impact on mortality of an increased application of thoracic endovascular aneurysm repair (TEVAR) for AD and TAA\textemdash s is not possible in the global setting as such data are not globally however Von Allmen and colleagues demonstrated that in the UK and there was no association between an increasing use of TEVAR and a decline in mortality\textsuperscript{2}.

One limitation of this study is the use of civil registration system mortality information from which completeness of data varies between countries although we did exclude countries with inadequate completeness of statistics and/or in availability of risk factor data. Furthermore, mortality from thoracic aneurysm and aortic dissection can be underestimated as 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 as individual patient data would be more accurate and informative. Population trends in mortality may be effected 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 findings from a group (or country), apply to an individual within that group which may not always be the case. This is termed the ecological fallacy. As individual patient level data is not currently available, ecological regression may be useful to make as much sense as possible from the available data. Another limitation of this model is that sensitivity analysis to check the stability of this analysis across age bands are not possible as although mortality data is available by age group, risk factor data is not. Some P values obtained through these analysis 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 classify both Stanford type A (involving the proximal, ascending aorta and Stanford type B aortic dissection (involving the descending aorta distal to the left subclavian artery) together (ICD I71.0) however they are not the same. Untreated, type A dissections are associated with a 90%\textsuperscript{21} mortality falling to a 16.9% to 20.2%\textsuperscript{22} 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 haemodynamic instability\textsuperscript{23}. Pooled early mortality with best medical therapy has been shown to be approximately 6.4% with up to 89% surviving to 5 years\textsuperscript{23}. This mortality based data is 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 TAD however ICD-10 does not differentiate these from those secondary to atherosclerosis. The most common of these disorders are Marfans syndrome which has a prevalence of 2-3 per 10,000 individuals\textsuperscript{24} and Ehlers Danlos Syndrome which effects approximately 1:25,000 patients\textsuperscript{25} therefore both are rare, however, may account for up to 20% of patients with TAA or TAD\textsuperscript{26}.

Conclusion

This study provides evidence that mortality secondary to thoracic aortic aneurysm and aortic dissection are generally on the decline. This decline is however, not equal between countries, gender 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 thoracic aortic aneurysm and aortic dissection however smoking cessation may not play a similar role to that seen in other aneurysmal disease.
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**Conflict of Interest Disclosures:** None.

**References:**


10. World Health Organisation. Tobacco control country profiles,


**Table 1.** Age range at Peak ASM for the years 2001 and 2009 (Thoracic aortic aneurysms).

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*Canada did not submit data for the year 2009*

**Table 2.** Age range at Peak ASM for the years 2001 and 2009 (Aortic dissections).

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*Canada did not submit data for the year 2009*
Figure Legends:

**Figure 1.** Trends in male (a) and female (b) age standardised TAA mortality showing heterogeneity between countries and gender.

**Figure 2.** Trends in male (a) and female (b) age standardised mortality from aortic dissection showing heterogeneity between countries and gender.

**Figure 3.** Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean systolic blood pressure and TAA mortality. Those countries with a reducing population systolic blood pressure also have a declining TAA mortality.

**Figure 4.** Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean total cholesterol and TAA mortality. Those countries with a reducing population cholesterol level also have a declining TAA mortality.

**Figure 5.** Linear regression revealing the negative association between temporal trends in male (a) and female (b) mean body mass index and TAA mortality. Those countries with an increasing population BMI also have a declining TAA mortality.

**Figure 6.** Linear regression revealing no clear association between temporal trends in male (a) and female (b) smoking prevalence and TAA mortality.
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.

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.
Figure 1

Thoracic Aneurysm – % Change in Mortality per year

a) Male

b) Female
Figure 2

a) Male

Aortic Dissection – % Change in Mortality per year

Country: Aus, Aut, Can, Den, Fin, Fra, Ger, Hun, Isr, Jap, Net, NZ, Nor, Rom, Spa, Swe, UK, USA

b) Female
Figure 3

a) Male - P = 0.016

b) Female - P = 0.013

Thoracic Aneurysm – % Change in Mortality per year

Trends in systolic blood pressure
Figure 4

a) Male - P = 0.012

b) Female - P = 0.033

Thoracic Aneurysm – % Change in Mortality

Trends in cholesterol

Trends in cholesterol
Figure 5

Trends in body mass index

Thoracic Aneurysm – % Change in Mortality per year

a) Male - P = 0.021

b) Female - P=0.024
Figure 6

a) Male – $P = 0.282$

b) Female – $P = 0.069$
Figure 7

a) Male – P = 0.048

b) Female – P = 0.28
Figure 8

a) Male - P=0.054

b) Female - P=0.032

Aortic Dissection – % Change in Mortality per year

Trends in body mass index

Trends in body mass index
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Data Supplement (unedited) at:

http://circ.ahajournals.org/content/suppl/2014/11/13/CIRCULATIONAHA.114.010890.DC1
SUPPLEMENTAL MATERIAL

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.
SUPPLEMENTAL MATERIAL 1

Errors in Variables Regression

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

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

where $\epsilon_i$ 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

$$\mu_y = \beta_0 + \beta_1 \mu_x$$

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

Similarly $y$ ~ $N(\mu_y, \sigma_y)$. 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 1 – Flow Diagram of included countries

National Level Data Completeness 70-100%*
55 Countries

I71 Data Completeness more than 90%**
25 Countries

WHO InfoBase / IMASS data availability***
18 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
Supplemental Figure 3

(a) Male - P = 0.086

(b) Female - P = 0.84
**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