Halving premature death

Richard Peto, CTSU
University of Oxford, UK
Halving premature death

considering separately ages 0-4, 5-34 & “middle age” (here defined as 35-69)
% survival to age 70: an example from the past
% survival to age 70: French males born in 1896

World War 1, 1914-1918
% survival to age 70: French males born in 1896

Ages
0-4

World War 1, 1914-1918
% survival to age 70: French males born in 1896

Ages 0-4

World War 1, 1914-1918

35-69
1860 rates: Liverpool, the highest mortality rates in all of England and Wales
1860 rates: males, all England & Wales
% survival at 1860 age-specific rates
1900 rates: males, England & Wales
% survival at 1900 age-specific rates
Male under-5 mortality, England & Wales 1838-2002

Source: Gary Whitlock, CTSU, from the reports of the Registrars-General for England & Wales
1950 rates: male, England & Wales
% survival at 1950 age-specific rates
2000 rates: males, England & Wales
% survival at 2000 age-specific rates
Years 1875-2000 (&2003)
Males, England & Wales: % survival at period rates
Females, England & Wales:
% survival at period rates
Worldwide childhood mortality decreasing, 1950s-2000s

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Under-5 mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950-4</td>
<td>23%</td>
</tr>
<tr>
<td>1970-4</td>
<td>14%</td>
</tr>
<tr>
<td>1990-4</td>
<td>9%</td>
</tr>
<tr>
<td>Present decade</td>
<td>~7%</td>
</tr>
</tbody>
</table>

(~10M / 130M)

Source: AD Lopez
130M/year now being born: future deaths among them (at current age-specific death rates)

<table>
<thead>
<tr>
<th>Age range</th>
<th>Future deaths</th>
</tr>
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<tbody>
<tr>
<td>0-34</td>
<td>~20M</td>
</tr>
<tr>
<td>35-69</td>
<td>~40M</td>
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<td>(70+)</td>
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Worldwide deaths, all causes: 60 M/year dying in the 2000s

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M = Million
Main causes of the ~10M deaths per year at ages 0-4

2.5 Perinatal (and, ~0.5M mothers die)
1.9 Acute respiratory infection (ARI)
1.6 Diarrhoea
1.1 Malaria
1.1 Vaccine-preventable diseases
   (0.6 measles, 0.3 pertussis, 0.2 tetanus)
0.3 HIV
~2M other causes

8M
7M annual deaths, age 5-34:

~2M HIV + ~5M other

Many from external causes (accident, violence & suicide):
important, & can be influenced
Worldwide, HIV still increasing

~3M deaths / year;
~ 6M new infections / year

Treatment, male circumcision & reducing infection via concurrent partners, sex workers & needles might halve 2020s HIV mortality
Worldwide deaths, all causes: 60 M/year dying in the 2000s

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M = Million
130M/year now being **born**: future deaths among them (at current age-specific death rates)

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130M BIRTHS/YEAR: at current death rates,
~20 M will die before middle age, &
~40M will die in middle age
(~15M vascular, 10M cancer)

Can current vascular & cancer death rates in middle age be halved?
Changing vascular mortality: prevention & treatment

Tobacco
(smoker @ 3x non-smoker risk)

Blood lipids*

Blood pressure*

Obesity

* Secondary prevention: high annual risk ÷ 3 by long-term statin, BP lowering & aspirin
Changing vascular mortality: secondary (2ry) prevention

• Long-term drug treatment of high risk: statin, BP lowering & aspirin in 1 pill

• Particularly relevant to 2ry prevention in middle age with good quality of life: 10-year recurrence risk is 1/6, not 1/2
Primary prevention: evidence for avoidability

- Every vascular disease common in one place is much less common elsewhere.
- Differences between population vascular disease rates are not chiefly genetic.
- Many big causes are already known.
- Many diseases vary, becoming much more or less common over a few decades.
UNITED KINGDOM 1950–2005: Males & Females Cerebrovascular disease mortality at ages 35–69

Death rate / 1000, age standardised

*Mean of annual rates in the seven component 5-year age groups

Source: WHO mortality & UN population estimates
UNITED KINGDOM 1950–2005: Males & Females
Cerebrovascular disease mortality at ages 35–69

Rate 1.5 / 1000 (5% dead)

Rate 0.3 / 1000 (1% dead)

*Mean of annual rates in the seven component 5–year age groups
Source: WHO mortality & UN population estimates
UNITED KINGDOM 1950–2005: Males & Females Ischaemic heart disease mortality at ages 35–69

Male

Male 2005 rate 1.5
(5% dead)

Male 1985 rate 4.5
(15% dead)

Male

Female

Death rate / 1000, age standardised*

*Male

*Female

Source: WHO mortality & UN population estimates

*Mean of annual rates in the seven component 5–year age groups
Top: 9 / 1000
(~30% dead, all vascular)
United Kingdom 1950–2005: Males & Females
All vascular mortality at ages 35–69

Rate 7.5 / 1000
(~25% dead)

Rate 4.5 / 1000
(~15% dead)

*Mean of annual rates in the seven component 5-year age groups
Source: WHO mortality & UN population estimates
UNITED KINGDOM 1950–2005: Males & Females
All vascular mortality at ages 35–69

Rate 7.5 / 1000 (~25% dead)

Rate 4.5 / 1000 (~15% dead)

Rates: 2.2M, 1.0F
(7%M, 3%F dead)

*Mean of annual rates in the seven component 5-year age groups
Source: WHO mortality & UN population estimates
UNITED STATES 1950–2005: Males & Females
All vascular mortality at ages 35–69

Rates: 2.6M, 1.3F
(risks: 9%M, 4%F)

*Mean of annual rates in the seven component 5–year age groups

Source: WHO mortality & UN population estimates
EU15 (15 countries) 1960–2000: Male & Female
All vascular mortality at ages 35–69

Death rate / 1000, age standardised*

*Mean of annual rates in the seven component 5–year age groups
Source: WHO mortality & UN population estimates
POLAND 1963–2005: Males & Females
All vascular mortality at ages 35–69

*Mean of annual rates in the seven component 5–year age groups
Source: WHO mortality & UN population estimates
RUSSIAN FEDN. 1980–2005: Males & Females
All vascular mortality at ages 35–69

*Male  
*Female

Death rate / 1000, age standardised*

*Mean of annual rates in the seven component 5–year age groups  
Source: WHO mortality & UN population estimates
Alcohol-attributed deaths in Russia, millions per decade at year 2000 mortality rates and % of all deaths

David Zaridze, unpublished findings
Changing vascular mortality rates in middle age (35-69): prevention

Tobacco, physical inactivity, obesity, type of dietary fat, extreme alcoholism

(all relevant to 1ry & 2ry prevention)
Tobacco
Blood pressure
Blood lipids
Obesity
THE MILLION WOMEN STUDY
Prof. Valerie Beral, Univ. Oxford & Cancer Research UK
(1,300,000 followed for 7 years: 1st public results on smoking)

First large prospective study of women who have smoked throughout adult life

Shows the full hazards (in middle age) of cigarette smoking for women

Big risks, even though UK cigarette yields have been lowered in recent decades
UK women born ~1940

VASCULAR mortality at age ~60+

Relative risk & CI, current versus never-smoker

Standardised for age, FU duration, BMI, 10 UK regions & 5 socioec. groups

![Graph showing the relationship between cigarettes per day and relative risk for coronary heart disease and stroke.](image-url)
Tobacco
Blood pressure
Blood lipids
Obesity
How important is blood pressure to vascular death?

20 mmHg systolic BP halves vascular mortality at 35-69

PSC: Prospective Studies Collaboration (60 studies, 1M adults, 0.1M deaths)
Lancet 2002; 360: 1903
Prospective Studies Collaboration (PSC)


Steering Committee — S Lewington (coordinator and statistician), S MacMahon (chair), R Peto (statistician), A Aromaa, C Baigent, J Carstensen, Z Chen, R Clarke, R Collins, S Duffy, D Kromhout, J Neaton, N Qizilbash, A Rodgers, S Tominaga, S Törnberg, H Tunstall-Pedoe, G Whitlock.

http://www.ctsu.ox.ac.uk/projects/psc/
34,000 IHD deaths at ages 40-89: age-specific risks vs. usual SBP

<table>
<thead>
<tr>
<th>Age</th>
<th>CHD mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>32</td>
</tr>
<tr>
<td>50-59</td>
<td>16</td>
</tr>
<tr>
<td>60-69</td>
<td>8</td>
</tr>
<tr>
<td>70-79</td>
<td>4</td>
</tr>
<tr>
<td>80-89</td>
<td>2</td>
</tr>
</tbody>
</table>

Lancet 2002; 360:1903-13

Usual systolic BP (mmHg)

20 mmHg halves risk

Age 20 mm↓Hg
60-69 46% ↓
50-59 50% ↓ risk
40-49 51% ↓ risk
70-79 40% ↓ risk
80-89 31% ↓ risk

256 128 64 16 8 4 2 1

20 mmHg halves risk
11,000 stroke deaths at ages 40-89: age-specific risks vs. usual SBP

Age 20 mm\text{↓}Hg
80-89 33\%\text{↓} risk
70-79 50\%\text{↓} risk
60-69 57\%\text{↓} risk
50-59 62\%\text{↓} risk
(40-49 64\%\text{↓} risk)

20 mmHg halves risk

Lancet 2002; 360:1903-13
Tobacco
Blood pressure
Blood lipids
Obesity
LDL and HDL particles carry most of the cholesterol (C) in the blood.

**Bad (B):** some or all types of LDL particle

- apo B on surface
- LDL-C inside

**All right (A1):** some types of HDL particle

- apo A₁ on surface
- HDL-C inside
ISIS case-control study of acute MI, UK, early 1990s: RR per 2SD higher 1. lipoproteins, 2. total cholesterol
Statins: efficacy & safety of big reductions in LDL chol.

1. Large-scale randomised evidence

2. Worldwide overview, with few subgroups
CTT collaborative meta-analysis, cancer incidence: 14 statin trials, 400,000 person-years, no sigt. hazard
Hypothesis generating: excess of cancer in 1 ezetimibe trial? Hypothesis testing: no apparent hazard in 2 other such trials

<table>
<thead>
<tr>
<th>Years</th>
<th>No. with cancer onset</th>
<th>Risk ratio (RR), active vs control, and confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=944)</td>
<td>Control (n=929)</td>
</tr>
<tr>
<td>SEAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 year</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>1–2 years</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>2–3 years</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>3+ years</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>All years</td>
<td>101/3810 py (2.7% pa)</td>
<td>65/3826 py (1.7% pa)</td>
</tr>
</tbody>
</table>

Trend test: $\chi^2 = 0.00$ (p = 1.00)

<table>
<thead>
<tr>
<th>SHARP/IMPROVE–IT</th>
<th>(n=10,319)</th>
<th>(n=10,298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 year</td>
<td>128</td>
<td>144</td>
</tr>
<tr>
<td>1–2 years</td>
<td>109</td>
<td>99</td>
</tr>
<tr>
<td>2–3 years</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>3+ years</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>All years</td>
<td>313/18,246 py (1.7% pa)</td>
<td>326/18,255 py (1.8% pa)</td>
</tr>
</tbody>
</table>

Trend test: $\chi^2 = 0.04$ (p = 0.84)
Tobacco
Blood pressure
Blood lipids
Obesity
BMI & main disease categories: PSC

Annual deaths per 10,000
(floated so mean =
EU 2000 rates
at age 35-69)

Adjusted for age, smoking & study; 1st 5 years of follow-up excluded
Effects of obesity on survival: PSC

% survival from age 35 yrs: normal build, overweight, obese

Median life expectancy at age 35: 3 yrs less if BMI 33 than if 23

PSC (& Cancer Prevention Study II) relative risks applied to EU15 mortality rates in 2000
Effects of severe obesity: PSC

% survival from age 35 yrs: moderate & severe obesity (dotted lines)

Median life expectancy at age 35: 10 yrs less if BMI 43 than if 23

PSC (& Cancer Prevention Study II) relative risks applied to EU15 mortality rates in 2000
Cancer mortality: screening, treatment and prevention

- Chronic infection, mainly in developing countries (eg, HBV, HCV, HPV, H. pylori, EBV, HIV, HHV, flukes, schistosomiasis)
- Occupational factors (eg, asbestos, radon, benzidine, coal & other smoke) worldwide
- Hormonal factors (eg, HRT, kids, obesity)
- Tobacco, first in developed and then in developing countries
Nationwide delay between increase in smoking by young adults

& main increase in tobacco deaths when those young adults reach middle & old age

eg, USA 1900-2000
US trends in cigarette consumption & lung cancer mortality

Cigarettes/day, (males + females)

Male lung cancer, 35–69

Annual mortality per 100,000
(mean of 7 age specific rates, ages 35–69)

Cigarettes per day (adults aged 18+)

United States, 1950–2005
MALE cancer mortality at ages 35–69

Not attributed to smoking
Attributed to SMOKING

Death rate / 100 000, age standardised*

*Mean of annual rates in the seven component 5-year age groups
Source: WHO mortality & UN population estimates
1950-2000 cancer mortality:

Effects of tobacco even more dominant in UK than in US men
United Kingdom, 1950–2005
MALE cancer mortality at ages 35–69

Attributed to SMOKING
NOT attributed to smoking

*Mean of annual rates in the seven component 5-year age groups
Source: WHO mortality & UN population estimates
UK women born ~1940

LUNG cancer mortality at age ~60+

Relative risk & CI, current versus never-smoker

Standardised for age, FU duration, BMI, 10 UK regions & 5 socioec. groups
Tobacco & all-cause mortality
Blood pressure
Blood lipids
Obesity
UK women born ~1940

ALL-CAUSE mortality at age ~60+

Relative risk & CI, current versus never-smoker

Standardised for age, FU duration, BMI, 10 UK regions & 5 socioec. groups
Three main messages for the individual smoker:

1. Risk is BIG: half are killed

2. 1/4 are killed in MIDDLE age (35-69), losing many years

3. STOPPING smoking works
Decrease in prevalence of smoking: UK 1950–2000

- **Males 35–59**
  - 1950: 70%
  - 2000: 27%

- **Females 35–59**
  - 1950: 50%
  - 2000: 30%
Population risk of a 35-year-old dying at ages 35–69 from smoking (shaded) or from any cause (shaded and white)
*eg, at year 2005 male death rates, out of 100 men aged 35, 22 would die before age 70 (with 5 of these deaths attributed to smoking)

<table>
<thead>
<tr>
<th>Year</th>
<th>Smoking Deaths</th>
<th>Any Cause Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>15</td>
<td>44%</td>
</tr>
<tr>
<td>1955</td>
<td>18</td>
<td>43%</td>
</tr>
<tr>
<td>1960</td>
<td>19</td>
<td>42%</td>
</tr>
<tr>
<td>1965</td>
<td>20</td>
<td>43%</td>
</tr>
<tr>
<td>1970</td>
<td>20</td>
<td>42%</td>
</tr>
<tr>
<td>1975</td>
<td>17</td>
<td>39%</td>
</tr>
<tr>
<td>1980</td>
<td>16</td>
<td>37%</td>
</tr>
<tr>
<td>1985</td>
<td>14</td>
<td>35%</td>
</tr>
<tr>
<td>1990</td>
<td>11</td>
<td>31%</td>
</tr>
<tr>
<td>1995</td>
<td>8</td>
<td>28%</td>
</tr>
<tr>
<td>2000</td>
<td>6</td>
<td>25%</td>
</tr>
<tr>
<td>2005*</td>
<td>5*</td>
<td>22%*</td>
</tr>
</tbody>
</table>
INDIA: 1 million smoking deaths per year during the 2010s

• Smoking: 10% of all Indian deaths at any age

• 70% of smoking deaths are at ages 30-69 (600,000 men and 100,000 women/year)

Jha et al, NEJM 2008
Chinese cigarette increase 40 years after US increase

Delayed hazard: proportion of all deaths at ages 35-69 due to tobacco

<table>
<thead>
<tr>
<th>Year</th>
<th>US, all adults</th>
<th>China (men)</th>
</tr>
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<tbody>
<tr>
<td>1950</td>
<td>12%</td>
<td>1990 12%</td>
</tr>
<tr>
<td>1990</td>
<td>33%</td>
<td>2030 33%</td>
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</table>
World: ~30 million new smokers per year (50% of young men, 10% of young women).

If this continues, & most don’t stop, world tobacco deaths eventually >10 million/year (100 million/decade)
World tobacco deaths, if current smoking patterns continue

<table>
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<th>Period</th>
<th>Estimate (in millions)</th>
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<tbody>
<tr>
<td>2000-2025</td>
<td>~150M</td>
</tr>
<tr>
<td>2025-2050</td>
<td>~300M</td>
</tr>
<tr>
<td>2050-2100</td>
<td>&gt;500M</td>
</tr>
<tr>
<td><strong>TOTAL for the 21st century</strong></td>
<td>~1000M (1 billion)</td>
</tr>
<tr>
<td>Compare with 20th century total</td>
<td>~100M (0.1 billion)</td>
</tr>
</tbody>
</table>
HIV & TOBACCO
& maybe OBESITY

are the only big causes of death increasing substantially,

after allowing for worldwide growth of population
HALVING PREMATURE DEATH

Child survival (improving)
HIV (worsening, despite better treatment)
Unrelated infectious & parasitic (improving: vaccination, TB control, IMCI & better drugs)

Vascular and neoplastic death
Attention to statistical detail has greatly increased the known importance of “classical” risk factors such as blood lipids, blood pressure & tobacco, and of many widely practicable treatments.