National cardiovascular prevention should be based on absolute disease risks, not levels of risk factors

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Introduction

The case for using absolute risk as a guide to the prevention of multicausal diseases such as heart attack and stroke in individuals was clearly spelt out by Law and Wald in 2002.¹ In the United Kingdom, this formulation now informs official guidance on the selection of patients to receive statins.² The extension of this argument to the population level has received less attention.

Law and Wald¹ illustrated how the traditional approach to the management of vascular risk in individuals based on single risk factors and thresholds (creating categorical states such as ‘hypertension’, ‘hyperlipidaemia’, etc.), results in a misallocation of preventive efforts and expenditures because those who would benefit most from risk factor reductions are not well identified in this way.

Their approach to the prevention of multicausal diseases rested on two key empirically evidenced premises:

1. Overall risk depends, in a multiplicative way, on the joint action of multiple risk factors. As a consequence, the absolute effects of any one risk factor depend on the levels of the other risk factors with which it acts jointly.
2. The relationship of disease risk (on a log scale) to an individual’s usual level of risk factors such as blood pressure and blood cholesterol concentration is close to linear across the range of values typical of populations in high-income countries. This means that sustained favourable shifts of equal absolute size produce a constant proportional change in risk, across a wide range of baseline or starting levels.

It follows that the benefits of a specified reduction in a risk factor depend not on its baseline level but rather on the overall (absolute) risk to which it contributes.

Here we illustrate this argument using data for European countries.

Methods

The population attributable fraction (PAF) allows estimation of the expected reduction in disease or death under a specified more favourable exposure distribution. The reductions in deaths and in years of life lost (YLL) that would be expected from sustained reductions of 5 mmHg in mean systolic blood pressures and 0.5 mmol l⁻¹ reductions in mean total blood cholesterol concentrations were estimated. Two groups of countries were included: the 15 members of the European Union before its expansion in May 2004 (EU10) and the new member states of the European Union, excluding Malta and Cyprus (EU10). Estimates were made for the year 2002.
**Computation**

For exposures treated as continuous the PAF is given by:

\[
PAF = \frac{\int_{x=0}^{\infty} RR(x)P(x)dx - \int_{x=0}^{\infty} RR(x)P(x)dx}{\int_{x=0}^{\infty} RR(x)P(x)dx}
\]

A discrete version of this was implemented in Excel using age-strata 30–44, 45–59 and 60–69. These fractions were applied to GBD 2002 estimates for vascular mortality to derive estimates of the total mortality that could be averted by the specified shifts in risk factor distributions. Deaths averted were estimated as the sum of four categories of vascular disease (table 1) and were expressed as both crude and standardized rates per 100,000 adult population aged 30–69 years.

We have not adjusted for changes upon the joint effect of risks due to changes of the risk factor of interest.

Similar calculations were performed to assess the effects of a 0.5 mmol l\(^{-1}\) reduction in mean cholesterol concentrations.

**Data sources**

Age-specific distributions of systolic blood pressure and blood cholesterol concentration were obtained from WHO (Information, Evidence and Research section). These were derived from survey data collated in the WHO Global Infobase.3

For each country, age- and sex-specific death rates were obtained from the WHO mortality database for the categories shown in table 1.

Further details on the specification of the change in exposure, on computation and on data sources are provided in supplementary data.

**Results**

Figure 1 shows the deaths/100,000 person-years from all cardiovascular diseases (CVD) at the age of 30–69 years predicted to be averted by sustained reductions of 5 mmHg in mean systolic blood pressure. The overall variation for male populations was over 6-fold, from 107.9/100,000 person-years in Bulgaria to 17.9/100,000 person-years in France. The largest predicted gains were all in Central and Eastern European countries, and the lowest ones in Mediterranean countries, Sweden and the Netherlands.

In figure 2, predicted YLLs averted are plotted against the corresponding average absolute risk of death from vascular causes, showing strong linear associations. In contrast, when YLL are plotted against mean blood pressure at the age of 30–69 years, there is a strong non-linear relationship across countries.

**Table 1 ICD 10 codes for disease categories comprising CVD**

<table>
<thead>
<tr>
<th>ICD 10</th>
<th>Disease Category</th>
</tr>
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<tbody>
<tr>
<td>I10–I15</td>
<td>Hypertensive disease</td>
</tr>
<tr>
<td>I20–I25</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>I60–I69</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>I26–I28, I34–I37, I44–I51, I70–I99</td>
<td>Other cardiovascular diseases</td>
</tr>
</tbody>
</table>

**Figure 1** Predicted deaths from all vascular causes at ages 30–69 occurring in 2002 that would have been averted by sustained reductions of 5 mmHg in mean systolic blood pressures. Countries ranked by crude rates per 100,000 person-years
of 30–69 years in the same countries the observed associations are much weaker.

Results for reductions of 0.5 mmol l\(^{-1}\) in usual blood cholesterol concentrations were qualitatively similar to those shown for systolic blood pressure.

**Discussion**

We have shown that the expected benefits from lowering a risk factor are much more closely associated with average absolute risks than with average levels of the risk factor of interest (figure 2). This confirms that the logic of the 'absolute risk approach' extends in a forceful manner to the population level.

Several limitations arising from our data and methods need to be acknowledged. We have used a normal approximation for what may be positively skewed risk factor distributions. In another similar study—of disease burdens attributable to blood glucose distributions—sensitivity analyses comparing the normal approximation with the true (positively skewed) distributions found results to be closely comparable.

We have assumed that risk is similarly related to risk factor levels in all populations—consistent with evidence from INTERHEART\(^5\) and from Asian populations. Furthermore, the common (hypothetical) reductions in mean risk factor levels represent proportionally greater changes in some of the populations at low risk, and so may require more substantial changes in determinants to produce them.

Our estimates also depend on the validity of the data inputs. Risk factor estimates for many of the countries will have substantial empirical uncertainty. For outcomes, we chose to analyse all vascular causes combined in part because they are more policy relevant, but also because these are less affected by varying national practices in assigning cause of death.\(^7\) Our results are, however, so striking that they are likely to be robust to plausible levels of uncertainty arising from data and analytic limitations.

The illustrated straight line relationship between absolute benefit and absolute risk suggests the former may be estimated from the latter directly, at the national level. However, a formal attributable burden calculation is still preferable as it is able to also take into account the contribution from the reduction in the standard deviation as the mean of the distribution falls. And whereas in individuals, risks are predicted rather than observed, in populations, average absolute risks are observable (for example via death rates from vascular causes). This allows greater empirical discrimination.

These calculations estimate the effects of long-term differences in exposure levels. Real world transitions from one exposure level to another will entail a lag before the full health benefits are enjoyed.

The implication or our results at a population level is analogous to that of Law and Wald\(^1\) at the individual level: preventive endeavours should be calibrated against the absolute level of risk—not against the level of the contributing risk factors. In particular, Central and East European countries, where risk levels are highest, stand to gain most from risk factor reductions (figure 1). They should therefore give much higher priority to reducing all modifiable risk factors—not mainly because their levels of these risk factors are higher, but because they will gain much bigger rewards from lowering them.

High levels of manifest vascular risk—for example in the female populations of Bulgaria and Romania (figure 1)—may coexist with unremarkable levels of conventional risk factors.

![Figure 2](https://academic.oup.com/eurpub/article-abstract/20/1/103/609557)
However, even where conventional risk factors provide an incomplete explanation of why observed risks are so high, the logic of risk attribution that we have employed remains valid. Whereas risk explanation employs a logic of risk combination, risk attribution employs a logic of risk subtraction. The effects of lowering established risk factors have been shown to be highly generalizable across diverse populations and this observation is, to a substantial extent, independent of the capacity of established risk factors, in combination, to account for manifest risk differences.

We have illustrated our argument mainly using blood pressure alone. However, favourable shifts in two or more major risk factors will have substantially larger benefits—in a multiplicative way—in populations with larger absolute risk even if each risk is small—a population version of the polypill argument. Once tobacco control is added, a substantial part of the absolute risk of premature death from vascular causes can be addressed—again with the biggest rewards awaiting those countries (or populations) with the highest absolute risks. As with individuals, the argument may be generalized from the major risk factors to all modifiable risk factors. For example, population-based measures to reduce salt consumption which are likely to be highly cost-effective in most settings, will be even more cost effective in high exposure/high-risk populations. Finally, the argument that we have illustrated using national data will also extend to other populations with varying levels of absolute risk: lower socio-economic strata, for example, stand to gain much more from risk factor reductions than more favoured strata with lower absolute risks.

Supplementary data
Supplementary data are available at EURPUB online.

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Conflicts of interests: None declared.

Key points
- The biggest benefits from risk factor reductions go to populations with the highest disease risks—not to those with the highest risk factor levels.
- Across the EU, gains from reducing blood pressure will be several times higher in Baltic and South-East European member states than in low-risk populations such as France and Spain.
- Absolute risk can be used to prioritize preventive efforts between populations as well as between individuals.
- Absolute risk can also be used to prioritize preventive efforts to high-risk strata within a population.