Risk factor thresholds: their existence under scrutiny

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Interventions to lower blood pressure, serum cholesterol, and other risk factors reduce the risk of cardiovascular disease regardless of initial levels. It follows, say Malcolm Law and Nicholas Wald, that the goal is not to “normalise” risk factors but to reduce them as much as possible. This means targeting everyone at high risk, as determined by age or known cardiovascular disease rather than by the level of the risk factors

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Physiological variables such as blood pressure, serum cholesterol, body mass index, and bone mineral density are important in the aetiology of common diseases. They are not direct environmental causes of disease, like smoking, but they may be seen as biochemical or biophysical variables, under partial genetic control, that are intermediates between environmental factors and disease itself. It is known that risk can be reduced by lowering high levels of these variables by drug treatment or lifestyle change. But there is a view that changing the average values of these physiological variables is not worth while, a view that implies the presence of thresholds in the dose-response relations between the level of the variable and the risk of disease. This view is reinforced by terminology that regards extreme values as indicating a disease state (such as hypertension, hypercholesterolaemia, osteoporosis, and obesity) and average values as being “normal” (normotensive, normocholesterolaemia). Clinical guidelines specify risk factor thresholds¹⁻⁵; these have been set at successively lower levels over time and redefined as “action levels” but they still deny treatment below specified values.

We examine seven important dose-response relations to determine whether it is useful to impose risk factor thresholds or whether there are better ways to identify patients who should be treated.

Methods

We examined seven dose-response relations between physiological variables and risk of disease that are medically important and for which a large body of data was available: (i-iii) ischaemic heart disease and blood pressure, serum cholesterol, and body mass index; (iv) stroke and blood pressure; (v) diabetes and body mass index; (vi) neural tube defects and maternal plasma folate; and (vii) hip fracture and bone mineral density. For each relation we used a published meta-analysis of cohort studies if one was available,⁶ otherwise the largest single cohort study.⁷⁻¹¹ Dividing each cohort into subgroups (usually fifths) defined by ranked values of the physiological variables, we plotted the risk of disease (vertical axis) against the level of the risk factor (horizontal axis), using the subgroups and measure of risk (incidence, mortality, or relative risk) adopted in

Summary points

Understanding the dose-response relations between “physiological variables” (blood pressure, serum cholesterol, body mass index, bone mineral density) and the diseases they cause is important to realise the full potential of prevention

The dose-response relations show that a given change in the variables reduces the risk of disease by a constant proportion of the existing risk irrespective of the starting level of the variable or of the existing risk

Interventions to change the risk factors should therefore be determined by a person's level of risk, not by the level of the risk factors

The best predictors of risk are risk factors that cannot be changed, such as previous disease (myocardial infarction or stroke), age, and sex

All reversible cardiovascular risk factors should be reduced in anyone at high risk

Terms like hypertension, hypercholesterolaemia, and osteoporosis that focus medical attention on the tails of the distributions of physiological variables are best avoided

the original papers. Randomised trials of risk factor modification were available for four of these seven dose-response relations¹²⁻²⁴; we examined these to assess whether they supported the conclusions from the observational studies.

The dose-response relations

Figures 1 and 2 show the seven dose-response relations. The data are from cohort studies because cohort studies best show dose-response relations; unlike randomised trials they show disease incidence across the entire range

An expanded version of figure 3 appears on bmj.com

Fig 1 Incidence (95% confidence interval) of ischaemic heart disease according to diastolic blood pressure (top),⁶ serum cholesterol (centre),⁷ and body mass index (bottom).⁸ Data from cohort studies; incidence (vertical axes) plotted on arithmetic scale (left hand plots) and proportional (or logarithmic) scale (right hand plots)

of values of a risk factor in the population. On the left hand side of the two figures, disease incidence is plotted by using an arithmetical scale, so that in figure 1 rates of 0, 1, 2, and 3 are evenly spaced on the vertical axis. These plots are curved. On the right hand side, incidence is plotted by using a proportional or logarithmic scale, so that in figure 1 rates of 0.25, 0.5, 1, and 2 are evenly spaced on the vertical axis; a given space on the vertical axis indicates a constant proportional change in incidence (such as a doubling). These plots yield reasonably straight lines, and this is so whether the level of the risk factor on the horizontal axis is plotted using an arithmetical or proportional scale. With an arithmetical scale the straight line fit is marginally better, or no worse, in every case but one (maternal plasma folate and neural tube defects). The plots on the right hand side in figures 1 and 2 therefore follow this "semi-logarithmic" approach in all the examples except this one, where a logarithmic scale is used on both axes.

In figures 1 and 2 the 95% confidence intervals about the risk estimates exclude a threshold within the population range of values, so that the lower the risk factor the lower the risk: no part of the dose-response

relation would fit a horizontal line. This is clear from the plots using logarithmic scales, but the curved plots with an arithmetical scale on the vertical axes may falsely suggest a threshold.

Identifying a straight line dose-response relation has an important advantage: the slope is constant, so a single number can summarise the dose-response relation. With a curved line there is no single summary of effect, so simplicity and generalisability are lost. The implications of a straight line dose-response relation according to whether arithmetical or logarithmic scales are used on the vertical and horizontal axes are set out in figure 3, together with the corresponding mathematical equations. Simple linear models (arithmetical scales on both axes) rarely fit risk factor-disease incidence relations, but the use of logarithmic vertical axes to plot incidence commonly yields a reasonable straight line fit, as is shown in figures 1 and 2. A straight line relation with a logarithmic (proportional) vertical axis scale indicates a constant proportional change in risk for a given change in the risk factor from any starting level.

Fig 2 Incidence (95% confidence interval) of stroke according to diastolic blood pressure,⁶ diabetes (non-insulin independent) according to body mass index,⁹ neural tube defects according to maternal plasma folate,¹⁰ and hip fracture according to bone mineral density.¹¹ Data from cohort studies; incidence (vertical axes) plotted on arithmetic scale (left hand plots) and proportional (or logarithmic) scale (right hand plots)

The constant proportional relations in the right hand plots indicate that the absolute reduction in risk from changing the risk factor will be large in people who are at high risk for any reason (existing disease or older age, for example), regardless of the starting value of the risk factor. So, for example, halving risk by lowering serum cholesterol would be more important in a man who has an average serum cholesterol concentration but is at high risk because of a previous myocardial infarction than in a man with high serum cholesterol but no history of myocardial infarction.

Table 1 gives the summary “dose-response” estimates for each of the seven relations—the percent-

age change in risk for a specified change in the risk factor from any starting level. The cohort study estimates are derived from the slopes of the best fitting straight lines in the right hand plots in figures 1 and 2, as illustrated in figure 3 (and explained more fully in the box on [bmj.com](#)). They are adjusted for regression dilution bias^{6 26} except where this was unnecessary because the risk factors show little random fluctuation (body mass index and bone density). The table also shows how the results of randomised trials of risk factor modification, where available, confirm the cohort study estimates of a constant proportional change in risk for a given change in risk factor. For different risk

Fig 3 Implication of straight line dose-response relations according to use of arithmetic or logarithmic scales

factors the randomised trials between them cover all or most of the range of values in Western populations.

Table 2, based on two large randomised trials of serum cholesterol reduction using statins, illustrates that the proportional reduction in risk is similar in groups at high and low risk. Coronary artery disease was recognised in all the participants in one of the trials (4S)²² and none in the other (WOSCOPS),²³ but otherwise participants were similar (age, cholesterol, other coronary risk factors). The incidence of major coronary events in the placebo group was four times higher in the trial of people with existing disease (5.2% v 1.4% per year), but the proportional risk reduction in the treated groups was similar in the two trials. Consequently the absolute reduction in risk was greater in those with existing disease (and would have been even greater but for preventive treatment in the high risk group²³). Trials of blood pressure lowering drugs show similar proportional reductions in risk in people with and without previous stroke or myocardial infarction.¹²⁻¹⁹ Another example is the randomised trial of folic acid supplementation in high risk women (with previous neural tube defect pregnancies), which showed the same proportional reduction in risk as that found in the general population with about a tenth of the background risk.^{24 25} In general, the constant proportional effect model holds among men and women, people of different ages, and people with and without existing disease.

Are average values necessarily normal?

Our central conclusion is that the proportional relation between these physiological variables and their associated diseases is constant across all levels of the variables and all levels of risk. The lower the risk factor the lower is the risk of disease, down to levels well below average Western values. This raises the question as to whether average Western values should be regarded as "normal." Today's average levels are not typical of values throughout human evolution. With the exception of bone density,²⁷ the variables in our ancestors cannot be measured, but indirect estimates are available from studies of isolated communities with

a hunter-gatherer lifestyle typical of the stone age. Table 3 contrasts typical values of the variables at age 60 in these communities with present Western values. The rise in the variables with age that is seen in Western populations^{30 31} does not occur in hunter-gatherer communities: throughout life blood pressure remains at about 110/70 mm Hg, serum cholesterol at 3.0-3.5 mmol/l, and body mass index at about 22 kg/m². The shift in the Western distributions makes the current averages high (or low in the case of bone density and plasma folate) in relation to the prehistoric values. Differences in lifestyle (diet and habitual exercise) underlie the differences in the physiological variables,^{32 35} and relatively recent changes are likely to have been responsible for the emergence of the associated diseases (ischaemic heart disease, non-insulin dependent diabetes, hip fracture). Present average values of certain key risk factors in Western populations should not be regarded as "normal."

Practical implications of continuous dose-response relations

We focus mainly on the implications for preventing ischaemic heart disease and stroke.

Treat anyone at high risk

Blood pressure lowering drugs should not be limited to people with high blood pressure, nor cholesterol lowering drugs to people with high serum cholesterol concentrations. The constant proportional relation means that there is value in modifying risk factors in people at high risk, whatever the reason for the high risk and regardless of the level of the risk factor.

The major determinant of risk is existing disease. Without preventive treatment, mortality from heart disease in people who have had a myocardial infarction in the past is about 5% per year for the rest of their life.³⁶ Mortality from stroke in people who have had a stroke is similar.^{36 37} Both rates are much higher than in people with no history of cardiovascular disease; coronary mortality is 0.3% per year in men aged 60, for example, or about 0.5% per year in men with high cholesterol or blood pressure.⁷ In people with existing disease,

Table 1 Estimates of proportional reduction of disease risk for specified changes in risk factors from cohort studies and, when available, from the randomised trials for seven dose-response relations shown in figures 1 and 2

Dose-response relation	Specified change in risk factor	Corresponding reduction (%) in risk of disease	
		Estimated from cohort studies	Estimated from randomised trials (95% CI)
Diastolic blood pressure and ischaemic heart disease ^{6 12-17}	5 mm Hg decrease	21	20 (16 to 23)
Serum cholesterol and ischaemic heart disease (age 55-64) ^{7 20-23}	0.6 mmol/l decrease	27	25 (1 to 35)†
Body mass index and ischaemic heart disease ⁸	1 BMI unit decrease‡	10	*
Diastolic blood pressure and stroke ^{6 12-19}	5 mm Hg decrease	34	33 (26 to 39)
Body mass index and diabetes ⁹	1 BMI unit decrease‡	10	*
Maternal plasma folate and neural tube defects ^{10 24 25}	100% increase	43	39 (14 to 57)
Bone mineral density and hip fracture ¹¹	0.1 g/cm ² (about 15%) decrease	53	*

*No data from randomised trials available.

†After 5 years.

‡Equivalent in a man of average height to a reduction of 3 kg body weight.

Table 2 Results of two randomised trials of statin drugs and major coronary events, showing relative and absolute reductions in risk according to incidence in placebo group

Trial	Known coronary disease	Incidence of major coronary events in placebo group (% per year)	Reduction in risk in treated group (95% CI)	
			Relative	Absolute (% per year)
WOSCOPS ²¹	No	1.4	39 (20 to 52)	0.5 (0.3 to 0.7)*
4S ²²	Yes	5.2	35 (27 to 42)	1.8 (1.4 to 2.2)*

*Indicating that events are prevented in 0.5% and 1.8% of all people treated each year (standardised to the average cholesterol reduction in the 4S trial).

however, the physiological risk factors do not predict recurrent events despite the fact that changing the risk factors alters risk. This is illustrated by data from the 4S trial (table 4): in the placebo group the incidence of recurrent events was similar in groups with high and low concentrations of low density lipoprotein cholesterol.²³ This finding, though at first sight surprising, is not unexpected: once an event has occurred and disease is present there is little for a risk factor to predict. Table 4 also shows that the proportional reduction in the incidence of recurrent events in the treated group (about 35%) was, as expected, independent of the initial cholesterol level. Since the initial absolute risk and the proportional risk reduction were not materially related to the initial cholesterol level, neither was the absolute risk reduction of about 2% per year. Similarly, in people who have had a stroke the incidence of recurrent strokes³⁷ and the proportional risk reduction with blood pressure lowering¹⁷⁻¹⁹ were not materially related to the initial blood pressure, so the absolute risk reduction will be substantial at any level of blood pressure. The conclusion is clear: anyone with existing disease (a previous myocardial infarction or stroke for example) should be treated irrespective of the level of the risk factors one seeks to modify.

In people without known cardiovascular disease, age is the most important determinant of risk. Mortality from ischaemic heart disease and from stroke doubles with about every eight years of increas-

ing age.¹⁷ In England and Wales 95% of deaths from heart disease occur in the 23% of the population at oldest age (men ≥ 55 and women ≥ 60). But in people without existing disease the screening performance of the physiological variables, while better than in people with disease, is still poor. The variables are important aetiologically but are poor screening tests; this apparent paradox has been discussed.³⁸ There is little separation between the distributions of these variables in people who over a specified period of time do and do not develop disease; this has been documented for serum cholesterol,³⁹ blood pressure,¹⁷ and bone mineral density.⁴⁰ Average values are high (table 3) and, as table 5 shows, the 10% in the population with the most extreme values of the physiological variables experience only about 20% of the disease events. As Rose pointed out, offering preventive treatment only to people with relatively high values of a variable means that only a small proportion of those destined to have disease events will be targeted.⁴³ People of a given age with relatively high values of the physiological variables are at similar risk as people a few years older with average levels, and present practice is illogical in offering preventive treatment to the former but not the latter. There are therefore two reasons for not focusing on the tails of the distributions: the lack of threshold and the fact that they are poor screening tests.

In people without cardiovascular disease, intervention to change risk factors could be introduced when a person's risk of a disease event over the next few years exceeds a specified value. Risk could be estimated from age alone, or age and sex. Values of the physiological variables might also be taken into account, but the limited additional discrimination may not justify the added complexity.

Change all relevant risk factors together

Because there is substantial benefit from lowering these physiological variables from any starting value in persons at high risk, all the reversible risk factors should be changed, not just those judged "abnormal."

Table 3 Average values of physiological variables in present day Western societies and values judged typical of prehistoric societies

Physiological variable	Prehistoric value	Current value	Proportion (%) of current Western population below prehistoric average
Blood pressure (mm Hg), age 60 ²⁸⁻³¹ :			
Systolic	110	145	<1
Diastolic	70	80	<5
Serum cholesterol (mmol/l), age 60 ²⁹⁻³⁴	3.2	6.0	<1
Body mass index (kg/m ²), age 60 ²⁹⁻³²	22	27	<10
Bone density loss in postmenopausal women (% decline/year) ²⁷	0.6	1.2	<5

Table 4 Major coronary events in patients with angina or previous myocardial infarction in Scandinavian simvastatin survival study (4S)²²: incidence in placebo group and proportional reduction in treated group, with trial participants divided into fourths according to initial concentration of low density lipoprotein (LDL) cholesterol

	Fourths of initial LDL cholesterol			
	≤4.39 mmol/l	4.40-4.48 mmol/l	4.85-5.34 mmol/l	≥5.35 mmol/l
Incidence in placebo group (% per year)	4.7	5.5	4.8	5.8
Proportional reduction in risk in treated group (%)	35	33	32	36
Absolute reduction in risk in treated group (% per year)	1.6*	1.8	1.5	2.1

*Events are prevented in 1.6% (that is, 35% of 4.7%) of all treated patients each year.

Reducing only variables with high values loses most of the potential benefit.

Aim for a large change to achieve a large benefit

There is an inappropriate tendency to accept small changes in reversible risk factors. Guidelines recommend the use of drugs to lower serum cholesterol after a myocardial infarction only if diet has failed.¹⁻³ This is not logical and creates a perverse incentive; those who ignore the dietary advice receive drugs that lower serum cholesterol four times as much as any realistic dietary change.²⁰⁻²² Similarly, there is no sense in aiming for a small reduction in blood pressure in a person who has had a stroke or myocardial infarction; this provides only partial treatment to those who need treatment most.

Carry out only necessary randomised trials

Randomised trials have shown that the continuous dose-response relations, shown in cohort studies, are reversible from values of the risk factor that are high, average, and, in a few trials,^{17-18, 22} below average. There is a view that additional trials are necessary to establish reductions in risk from successively lower starting values. The evidence from large cohort studies, however, makes this unnecessary. Randomised trials show that once the straight line dose-response relation observed in cohort studies is reversible across the upper portion of the distribution of the risk factor, it can be judged to be reversible over the whole distribution: any alternative explanation for the straight line relation would have to be based on so implausible an assembly of coincidental observations as to be untenable. In the case of serum cholesterol and ischaemic heart disease (fig 4), one would need to postulate an important but unknown cause of heart disease that is highly correlated with serum cholesterol (no known cause is) and to postulate that increasing levels of this confounding factor increased the risk of heart disease and stroke only up to a plateau. The plateau where the confounding effect would end would have to coincide with the serum cholesterol threshold above which the causal association would begin. The magnitude of the relation between the unknown confounding factor and ischaemic heart

Fig 4 Straight line relation between serum cholesterol and ischaemic heart disease (as for serum cholesterol in fig 1) and explanation to account for straight line being cause and effect across upper portion of serum cholesterol distribution (where it has been confirmed by randomised trials) but not across the lower portion

disease would have to be the same as that between serum cholesterol and heart disease because the slope of the line remains the same, and it would have to replicate the decreasing slope with age.^{7, 20} This non-causal alternative explanation for the straight line relation is so implausible that it can be rejected.

Trials have low statistical power at low risk factor levels (because there are relatively few people at low risk and because the event rates are lower), so their results tend to be inconclusive. In three trials testing cholesterol reduction from low starting levels (<5.2 mmol/l) the confidence intervals were consistent both with no reduction in the event rate and with the expected reduction from the cohort studies.⁴⁴⁻⁴⁷ It is inappropriate to require randomised trials to exclude successively lower thresholds of effect; the trials are large, expensive, and unnecessary. It is inappropriate to restrict cholesterol lowering drugs to people with concentrations above 5 mmol/l or blood pressure lowering drugs to people with pressures above 140 mm Hg systolic or 90 mm Hg diastolic, as currently recommended,^{4, 5} when cohort studies have shown continuous relations down to cholesterol concentrations of 3.8 mmol/l²⁶ and blood pressure of 118 systolic and 76 diastolic.⁷ In contrast, it is appropriately recommended that all women with a previous neural tube defect pregnancy take folic acid regardless of their serum folate (which is usually not even measured).

Concern over lowering levels of risk factors too far

Thresholds have been excluded down to cholesterol levels (3.8 mmol/l)²⁶ and blood pressure levels (118

Table 5 Extent to which disease is concentrated in the 10% of the population with the most extreme values of physiological variables

Physiological variable	Associated disorder	Proportion (%) of cases of disorder in 10% of population with most extreme values
Systolic blood pressure ⁴¹	Stroke	28
Systolic blood pressure ⁴¹	Ischaemic heart disease	21
Serum cholesterol ⁴²	Ischaemic heart disease	21
Body mass index ⁸	Ischaemic heart disease	22
Body mass index ⁹	Diabetes	23
Bone mineral density ⁴⁰	Hip fracture	22

systolic/76 diastolic)⁷ that are close to the prehistoric levels (table 3). The condition of heterozygous familial hypobetalipoproteinaemia, in which total serum cholesterol is as low as 2 mmol/l, provides an important natural experiment: life expectancy is prolonged because coronary artery disease is avoided, but no adverse effects from the low cholesterol are recognised.^{47, 48} There must be lower limits to the physiological variables we have considered, beyond which harm will arise: everyone needs blood pressure, and cholesterol is essential for life. These lower limits are, however, beyond Western values and not reached by current dietary or drug interventions. They should not be invoked as obstacles to offering effective preventive treatments.

Conclusions

Practical conclusions arise from the simple observations that certain key dose-response relations have no threshold and yield straight lines when risk of disease is plotted on a logarithmic scale. The most important are that, irrespective of the level of the risk factor, a given change in risk factor results in the same proportional reduction in risk regardless of the initial risk; the selection of individuals for preventive treatment should be based only on a person's absolute level of risk; and individuals at high risk should receive drug treatment to modify all important reversible risk factors simultaneously.

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