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Assessing Risk Factors as Potential Screening Tests

A Simple Assessment Tool

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Many risk factors for disease are suggested as screening tests when there is little prospect that they could be useful in predicting disease. To avoid this, it is useful to know the relationship between the relative risk of a disease or disorder in people with high and low values of a risk factor, and the equivalent screening performance in terms of the detection rate (sensitivity) for a specified false-positive rate. We describe an interactive Risk-Screening Converter, accessible from the Internet (http://www.wolfson.qmul.ac.uk/rsc/), that transforms an odds ratio into the equivalent estimates of detection and false-positive rates. The converter is intended for general clinicians, for people engaged in research into risk factors and disease, and for those who give advice on applying such research findings into medical practice. It should help to distinguish effective screening methods from ineffective ones, and so improve clinical guidelines relating to screening and the prediction and prevention of disease. *Arch Intern Med. Published online October 25, 2010. doi:10.1001/archinternmed.2010.378*

Most risk factors are not useful as screening tests for the diseases with which they are associated because the association is too small, even if they are large enough to have important causal implications.[1] A risk factor (which may be causal or noncausal) has to be very strongly associated with a disease to be seriously considered as a possible screening test. For example, the odds ratio between the highest and lowest 20% of the population needs to be about 50 or more. Despite this, it is often suggested that a particular risk factor may be a useful screening test or disease predictor, even though it can be deduced from published relative risk estimates that this cannot be the case. For example (considered further in the subsection titled "Example 1: CRP as Possible Test for CHD" in the "Four Examples" section), we show that C-reactive protein (CRP) is not useful as a screening test, even though it has been suggested as a possible predictor of ischemic heart disease.[2]

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There are few risk factors with odds ratios that are high enough to qualify as disease predictors or screening tests. DNA polymorphisms, sometimes promoted as being predictive of common diseases, are, for practical purposes, useless when used in this way—most polymorphisms associated with particular diseases have relative risks of less than 2. Their utility lies in elucidating the pathogenesis of disease rather than predicting disease.[3] Even etiologically important risk factors, such as blood pressure and serum cholesterol (or apolioprotein B), that are important causes of cardiovascular disease (CVD), have odds ratios too low to be of much value in predicting disease.[4] Herein, we limit our consideration of risk factors to their use as predictors of disease.

CAUSAL RISK FACTORS ARE USUALLY POOR PREDICTORS

It may seem a paradox that important causal risk factors are usually poor predictors of the disease that they cause. The reason, as previously explained,[1] is that the

causes of disease within a community are usually widespread, so that nearly everyone is exposed to these causes, even though not everyone succumbs to the clinical effects of the exposure. For example, nearly everyone increases their blood pressure throughout their lives, largely due to consuming a diet high in salt. Most people do not have a stroke, despite the much higher risk of stroke in people with a higher blood pressure. The widespread exposure means that causal risk factors usually do not discriminate well between individuals who will and will not develop the disease in question. In contrast, useful screening tests are usually early manifestations of the disease being screened for (eg, a high maternal serum alphafetoprotein concentration in a pregnancy with spina bifida, or a positive mammogram result in a woman with early breast cancer).

ODDS RATIOS AND MEASURES OF SCREENING PERFORMANCE

The performance of a screening test is principally defined in terms of the detection rate for a specified false-positive rate, or a false-positive rate for a specified detection rate. The detection rate (sensitivity) is the proportion of affected individuals, or those who become affected during a given period of time, with positive test results, and the false-positive rate (1 – specificity) is the proportion of unaffected individuals with positive test results. There is a direct relationship between the odds ratio of a risk factor and the measures of screening performance defined by the detection rate for a specified false-positive rate, or the false-positive rate for a specified detection rate. The figure in an earlier article[1] illustrates the relationship between an odds ratio and the corresponding detection rate for a given false-positive rate. Unless the disorder being screened for is common (prevalence or incidence over a period of follow-up of more than about 5%), the odds ratio and relative risk estimates are numerically almost the same, so the relative risk, which is often given in articles, can usually be used instead of the odds ratio. The following glossary of terms shows that even if the prevalence is 10%, the odds ratio and relative risk estimates are similar (10 to 11):

- **Detection rate (sensitivity):** Proportion of affected individuals with positive test results. (In screening for future disease, affected individuals are those who are diagnosed as having the disease during a given period of time.)
- **False-positive rate (1 – specificity):** Proportion of unaffected individuals with positive test results. (In screening for future disease, unaffected individuals are those who are not diagnosed as having the disease during the same period used to determine the detection rate.)
- **Odds of being affected given a positive result (OAPR):** The OAPR is the ratio of the number of affected to unaffected individuals among those with positive results. It is the ratio of true-positive individuals to false-positive individuals. The positive predictive value is an alternative to OAPR; it is the number of true-positive individuals divided by the total number of individuals with positive results (true positives + false positives) expressed as a percentage. So, for example, an OAPR of 1:3 is the same as a positive predictive value of 1/(1 + 3), or 25%.
- **Relative risk:** The incidence of a disease in one group divided by the incidence in a reference group.
- **Odds ratio:** The number of affected individuals divided by the number of unaffected individuals in each of 2 groups yields 2 odds; one divided by the other is the odds ratio.
- **Relationship between relative risk and odds ratio:** For example, if the incidence were 100 per 1000 per year in one group and 10 per 1000 per year in the reference group, the relative risk would be 10 (100/1000 divided by 10/1000). The equivalent odds ratio would be 11 (100/900 divided by 10/990).

RISK-SCREENING CONVERTER

To help assess the value of a risk factor as a screening test in the prediction of disease, we have produced a Risk-Screening Converter that converts an odds ratio (or relative risk estimate) into measures of screening performances accessible from the Internet (http://www.wolfson.qmul.ac.uk/rsc/). The use of this may avoid inappropriate proposals suggesting that a risk factor may be useful as a disease predictor when this is unlikely. The Risk-Screening Converter can be used without access to the original data.

The Risk-Screening Converter is derived from the method and equation described by Wald et al,[1] adopting the assumptions that the standard deviation (SD) of the risk factor in affected individuals is the same as that in unaffected individuals, and that the risk factor distributions are Gaussian. In practice, these assumptions are usually sufficiently valid to provide accurate estimates of screening performance. The detection rates, false-positive rates, and odds ratios are calculated on the basis of the proportions in the highest and lowest categories of the unaffected population, which is formally correct, rather than on the proportions of the whole population. However, this makes little difference if the prevalence or incidence over a specified period of time is not high.

The Risk-Screening Converter uses the proportion of individuals in the highest and lowest portions of the distribution of the risk factor in the population in question—for example, the highest 20% and the lowest 20% (ie, top and bottom quintile groups). It then performs the following conversions:

1. A specified odds ratio into a figure showing the detection rate according to the false-positive rate;
2. A specified false-positive rate into a table and a figure showing the odds ratio according to the detection rate;
3. A specified detection rate into a table and a figure showing the odds ratio according to the false-positive rate.

Some articles report the strength of an association between a risk factor and a disease in terms of the odds ratio for a 1-SD difference in the value of the risk factor. This avoids the need to specify the proportions of individuals in the highest and lowest proportion of the distribution of the risk factor. The Risk-Screening Converter then converts:

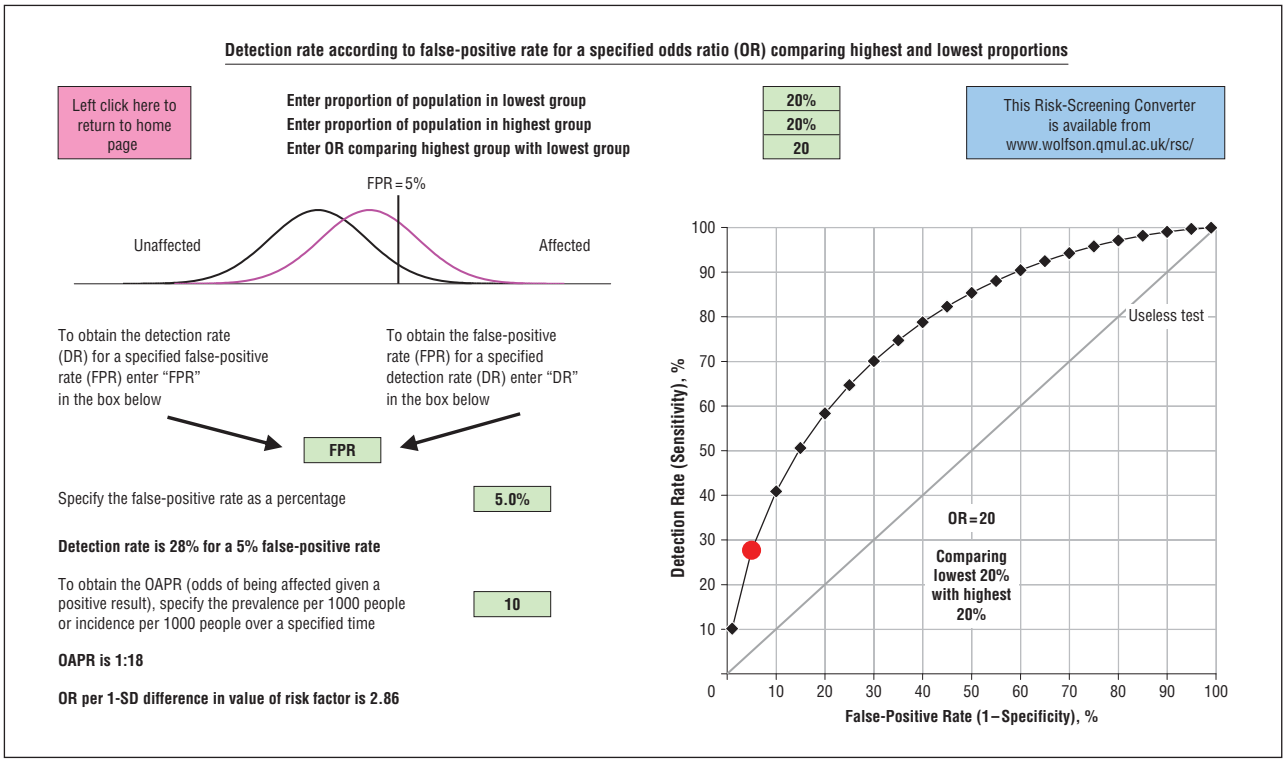

Figure 1. Illustration of Web page showing detection rate according to the false-positive rate for a specified odds ratio (OR) comparing lowest and highest groups of a risk factor. The Gaussian curves in the top left-hand corner indicate the relative distribution of the risk factor in affected and unaffected individuals. OAPR indicates odds of being affected given a positive result.

4. A specified odds ratio for a 1-SD difference in the value of the risk factor into a figure showing the detection rate according to the false-positive rate.

Converting an Odds Ratio Into Estimates of Screening Performance

Figure 1 shows an illustration of conversion 1, in which an odds ratio of 20 across the top and bottom quintile groups of the distribution of the risk factor is converted into a graph showing the detection rate against the false-positive rate (sometimes referred to as a receiver operating characteristic curve). The Risk-Screening Converter allows users to obtain the detection rate for a specified false-positive rate, and the false-positive rate for a specified detection rate, by entering either the false-positive rate or the detection rate into a box that automatically calculates the precise result.

The Risk-Screening Converter also allows users to obtain an estimate of the odds of being affected given a positive result (see the glossary of terms on the previous page) if an estimate of the prevalence of the disorder being screened for (or its incidence over a specified period of time) is entered in the appropriate box.

The odds ratio between the highest and lowest groups is 20, but an odds ratio as high as this is rarely observed in epidemiological associations. It is equivalent to a 28% detection rate for a 5% false-positive rate. This is only modest discrimination. The figure shows the overlapping relative Gaussian distributions of the risk factor in affected and unaffected individuals with the specified detection rate (or false-positive rate) indicated as a vertical line. As the odds ratio increases, the overlapping distributions separate, providing a visual indication of the discriminatory value of the risk factor. The figure also shows the odds ratio for a 1-SD increase in the value of the risk factor (2.86 in this example), and the odds of being affected given a positive result is 1:18 if the prevalence of the disorder is 10 per 1000.

Combining several risk factors that, individually, have modest risk associations with disease into a single risk estimate confers little improvement in screening performance.[5] This applies to most so-called novel risk factors as well as to traditional ones, such as serum cholesterol and blood pressure.[6] The Risk-Screening Converter can be used for risk scores or risk estimates based on several risk factors combined in the same way as it can be used with individual risk factors. The Risk-Screening Converter can be used to assess the value of adding a marker. This can be performed by entering the odds ratios with and without the additional marker.

Converting Screening Performance Into an Odds Ratio

Figure 2 shows an illustration of conversion 2, in which a false-positive rate of 10%, with proportions in the highest and lowest groups both set at 20%, is converted into a graph of the odds ratio plotted against the detection rate. The tabulation within Figure 2 provides the precise estimates and also the odds ratio corresponding to a 1-SD increase in the risk factor. Figure 2 shows, for example, that to achieve a detection rate of 50% for

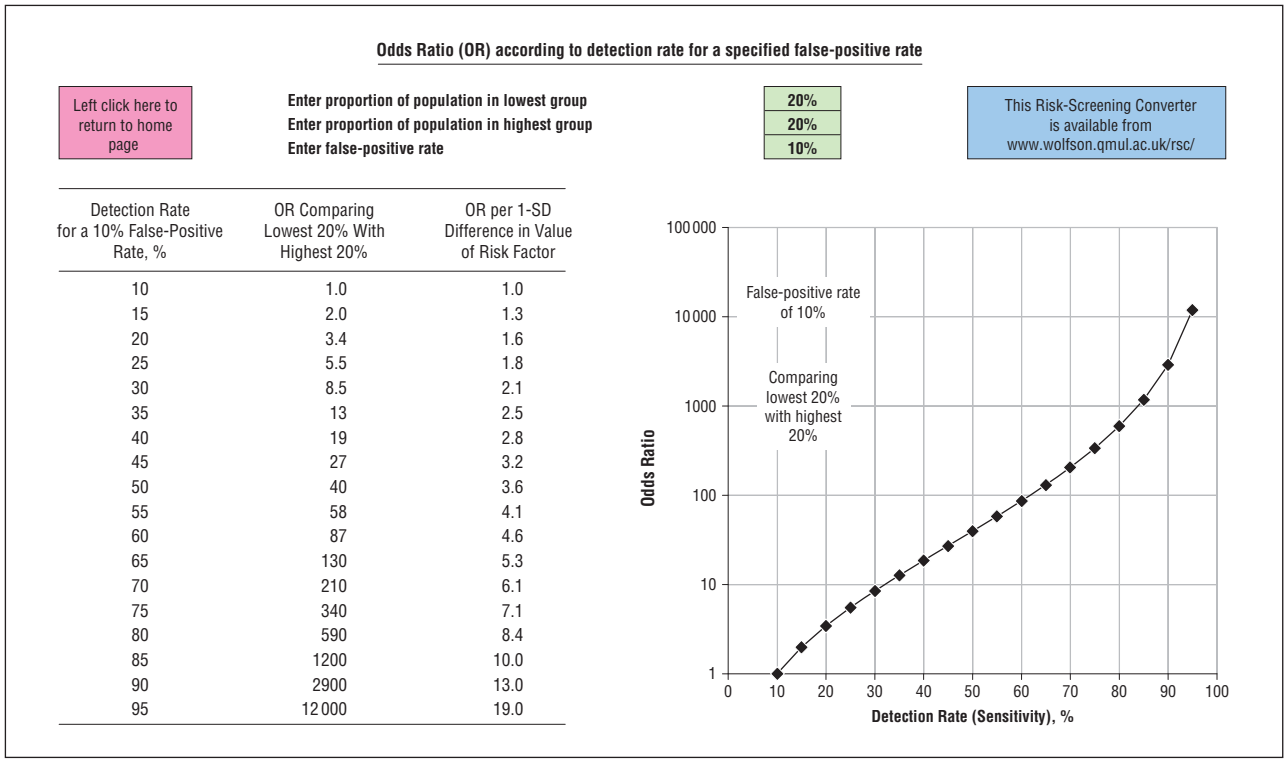

Figure 2. Illustration of Web page showing odds ratio (OR) comparing lowest and highest groups of a risk factor according to the false-positive rate for a specified detection rate.

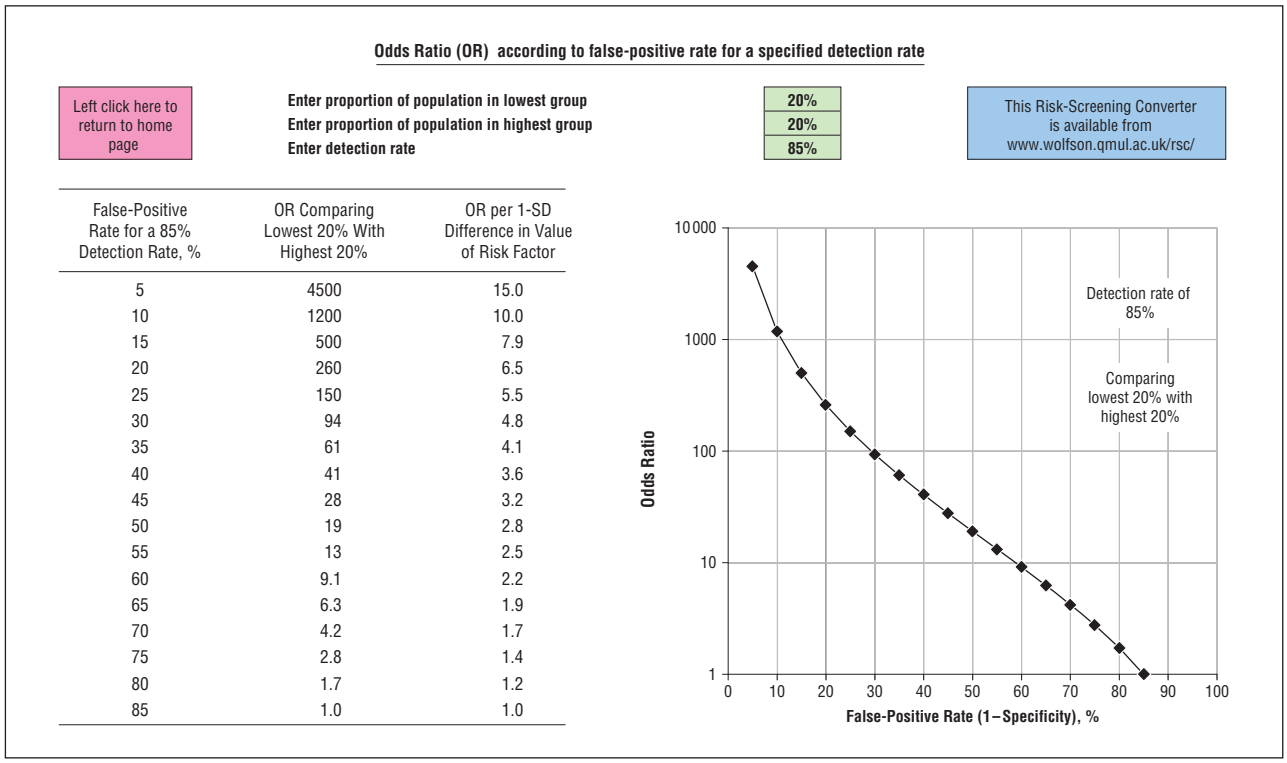

Figure 3. Illustration of Web page showing odds ratio (OR) comparing lowest and highest groups of a risk factor according to the detection rate for a specified false-positive rate.

the specified 10% false-positive rate, the odds ratio comparing the top and bottom quintile groups would have to be 40.

Figure 3 shows, in a way similar to that of Figure 2, an illustration of conversion 3, in which a detection rate of 85%, with proportions in the highest and lowest groups again both set at 20%, is converted into a graph of the odds ratio plotted against the false-positive rate.

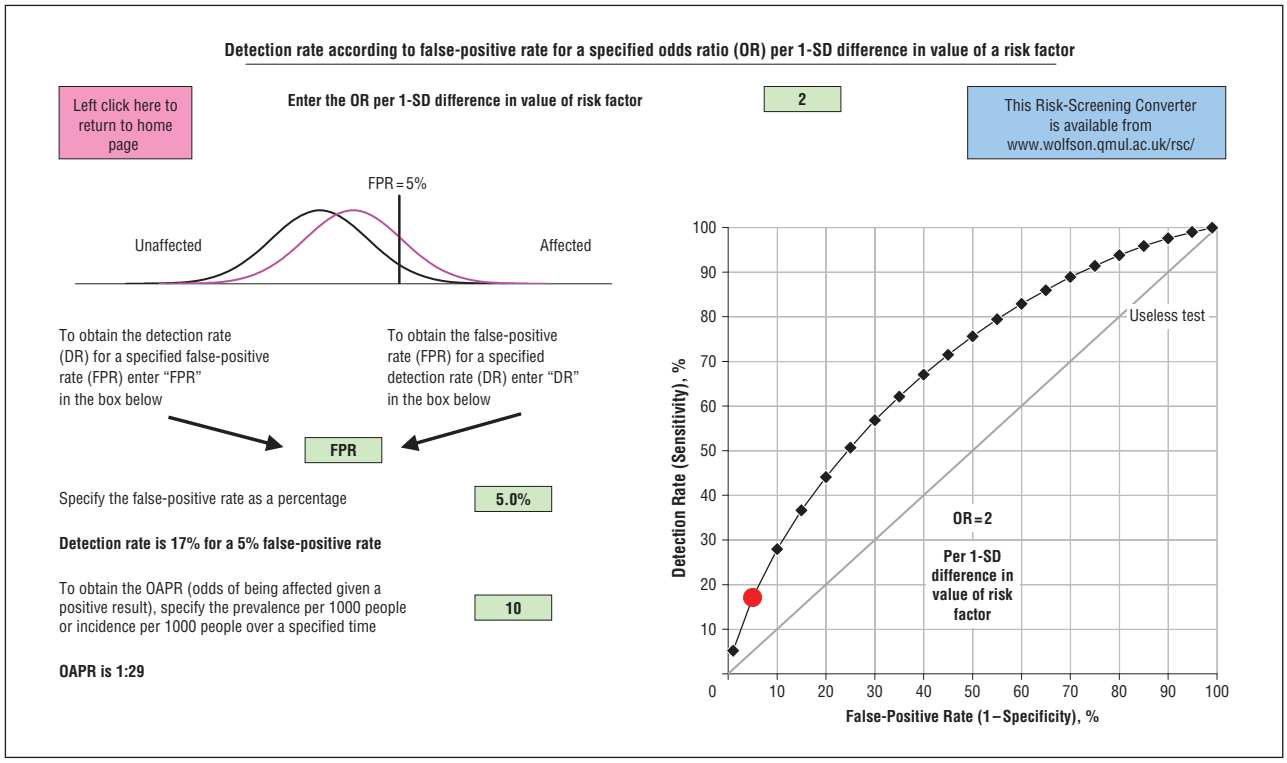

Figure 4. Illustration of Web page showing detection rate according to false-positive rate for a specified odds ratio per 1-SD difference in the value of a risk factor. The Gaussian curves in the top left-hand corner indicate the relative distributions of the risk factor in affected and unaffected individuals. OAPR indicates odds of being affected given a positive result.

Figure 3 shows, for example, that to achieve a 5% false-positive rate the odds ratio comparing the top and bottom quintile groups would have to be 4500.

Converting an Odds Ratio for 1-SD Difference in the Value of a Risk Factor Into Estimates of Screening Performance

Figure 4 shows, in a way similar to that of Figure 1, an illustration of conversion 4, in which an odds ratio of 2 for a 1-SD difference in the value of the risk factor is converted into a graph showing the detection rate against the false-positive rate.

FOUR EXAMPLES

Example 1: CRP as Possible Test for CHD

The Emerging Risk Factors Collaboration[7] performed a meta-analysis of CRP and future coronary heart disease (CHD). Figure 3 in that article shows that the CHD odds ratio between the highest 10% and the lowest 10% of the CRP distribution in the whole population is about 3. The use of the page labeled "Specified Odds Ratio Comparing Highest and Lowest Proportions" (Figure 1) on the Risk-Screening Converter shows that if these values are entered into the boxes, the detection rate for a 5% false-positive rate is 9%, indicating only minor discrimination, which is of no practical value in prediction or screening. The Emerging Risk Factors Collaboration report[7] also provides an estimate of the odds ratio for a 1-SD difference in CRP concentration (1.63). This is inserted into the appropriate box on the page labeled "Specified Odds Ratios per 1-SD Difference in Value of a Risk Factor" (Figure 4). It produces estimates of screening performance similar to those obtained here using an odds ratio of 3 between the highest and lowest 10% of the CRP distribution.

Example 2: Coronary Calcification as Possible Test for CHD

The Rotterdam Coronary Calcification Study[8] determined coronary calcification scores using computed tomographic scanning on 1795 asymptomatic participants aged 62 to 85 years. Table 2 in that article shows that the relative risk of developing a CHD event between the highest 11% and the lowest 50% of the calcification score distribution is 8.3. Again, the use of the "Specified Odds Ratio Comparing Highest and Lowest Proportions" page on the Risk-Screening Converter (Figure 1) shows that, with these values entered into the boxes, the detection rate for a 5% false-positive rate is 22%. Although this degree of discrimination is low, computed tomographic scanning of the heart to measure coronary calcification has been judged to be a strong predictor of CHD. If the annual incidence of CHD were 1%, the risk in "screen-positives" would be about 4% [1% × (22/5)], and because 22% of cases are detected, 78% of CHD events would be missed.

Example 3: Glycated Hemoglobin as Possible Test for DM and CHD

The Atherosclerosis Risk in Communities study[9] measured glycated hemoglobin in 11 092 adults who did not have a history of diabetes mellitus (DM) or CVD. The top of

Table 2 in that article shows that the relative risk of developing DM (based on an elevated fasting glucose) between the highest 4% (479 of 11 092) and the lowest 9% (949 of 11 092) of the glycated hemoglobin distribution is 50.73/0.49 or 103.5. Again, the use of the "Specified Odds Ratio Comparing Highest and Lowest Proportions" page on the Risk-Screening Converter (Figure 1) shows that, with these values entered into the boxes, the detection rate for a 5% false-positive rate is 32%, indicating that the measurement of glycated hemoglobin could be used as a moderately good screening test for DM. In contrast, the relative risk of developing CHD between the highest 4% and the lowest 9% of the glycated hemoglobin distribution is 2.91/0.89 = 3.3, yielding a 9% detection rate for a 5% false-positive rate, so glycated hemoglobin is of no practical value in prediction or screening.

Example 4: QRISK Score for Predicting 10-Year Risk of CVD

QRISK is a multifactor CVD risk prediction algorithm based on age, sex, blood pressure, smoking status, serum cholesterol, high-density lipoprotein ratio, body mass index, family history of CVD, a social deprivation index, and the use of antihypertensive drugs. QRISK was assessed in 1.07 million people with 43 990 future cardiovascular events.[10] Table 2 in the article[10] shows that the relative risk of having a CVD event between the highest 10% and the lowest 10% of the QRISK score was 41.2 for women (20.19/0.49) and 20.8 for men (26.26/1.26). Use of the "Specified Odds Ratio Comparing Highest and Lowest Proportions" page on the Risk-Screening Converter (Figure 1) shows that, with these values entered into the boxes, the detection rate for a 5% false-positive rate is 28% for women and 22% for men. The authors[10] recommend QRISK for use in screening for CVD in preference to the more widely used Framingham risk equations, the performance of which can be assessed from the same article using the Risk-Screening Converter.

INTENDED USE OF RISK-SCREENING CONVERTER

Appreciation of the numerical equivalence between odds ratio and measures of screening performance given in terms of the detection rate for a given false-positive rate (or the false-positive rate for a given detection rate) will help researchers, general clinicians, and health policy makers determine whether a particular risk factor is likely to be useful in screening and disease prediction. The Risk-Screening Converter should achieve this objective by showing this equivalence in a simple, interactive way.

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