The Observation That Risk Increases According to the Number of Components does not Necessarily Indicate that Each Component is a Risk Factor

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There are several diagnostic criteria for metabolic syndrome, and the diagnosis is essentially based on whether the number of components surpasses a particular cutoff value\(^1,2\). On the other hand, controversy still exists over which components should be included in the diagnosis for the prediction of cardiovascular complications\(^3\). It has been demonstrated that the risk of cardiovascular disorder increases according to the number of features of metabolic syndrome\(^4\), which may suggest that each component has been properly selected and may be of clinical use. However, here we generated the following artificial model to show that when risk increases according to the number of components, it does not necessarily indicate that each component is a risk factor.

- Components of the five diagnostic criteria: \(c_i\) \((i = 1, 2, 3, 4, 5)\).
  - The prevalence of all five components is 0.2, and \(c_i\) \((i = 1, 2, 3, 4, 5)\) is hypothesized to occur independently.
  - The probability of any of “\(n\) \((n = 1, 2, 3, 4, 5)\)” component(s) being positive, defined as \(P(n)\), is calculated as follows:
    \[
P(n) = (0.2)^n \times (0.8)^{(5-n)} \times sC_n
    \]
  - The probability of “\(n\)” components, including \(c_1\), being positive, is designated as \(P(n, c_1 = 1)\). For example, \(P(1, c_1 = 1)\) indicates that the probability of \(c_1\) alone is positive:
    \[
P(n, c_1 = 1) = 0.2 \times (0.2)^{n-1} \times (0.8)^{(5-n)} \times sC_{n-1} = P(n) \times sC_{n-1}/sC_n
    \]
  - The probability of an event (or of developing a disease) when \(c_i\) is positive and negative is defined as \(p(c_i = 1)\) and \(p(c_i = 0)\), respectively.
    - The relative risk of \(c_i\) \((i = 1, 2, 3, 4, 5)\), designated as \(rr_i\) \((i = 1, 2, 3, 4, 5)\), is the risk of an event (or of developing a disease) relative to exposure:
      \[
      rr_i = \frac{p(c_i = 1)/p(c_i = 0)}{(i = 1, 2, 3, 4, 5)}
      \]
    Here, \(rr_i\) is determined as follows:
    \[
    rr_i = a (i = 1), \text{ and } rr_i = b (i = 2, 3, 4, 5)
    \]
    - \(RR(n)\) is then defined as the risk of an event (or of developing a disease) when \(n\) component(s) are present, as compared with the reference group comprising individuals without any of the five components. \(RR(n)\) is calculated as follows:
      \[
      RR(n) = \frac{[a \times b^{(n-1)} \times P(n, c_1 = 1)] + [b^n \times (P(n) - P(n, c_1 = 1))]}{P(n)}
      = [a \times b^{(n-1)} \times sC_{n-1}/sC_n] + [b^n \times (1 - sC_{n-1}/sC_n)]
      = sC_{n-1}/sC_n \times [(a \times b^{(n-1)} - b^n)] + b^n
      = sC_{n-1}/sC_n \times b^{(n-1)} \times (a - b) + b^n (n = 1, 2, 3, 4, 5)
      \]
    If \(a = 2\) and \(b = 1\), which indicates that only component \(c_1\) is a real positive risk factor, then \(RR(n)\) \((n = 1, 2, 3, 4, 5)\) is calculated as follows:
    \[
    RR(1) = 1.2, RR(2) = 1.4, RR(3) = 1.6, RR(4) = 1.8, RR(5) = 2.0
    \]
    Further, if the relative risk of \(c_2, c_3, c_4, \text{ and } c_5\) for a certain disease condition is 0.9, and that of \(c_1\) is 4, indicating that component \(c_1\) is a positive risk factor, while others are in fact negative predictors, then it follows:
    \[
    RR(1) = 1.52, RR(2) = 1.93, RR(3) = 2.24, RR(4) = 2.46, RR(5) = 2.62
    \]
    Although \(RR(3)\) is calculated to be 2.24, the probability of an event (or of developing a disease) in subjects in whom \(c_2, c_3, \text{ and } c_4\) are positive, but \(c_1\) and \(c_5\) are negative, is actually 0.73 \((= 0.9^3)\), when compared with individuals without any of the five components.

In the current study, our discussion is based only...
on artificial data. On the other hand, by analyzing the data in the Japan Public Health Center-based Prospective (JPHC) Study, Noda et al. have recently shown that any one of high glucose, high triglycerides, or being overweight was not a significant predictor of ischemic cardiovascular disease, although increasing the number of metabolic syndrome components (i.e., high blood pressure, high glucose, low HDL cholesterol, high triglycerides, being overweight) showed a graded increase in the risk of ischemic cardiovascular disease in women. Hence, it should be noted that even when the risk of an incident or of an event increases according to the number of certain selected components, it does not necessarily indicate that each component is a risk factor for the incident or the event, as has been demonstrated by the current mathematical consideration. We have to assess whether each component will actually increase (or decrease) the prevalence or incidence of the outcome before analyzing the effects of the combination of some of these components on the prevalence or incidence of the target outcome.

References