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Combining Risk Estimates from Observational Studies with Different Exposure Cutpoints: A Meta-analysis on Body Mass Index and Diabetes Type 2

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ABSTRACT

Studies on a dose-response relation often report separate relative risks for several risk classes compared with a referent class. When performing a meta-analysis of such studies, one has to convert these relative risks into an overall relative risk for a continuous effect. Apart from taking the dependence between separate relative risks into account, this implies assigning an exposure level to each risk factor class and allowing for the nonlinearity of the dose-response relation. The authors describe a relatively simple method solving these problems. As an illustration, they applied this method in a meta-analysis of the association between body mass index and diabetes type 2, restricted to results of follow-up studies (n = 31). Results were compared with a more ad hoc method of assigning exposure levels and with a method in which the nonlinearity of the dose-response method was not taken into account. Differences with the ad hoc method were larger in studies with fewer categories. Not incorporating the nonlinearity of the dose response leads to an overestimation of the pooled relative risk, but this bias is relatively small.

INTRODUCTION

Many epidemiologic studies of associations between an exposure and a disease report a dose-response relation in terms of relative risk for grouped exposure levels (risk factor classes) compared with a referent class. Such meta-analyses are usually performed by using the assigned dose method, in which all individuals in a certain risk factor class are assigned to a single, often arbitrarily chosen level of exposure, for instance, the midpoint of the risk factor class. This level is then associated with the relative risk of this specific risk factor class, and a meta-regression is performed. Especially in the case of broad dose categories, this might not be a valid method. Several studies (1–3) have shown that the choice of the assigned value may substantially influence the results of the meta-analysis. A related issue is that, in epidemiology, generally a linear relation is assumed between exposure and the logarithm of outcome, that is, a nonlinear relation between exposure and relative risk. In that case, the average of the relative risks

of the separate exposures in each category is not equal to the relative risk of the average exposure in each category, as pointed out by Shi and Copas (3). They also suggested a statistical solution for these problems, which, however, is not easily implemented (2).

Another problem that has to be accounted for is the fact that the variances of the relative risks within a study are mutually dependent, since all relative risks are relative to the same referent class. Since in a meta-regression the contributions of the studies are weighted with the inverse of the individual variances, this directly influences the outcome of the meta-analysis. Greenland and Longnecker (4) developed a method to deal with this issue but not with those of assigning exposure levels or taking the nonlinearity of the relation between exposure and relative risk into account. We will describe a comparatively simple method to addresses all three problems in the case that the exposure can be assumed to follow a specific distribution and illustrate our method with a meta-analysis on the relation between body mass index and diabetes type 2.

METHOD TO CONVERT RELATIVE RISKS PER EXPOSURE CLASS TO RELATIVE RISKS PER UNIT OF EXPOSURE

In many publications on continuous risk factors, a series of grouped dose-specific relative risks is given, with one exposure class serving as a referent group. To transform these into a risk estimate per unit of exposure, we assign in our method a dose value to each dose group, assuming a specific parametric distribution for the exposure in the population. First, we will describe this for a linear dose-response relation. Second, we will describe how to take into account the nonlinearity of the dose-response relation.

Assigning dose values for a linear dose-response relation

In the case of a linear relation between risk factor and the disease, the relative risk in a class will be equal to that of the average risk factor level of that class but not to that of the midpoint of the class or to the median of the exposure. When the type of the distribution of the risk factor in the population is (assumed) known, this distribution can be fitted to the data and used to estimate the average risk factor level in each class. This method is easily implemented and has the advantage that it does not depend on other data sets or at hoc rules to estimate the average in open-ended categories. In addition, the expected value is a better estimate of the class average than is the midpoint of a class. For our case study on body mass index and diabetes, we fit a gamma distribution to the body mass index distribution over the classes, as this fit our data better than did a normal distribution. Often, the parameters γ and β of the gamma distribution can be calculated from the mean body mass index in the study population and its standard deviation (SD), as reported in the papers:

$$\hat{\gamma}=\left(\frac{\text{mean}}{\text{SD}}\right)^2 \text{ and } \hat{\beta}=\frac{\text{SD}^2}{\text{mean}}. \quad (1)$$

If the sample mean and/or standard deviation is not reported, the parameters can be estimated by fitting the distribution to the observed numbers in the different body mass index classes, for example, by minimizing chi square. With these estimates of parameters, we can calculate the expected value of body mass index and its variance in each body mass index class with boundaries c_0 and c_1 as follows:

$$E_i(X)=\frac{\hat{\gamma}\times\hat{\beta}\times P((c_0,c_1)|\hat{\gamma}-1,\hat{\beta})}{P((c_0,c_1)|\hat{\gamma},\hat{\beta})} \quad (2)$$

$$\mathrm{Var}_i(X)-\frac{\gamma\times(\hat{\gamma}+1)\hat{\beta}^2\times P((c_0,c_1)|\hat{\gamma}+2,\hat{\beta})}{P((c_0,c_1)|\hat{\gamma},\hat{\beta})}-E_i(X)^2, \quad (3)$$

where X = the risk factor value (in our example, body mass index), $\hat{\beta}$ and $\hat{\gamma}$ are the parameters of the gamma distribution as estimated in equation 1, and $P((c_0,c_1)|\gamma,\beta)$ is the probability that a random variable with a gamma distribution with parameters ß and γ has a value in the interval (c_0, c_1). The variance (Var) from equation 3 is not used here but is already given as it is needed to adjust for nonlinearity.

Assigning a dose value, adjusting for nonlinearity

In the case of a linear relation between exposure and outcome, the average relative risk in each class equals the relative risk of the average exposure in this class. However, in many epidemiologic studies, a linear relation is assumed between exposure and the logarithm of outcome. This implies a nonlinear relation between exposure and relative risk, and thus the average of the relative risks of the exposures is not equal to the relative risk of the average exposure (3). This problem can be solved by calculating an assigned value for which the relative risk is equal to the average relative risk in the particular risk factor class. This, however, requires knowledge of the relative risk per unit of exposure and thus can be solved only iteratively. For this, we used the following method. Let $f_i(X)$ be the distribution of X in interval i, and let disease incidence be modeled as

$$\ln(\text{incidence}|X)=\beta_0+\beta_1 X.$$

We then can approximate

$$\begin{aligned} Y_i &= \ln(\text{incidence}|\text{interval } i) \\ &= \ln\left(\int_i \exp(\beta_0+\beta_1 X) f_i(X)\,dX\right) \\ &\approx \beta_0+\beta_1\bar{X}+\frac{1}{2}\beta_1^2\,\mathrm{var}_i(X), \end{aligned} \quad (4)$$

where $\bar{X}_i$ is the average exposure in interval i, and $\mathrm{var}_i(X)$ is the variance of X in interval i.

$ß_1$ can be estimated by nonlinear regression, for example, using iterated least squares and the linearization method as described by Draper and Smith (5). We used the following algorithm.

1. Estimate $ß_1$ by fitting relative risk (RR) $\mathrm{RR}_i=\beta_1\times(X_i-X_0)$, where i = 0 is the referent class, and $RR_i = Y_i - Y_0$ using the method described in the next section, which takes the correlation between the RR_is into account.

2. Calculate the residuals $\mathrm{RR}_i^* = \mathrm{RR}_i - (\beta_1(\bar{X}_i - \bar{X}_0) + \frac{1}{2}\beta_1^2(\mathrm{var}_i(X) - \mathrm{var}_0(X))$ and the corrected $X_i^* = X_i + \beta_1 \mathrm{var}_i(X)$. Note that the term "$\frac{1}{2}\beta_1^2 \mathrm{var}_0(X)$" is a constant, and therefore the algorithm also works without it.
3. Calculate the weighted regression of RR_i^* on $\bar{X}_i^*$ to obtain a correction term for β_1.
4. Add these to the existing value of β_1 and repeat from step 2 above until convergence is reached.

In our application, two iterations were sufficient to reach convergence.

In the case where $f_i(X)$ follows a gamma distribution, an assigned value can be calculated without approximation, as one can directly calculate the assigned value X_{Ai} for which the relative risk is equal to the average relative risk in the particular risk factor class from step 4 above.

$$X_{Ai} = (Y_i - \beta_0)/\beta_1 = \ln\left(\int_i \exp(\beta_1 X) f_i(X) dX\right)/\beta_1$$
$$= [\hat{\beta}/(\hat{\beta} - \beta_1)]^{\hat{\gamma}} [P((c_0, c_1)|\hat{\gamma}, \hat{\beta} - \beta_1)/P((c_0, c_1)|\hat{\gamma}, \hat{\beta})].$$

In this case, one can proceed after step 1 by calculating the X_{Ai}s for each risk factor class from β_1, as calculated in step 1, and use these in the regression described in the next section to calculate a new β_1, and repeat this until convergence.

Here, however, we choose to present the algorithm based on the approximation, as this algorithm can be easily generalized to other distributions.

Calculating risk estimates per unit of body mass index, taking the correlation between relative risks into account

In order to calculate per study the natural logarithm of the relative risk per unit of body mass index (β_1), we should take into account that, within studies, estimates as well as standard errors are not independent. Greenland and Longnecker (4) give a method to estimate β_1 taking the mutual correlation into account. Since this method is difficult to use with the iterative method given above, we simplified it. Instead of using fitted cell counts to estimate the amount of correlation and using the variance of the relative risks as reported (as Greenland and Longnecker do), we simply assume that both the covariance between the risk classes and the variance of each relative risk depend solely on the observed number of cases within the exposure groups. This is a reasonable assumption when the effects of adjustments are moderate, as is usually the case in epidemiologic studies without strong confounding. Then β_1 can be estimated as:

$$\beta_1 = \frac{\sum_0^k (A_i - \bar{A})\mathrm{RR}_i c_i}{\sum_0^k (A_i - \bar{A})^2 c_i} \text{ with}$$
$$\mathrm{var}(\beta_1) = \frac{1}{\sum_0^k (A_i - \bar{A})^2 c_i}, \quad (5)$$

where A_i is the value assigned to exposure group i, $\bar{A} = \frac{\sum_0^k A_i c_i}{\sum_0^k c_i}$, and c_i = the number of cases in exposure group i.

Observe that the referent category is included in these computations. Actually, the estimate for $ß_1$ can be thought to be derived from the regression of ln(incidence rate$_i$) (which has sampling variance $1/c_i$) on A_i. Subtracting a constant from the Y variate does not alter the slope, so ln(incidence rate$_i$) could well be replaced by ln(RR$_i$). This leads to the equation above.

A SAS macro (SAS Institute, Inc., Cary, North Carolina) carrying out these calculations is referred to as the "Web appendix," which can be downloaded from the website of either the National Institute of Public Health and the Environment (Bilthoven, the Netherlands) (www.rivm.nl/sasmacros) or the *Journal* (http://aje.oxfordjournals.org/).

EXAMPLE META-ANALYSIS

Studies used in the example meta-analysis

We selected suitable studies for our meta-analysis by performing an electronic search in PubMed, SciSearch, and EMBASE with the following search criteria: terms for both diabetes ("diabetes," "diabetic," "niddm," "diabetes-mellitus") and overweight ("obesity," "body mass index," "BMI," "weight," "overweight," "waist hip ratio," "whr," "waist circumference," "adiposity," or "metropolitan life") in the title, subheading, or major MeSH (MJME) field; describing an epidemiologic study ("cohort stud*," "case control stud*," "follow up stud*," "incidence stud*," or "prospective-stud*"); and not referring to a clinical trial (not "clinical-trials"). From these articles, prospective cohort studies on the relation between body mass index or overweight and diabetes type 2 were included. References in publications were searched for other relevant articles. We also asked experts in the field for further references. Clinical trials and other intervention studies aiming to reduce obesity were not included. To prevent disturbance by reversed causality (diabetes influencing weight patterns) and recall bias, we excluded cross-sectional studies and case-control studies. All included studies had a follow-up period of at least 4 years. Since the aim of the meta-analysis was to derive a risk estimate for the Dutch population, we restricted the meta-analysis to studies that consisted of at least 80 percent Caucasians, as it is known (6) that several non-Caucasian populations have a different relation between body mass index and risk of diabetes (7). Publications from 1979 or earlier were excluded, because before 1980, diabetes criteria differed substantially from the criteria that were used afterwards. If results from a study were reported in more than one article, we used the most suitable article (most recent publication, highest number of participants, or longest period of follow-up). Studies presenting only results that were adjusted for change in body mass index were excluded.

This selection yielded 31 articles on epidemiologic studies that gave an estimate for the relative risk (risk ratio, hazard ratio, or odds ratio) of diabetes type 2 as a function of body mass index and at least some kind of confidence interval, standard error, or p value (table 1). If several risk estimates were given, we preferably used only the age- and sex-adjusted relative risk or else a relative risk with as few adjustments as possible, since adjustments other than age may hamper the comparison between studies. This is especially true for adjustments for other body fat-related measures, such as waist circumference, waist/hip ratio, or skinfold thickness. If risk estimates were reported for men and women separately, the risk estimates were first recalculated to a relative risk per unit of body mass index for each sex separately and then pooled, weighting with the inverse variance.

TABLE 1. Characteristics of the individual studies included in the meta-analysis

Authors (reference)	Study and study area	Follow-up (years)	Study size (no.)	Cases (no.)
Folsom et al. (11)	Iowa Women's Health Study, United States	9.5	31,702	1,578
Cassano et al. (12)	Normative Aging Study, United States	18	1,419	226
Wilson et al. (13)	Framingham Heart Study, United States	20.5	5,209	107*
Colditz et al. (14)	Nurses' Health Study, United States	13	11,4281	2,197
Shaper et al. (15)	British Regional Heart Study, United Kingdom	15	7,575	245
Field et al. (16)	Health Professionals Follow-up Study, United States	10	44,520	1,207
Burke et al. (17)	San Antonio Heart Study, United States	7.5	1,232	69
Brancati et al. (18)	Johns Hopkins Precursors Study, United States	16	798	35
Skarfors et al. (19)	Uppsala Study, Sweden	10	1,860	77
Ohlson et al. (20)	Study of men born in 1913, Sweden	13.5	766	47
Snijder et al. (21)	The Hoorn Study, the Netherlands	6.4	1,357	64
Bhargava (22)	Framingham Offspring Study, United States	20	3,718	204
Stevens et al. (23)	ARIC□ Study, United States	8	9,895	1,013
Meisinger et al. (24)	MONICA□ Study, Augsburg, Germany	8	6,166	213
Feskens and Kromhout (25)	The Zutphen Study, the Netherlands	25	841	58
Salonen et al. (26)	The Kuopio Ischaemic Heart Disease Study, eastern Finland	4	944	45
von Eckardstein et al. (27)	PROCAM□ Study, Munster, Germany	6.5	3,737	200
McPhillips et al. (28)	Rancho Bernardo Study, California, United States	12	1,847	219
Lipton et al. (29)	NHEFS,□ United States	16	9,531	671
Strandberg and Salomaa (30)	Helsinki Businessmen Study, Finland	20	1,802	94
Njolstad et al. (31)	Finnmark Study, Finnmark County, Norway	12	11,654	162
Field et al. (32)	Nurses' Health Study II, United States	6	46,634	418
Dagenais et al. (33)	HOPE□ Study, North/South America, Europe	4.5	5,886	261
Hu et al. (34)	Finnish regions study, Finland	9.4	4,369	120
Dotevall et al. (35)	BEDA□ study	16.5	1,351	73
Weinstein et al. (36)	Women's Health Study	6.9	37,878	1,361
Kumari et al. (37)	Whitehall II study	10.5	10,308	361
Manson et al. (38)	Physicians' Health Study	4.9	21,271	285
Freeman et al. (39)	WOSCOPS□	5	5,974	139
Helmrich et al. (40)	Pennsylvania alumni, United States	14	5,990	202
Gurwitz et al. (41)	East Boston (EPESE□), United States	5.1	4,682	185

* Approximate (estimated from incidence rates).
□ARIC, Atherosclerosis Risk in Communities; MONICA, MONitoring trends and determinants In CArdiovascular disease; PROCAM, PROspective CArdiovascular Munster; NHEFS, National Health and Nutrition Examination Survey Epidemiologic Follow-up Study; HOPE, Heart Outcomes Prevention Evaluation; WOSCOPS, West of Scotland Coronary Prevention Study; EPESE, Established Populations for Epidemiologic Studies of the Elderly.
□"BEDA" is not an acronym but the archetypal Göteborg woman: tough, sharp witted, and with a generous heart.

Statistical methods

For studies that reported a relative risk estimate per unit of body mass index or per standard deviation from the mean, we could directly use the natural logarithm of the relative risk per unit of body mass index. However, in most publications, a series of grouped dose-specific relative risks was given, with one body mass index class serving as a referent group. These were transformed into a risk estimate per unit of body mass index. Thereto we assigned a dose value to each dose group using three methods, of which our method was the most complex one, in order to

see whether the added complexity substantially changed the results. These methods are described below.

Method 1.
Assign the midpoint of the cutpoints of the class as the dose value. This is the simplest method and is often used in practice. In the example of a body mass index class of 25–30, the assumed body mass index in this group is 27.5. For open-ended risk factor classes (e.g., <25 or >35), we assigned a value following the algorithms suggested by Il'yasova et al. (2), choosing from them those algorithms that yielded the most plausible results for body mass index. For the upper open-ended category, we assigned the value of its lower bound plus the width of the previous (second-to-highest) interval. So, in the previous example, if the upper open-ended category is >30, we assigned a value of 30 + (30 – 25) = 35; for the lower open-ended category, we assigned the value of its upper bound plus half the width of the next (second-to-lowest) interval. So, in the example: 25 – 0.5(30 – 25) = 22.5.

Method 2.
Assign the expected value of the fitted gamma distribution, using equation 2, as the dose value.

Method 3.
Use the entire new method as described in the section, "Method to Convert Relative Risks per Exposure Class to Relative Risks per Unit of Exposure."

Our method assumes a linear relation between the natural logarithm of the relative risk for diabetes and body mass index. To check this assumption, we plotted the ln(RR)s of the studies presenting relative risks for at least three different grouped exposure levels against the assigned body mass index dose for this category, after subtracting a factor $ß_1 \times (X_{Aref} - 22.5)$ from $\ln(RR_i)$, where X_{Aref} is the assigned dose in the referent category (figure 1). This adjustment means that the dose-response curve for each study has a relative risk = 1 for body mass index = 22.5. Figure 1 shows no important deviations from linearity.

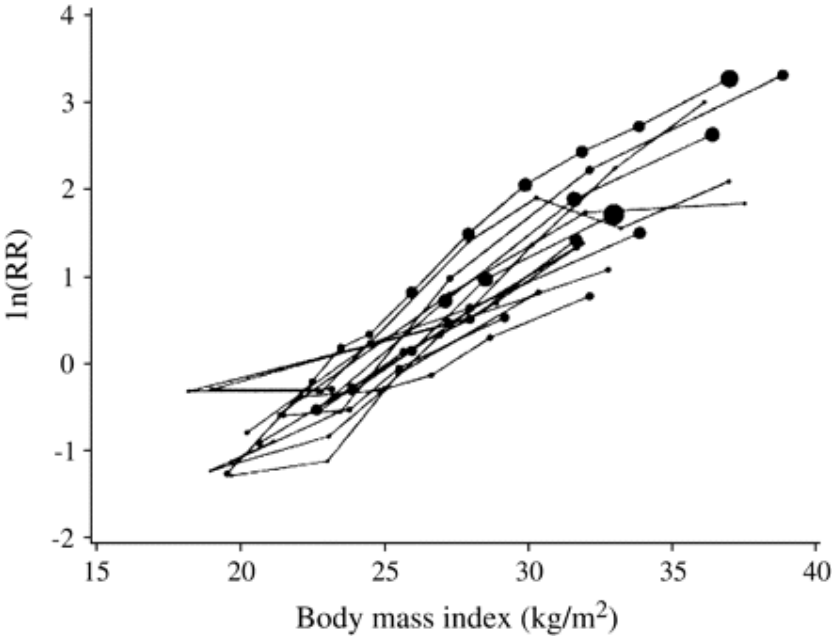

FIGURE 1. Adjusted natural logarithm of relative risk (ln(RR)) for diabetes plotted against the assigned body mass index dose for studies that present relative risks in at least three different exposure categories. ln(RR) is adjusted by subtracting a factor $ß_1 \times (X_{Aref} - 22.5)$, where X_{Aref} is the assigned dose in the referent category. The size of the symbol represents the number of cases on which the relative risk is based.

After deriving the natural logarithm of the relative risk per unit of body mass index for all the studies, we calculated a pooled estimate using SAS PROC MIXED software (SAS Institute, Inc.) to fit a random-effect model (8), as a likelihood ratio test showed that the random-effect model fitted the data significantly better than did a fixed-effect model. We furthermore performed a meta-regression with the following as covariates: whether the relative risk was adjusted for a particular confounder, average age, sex, country of origin (United States vs. Europe), number of participants, and the method of ascertaining diabetes. The between-study variances of the models with and without these covariates are compared to see whether heterogeneity in the covariates can explain part of the between-study variance.

RESULTS

Differences in results among the methods

Using the three different methods to assign exposure values that were described in Materials and Methods, we compared the relative risks derived from the individual studies that used grouped body mass index values. In short, method 1 consists of calculating the assigned value of a body mass index class by taking the average value of the upper and lower cutpoints. Method 2 involves calculating the average of a class from gamma distribution that is fitted over all the body mass index classes, and method 3 recalculates this average value in an iterative process to adjust for nonlinearity.

Table 2 and figure 2 show that, in general, the more body mass index classes were used in a study, the more alike the relative risk estimates among the methods became. The results from the first method diverged most from the other results. This was also the case when different ad hoc methods for assigning dose values to open-ended categories were used (results not shown). One would expect that not adjusting for nonlinearity would cause a bias in the direction of unity and, thus, higher relative risk estimates from method 2 than from method 3. This is indeed generally the case, although there are a few individual studies in which the estimate from the second method is lower than that from the third. The difference between the second and the third methods is especially large for study 15, a study that presented results for only the highest versus the lowest quartile of body mass index. The outcome of the meta-analysis as a whole (table 3) was highest for the second method and lowest for the first method. For all methods, there was clear evidence of heterogeneity among studies. In the remainder of the results, we will use the ß values derived by only the third method.

TABLE 2. Natural logarithm of relative risks derived from studies using three different methods to assign exposure*

Authors (reference)	No. of classes	Method 1		Method 2		Method 3		Difference (%)†
		ln(RR)‡	SE‡	ln(RR)	SE	ln(RR)	SE	
Folsom et al. (11)	5	0.2071	0.0068	0.2112	0.0069	0.1979	0.0062	4.6
Cassano et al. (12)	3	0.1067	0.0412	0.0966	0.0371	0.0957	0.0364	11.5
Wilson et al. (13)	3	0.0361	0.0165	0.0450	0.0310	0.0450	0.0308	19.7
Colditz et al. (14)	10	0.2369	0.0044	0.2326	0.0043	0.2255	0.0042	5.0
Shaper et al. (15)	7	0.2240	0.0200	0.2330	0.0209	0.2260	0.0198	0.9
Field et al. (16)	4	0.1687	0.0043	0.2254	0.0057	0.2262	0.0057	25.4
Burke et al. (17)	4	0.1402	0.0237	0.1599	0.0256	0.1568	0.0258	10.6
Brancati et al. (18)	2	0.2357	0.0715	0.2724	0.0826	0.2829	0.0892	16.7
Stevens et al. (23)	4	0.12008	0.0092	0.1751	0.0115	0.1648	0.0104	21.9
Feskens and Kromhout (25)	2	0.1390	0.0597	0.1283	0.0552	0.1849	0.0752	24.9
von Eckardstein et al. (27)	3	0.2282	0.0342	0.2104	0.0283	0.1993	0.0287	14.5
Field et al. (32)	5	0.1969	0.0083	0.2278	0.0096	0.2126	0.0085	7.4
Dagenais et al. (33)	5	0.1383	0.0189	0.1311	0.0181	0.1292	0.0174	7.0
Hu et al. (34)	3	0.1562	0.0205	0.2006	0.0266	0.1939	0.0245	19.4
Dotevall et al. (35)	4	0.2422	0.0371	0.2435	0.0375	0.2315	0.0337	4.6
Weinstein et al. (36)	3	0.1949	0.0058	0.2220	0.0065	0.2109	0.0059	7.6
Kumari et al. (37)	4	0.1123	0.0117	0.1447	0.0153	0.1417	0.0148	20.7
Manson et al. (38)	3	0.1970	0.0256	0.1783	0.0235	0.1744	0.0221	13.0
Helmrich et al. (40)	3	0.1204	0.0354	0.1209	0.0371	0.1220	0.0368	1.3
Gurwitz et al. (41)	3	0.0996	0.0218	0.0997	0.0219	0.0954	0.0199	4.4

* Studies from table 1 presenting a suitable relative risk per unit of body mass index are not included.

† Percentage difference between the natural logarithm of relative risks retrieved by methods 1 and 3 (refer to the text for information about these methods).

‡ ln(RR), natural logarithm of relative risk; SE, standard error.

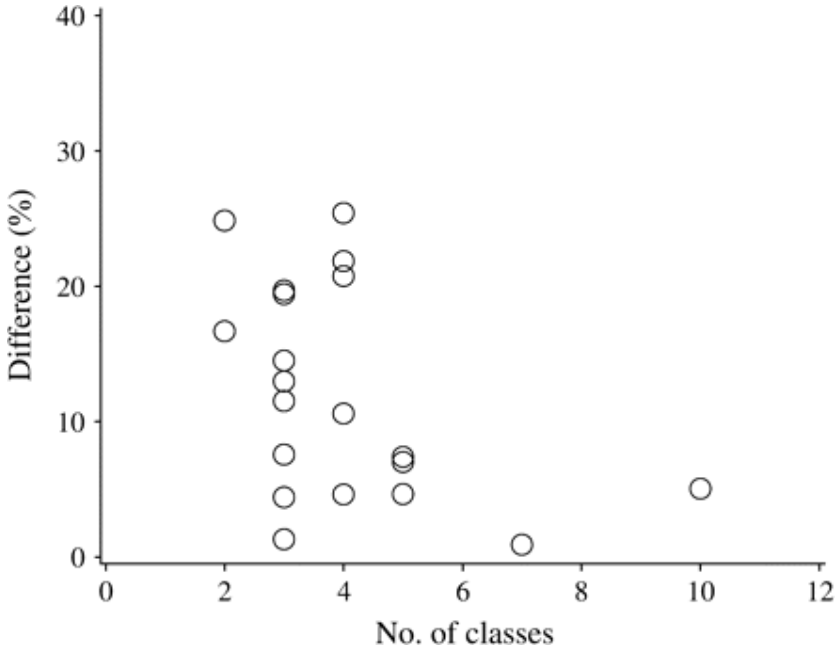

FIGURE 2. Difference (%) between the natural logarithm of relative risk for diabetes for one unit of body mass index derived by methods 1 and 3, plotted against the number of body mass index classes in the study (refer to the text for information about these methods).

TABLE 3. Results of meta-analyses of the same data (31 studies) using different methods of assigning the exposure

	Method 1		Method 2		Method 3	
Chi-square and *p* value for heterogeneity	391.8	<0.00001	282.2	<0.00001	273.3	<0.00001
Relative risk* from fixed-effects model	0.188 (0.184, 0.192)†		0.207 (0.203, 0.212)		0.201 (0.197, 0.205)	
Relative risk* from random-effects model	0.163 (0.144, 0.182)		0.171 (0.152, 0.190)		0.168 (0.150, 0.186)	
Square root of between-study variance‡	0.046 (0.035, 0.068)		0.047 (0.035, 0.071)		0.043 (0.032, 0.067)	

* Relative risk of diabetes per unit of body mass index.

†Numbers in parentheses, 95% confidence interval.

‡From the random-effects model. This entity is an estimate of the magnitude of between-study differences.

Publication bias

To assess the extent of publication bias, we made funnel plots, plotting the natural logarithm of the relative risks per unit of body mass index against the inverse of the standard error (figure 3). Since there is no gap at the lower left side of the "funnel," we believe there is no reason to assume major publication bias or small-study bias.

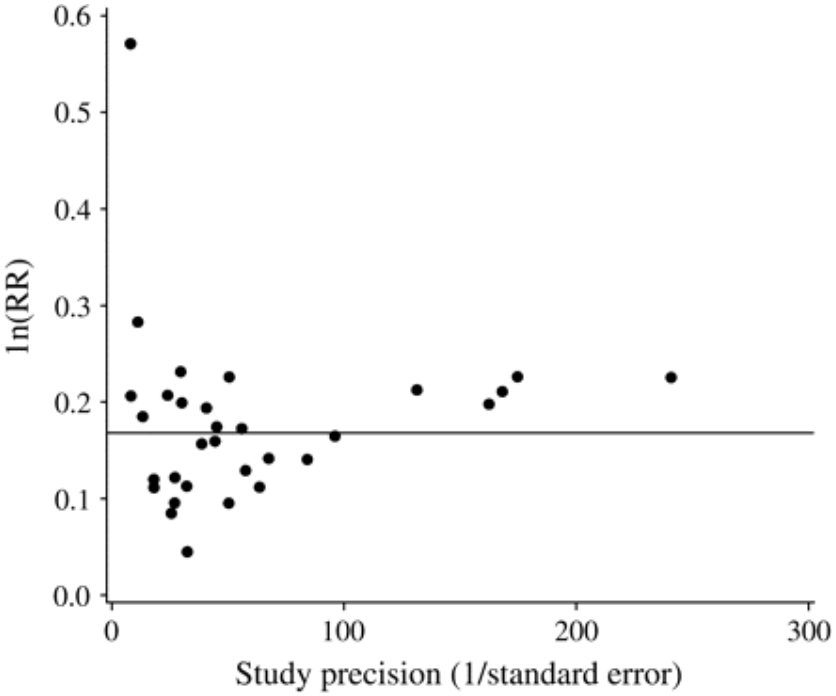

FIGURE 3. Funnel plot showing the natural logarithm of the relative risk (ln(RR)) for diabetes for one unit of body mass index from the individual study plotted against the precision (1/standard error). The horizontal line gives the pooled ln(RR) based on all studies.

Exploring heterogeneity

Figure 4 shows a forest plot of the studies, ordered by the number of cases in each study. To study whether the heterogeneity of the studies might be due to differences in the confounders for which the relative risks were adjusted, we carried out a meta-regression analysis (table 4). Only adjustment for body fat-related factors (hip/waist ratio or skinfold thickness) seemed to influence the relative risk to some extent. Excluding the two studies that presented relative risks with only such adjustments, the pooled relative risk became 1.19 (95 percent confidence interval: 1.17, 1.21). Continuing to exclude these two studies, we performed further meta-regressions examining the effect of duration of follow-up, sex of participants, country of origin, number of study participants, and method of ascertaining diabetes status (table 5). Studies that assessed diabetes by screening the whole population with a blood test at the end of follow-up

reported lower relative risks than did studies that used oral glucose tests or a physician's diagnosis, death certificates, or medical records. In addition, larger studies reported higher relative risks, but larger studies less often use blood tests on all participants to ascertain diabetes. If both factors are entered simultaneously into the regression model, the statistical significance of both is reduced ($p = 0.73$ for ascertainment method, and $p = 0.02$ for study size). Furthermore, studies that presented relative risks for a continuous body mass index variable reported slightly lower relative risks than did those that used grouped exposure categories. Sex of the participants, country of origin, publication year, and follow-up duration did not explain the heterogeneity, while the mean age of participants during follow-up had only a small and nonsignificant effect. Exclusion of the Helsinki Businessmen Study, the most outlying study, yielded a relative risk of 1.18 (95 percent confidence interval: 1.16, 1.20) per unit of body mass index. The estimated between-study variance was only 5 percent smaller after exclusion of this study.

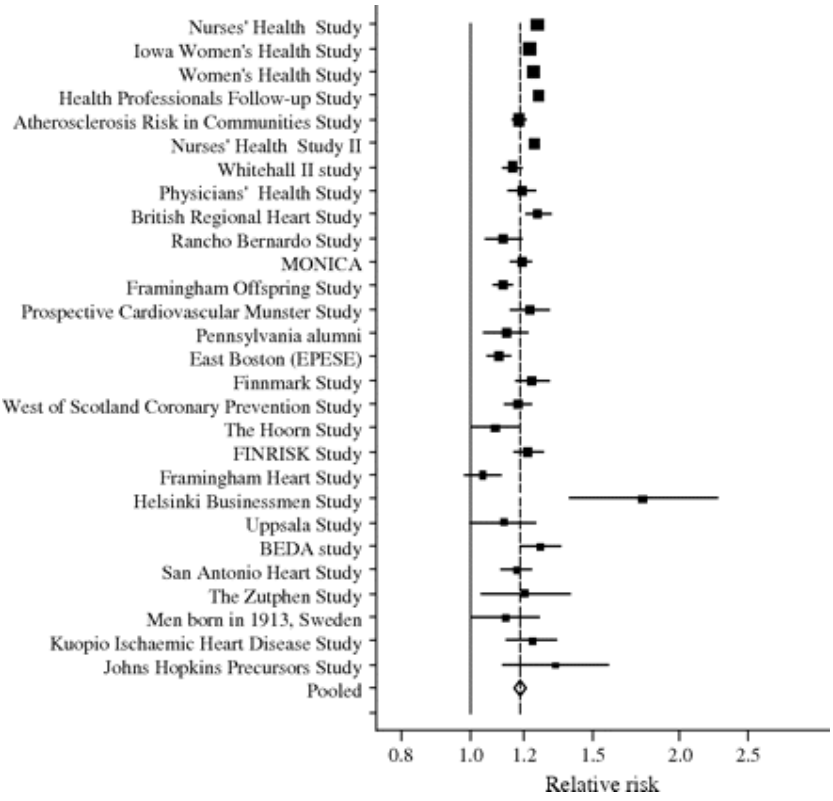

TABLE 4. Results of meta-regression in the 31 studies of table 1 showing differences between studies that did or did not adjust for particular confounders

Adjustments	No. of studies	ln(RR)* (SE*)	% of heterogeneity explained	*p* value of variable in meta-regression
Age			8	0.34
Yes	24	0.172 (0.010)		
No	7	0.148 (0.023)		
Smoking			–†	0.39
Yes	11	0.179 (0.016)		
No	20	0.162 (0.012)		
Physical activity			7	0.34
Yes	6	0.150 (0.021)		
No	25	0.172 (0.010)		
Family history			2	0.65
Yes	4	0.181 (0.031)		
No	27	0.167 (0.010)		
Systolic blood pressure			2	0.77
Yes	6	0.162 (0.024)		
No	25	0.169 (0.010)		
Serum cholesterol			10	0.21
Yes	3	0.137 (0.026)		
No	28	0.172 (0.010)		
Socioeconomic status			1	0.88
Yes	5	0.165 (0.022)		
No	26	0.169 (0.010)		
Waist/hip ratio or skinfold thickness			10	0.12
Yes	2	0.116 (0.035)		
No	29	0.172 (0.009)		

[*] ln(RR), natural logarithm of relative risk; SE, standard error.

[†] –, estimated variance was larger in the model without the covariate.

TABLE 5. Results of a meta-regression examining the influence of study characteristics on the natural logarithm of the relative risk of one unit of body mass index on diabetes[*]

Variable	Mean (SD[†]) or no. of studies	Effect estimate (SE[†])	% of between-study variance explained	*p* value of variable in meta-regression
Fraction males	0.63 (0.39)	–0.015 (0.026)	4	0.36
Follow-up duration, years	11.2 (5.5)	–0.0008 (0.0020)	3	0.71
Age in years during follow-up	55.6 (8.5)	–0.0015 (0.0011)	3	0.18
Square root of study size	92 (74)	0.00031 (0.00009)	51	0.001
Publication year	1998.4 (5.2)	0.0019 (0.0021)	3	0.37
Type of analysis			14	
Categorical body mass index	18	0.028 (0.020)		0.17
Continuous body mass index	10	0		
Origin			0	
United States	14	–0.014 (0.020)		0.47
Europe	14	0		
Diabetes ascertainment			24	
With blood test	16	–0.033 (0.018)		0.07
Self-report or clinical records	12	0		

[*] Studies adjusting for waist/hip ratio or skinfold thickness (n = 3) are excluded.

[†] SD, standard deviation; SE, standard error.

DISCUSSION

Like others (1–3), we found that the method of assigning exposure levels to body mass index categories can have a large impact on risk estimates. The natural logarithm of the relative risk per unit of body mass index in an individual study could vary by as much as 25 percent between different methods. In our meta-analysis, these differences in individual risk estimates did not substantially influence the overall outcome. Yet even differences of smaller magnitude may lead to important differences in predictions on the effect of prevention programs of mathematical models that use data from meta-analyses. This might be of even more importance for risk factors where the exposure is divided into fewer classes than is common for body mass index.

Our method of fitting a distribution to an exposure in order to assign a risk factor level to an exposure category is easily applicable in other meta-analyses, especially when the exposure distribution is known or easily estimated from data, such as blood pressure, cholesterol, and so on. In our example, we assumed that body mass index follows a gamma distribution, but the method can also be used for other distributions, for example, a normal distribution. The method is probably less suitable for irregularly distributed exposures.

Our method essentially simplifies that of Shi and Copas (3). Another approach to meta-analysis of studies with group exposure data models the exposure as a multinomial distribution (9, 10). However, this method cannot be applied when open-ended categories exist.

Our method assumes that the variance of the relative risks for each category of exposure is equal to the sum of the inverse of the number of cases in the exposure group and that in the referent group. When confounding factors are balanced, this will be exactly true. In practice, however, this may not be the case, and the real variance will be larger. This will not importantly bias the estimate of the overall relative risk $ß_1$, but its variance will be underestimated. In principle, the real variance is available from the confidence intervals or *p* values published with the relative risks for each exposure class. These might be incorporated in the method to obtain a better estimate. However, ad hoc assumptions are needed in order to do so.

By not taking the nonlinearity into account, one overestimates the effect of a risk factor per unit of exposure. Although this effect is not always clear in the individual studies, the overall estimate is lower when nonlinearity is taken into account. However, the effect is weaker than that of using a different method to assign dose values. In situations where the effect studied is weaker than the effect in our example, the bias by not taking nonlinearity into account will be even smaller.

Not surprisingly, our meta-analysis shows that overweight is an important risk factor for diabetes, despite clear heterogeneity of studies. From our meta-analysis, we can conclude that differences between populations and the difference in adjustment strategies may not be the largest sources of heterogeneity. In the case of diabetes, the method of ascertaining diabetic status seems to be more important for the outcome of an individual study, perhaps because ascertainment via self-report and clinical records only produces cases with clinical diabetes, whereas blood tests detect diabetes at an earlier stage. Similar phenomena might be true for other diseases as well, so the differences in definition of disease

should be taken into account in meta-analysis. Another, rather puzzling finding was that both smaller studies and studies that analyzed body mass index as a continuous variable tend to report lower relative risks than did those analyzing it as a categorical variable. A possible explanation for the former finding is that most of the larger studies were carried out among health professionals, who may report diseases more accurately than do subjects from a lay population. A possible explanation for the latter finding is that the more powerful analysis using a continuous variable is preferentially used by studies that get only borderline statistically significant results, while studies with clearly statistically significant results present the more detailed relative risks per risk factor class.

In summary, different methods of assigning dose values in studies presenting relative risks for groups' exposure categories yield different results in the effect estimates for the different studies. Not incorporating the nonlinearity of the dose response leads to an overestimation of the pooled relative risk, but this bias is relatively small.

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