American Journal of Epidemiology

Vol. 176, No. 11
DOI: 10.1093/aje/kws172
Advance Access publication:
November 9, 2012

Systematic Reviews and Meta- and Pooled Analyses

Comparisons of the Strength of Associations With Future Type 2 Diabetes Risk Among Anthropometric Obesity Indicators, Including Waist-to-Height Ratio: A Meta-Analysis

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Initially submitted September 26, 2011; accepted for publication March 13, 2012.

The aim of this meta-analysis was to compare the association of waist-to-height ratio (WHtR) with risk of incident diabetes with the associations of 3 other conventional obesity indicators (body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR)) with risk of incident diabetes. Literature searches in MEDLINE (January 1950 to April 27, 2011) and EMBASE (January 1974 to April 27, 2011) were conducted for prospective studies that made it possible to estimate the relative risk of diabetes per 1-standard deviation increase in WHtR, in addition to the RR of BMI, WC, or WHR. Strength of the estimated pooled relative risk for a 1-standard deviation increase of each indicator (expressed as RR_{WHtR}, RR_{BMI}, RR_{WC}, and RR_{WHR}) was compared with a bivariate random-effects model. Pooled relative risks of the 15 eligible studies with 6,472 diabetes cases were 1.62 (95% CI: 1.48, 1.78) for RR_{WHtR}, 1.55 (95% CI: 1.43, 1.69) for RR_{BMI}, 1.63 (95% CI: 1.49, 1.79) for RR_{WC}, and 1.52 (95% CI: 1.40, 1.66) for RR_{WHR}. WHtR had an association stronger than that of BMI ($P<0.001$) or WHR ($P<0.001$). The present meta-analysis showed that WHtR has a modestly but statistically greater importance than BMI and WHR in prediction of diabetes. Nevertheless, measuring height in addition to WC appeared to have no additional benefit.

anthropometry; meta-analysis; obesity; type 2 diabetes mellitus

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

It is commonly recognized that obesity is an established risk factor for type 2 diabetes mellitus. Body mass index (BMI, calculated as weight (kg)/height $(m)^2$), waist circumference (WC), and waist-to-hip ratio (WHR) traditionally have been proposed as major anthropometric obesity indicators that have a substantial association with future diabetes risk. However, these obesity indicators represent different aspects of body composition: Whereas BMI reflects total body mass, WC and WHR reflect abdominal obesity, for which visceral fat is largely responsible. In particular, WC values are simpler to obtain than are those for BMI or WHR because only 1 measurement must be made. Moreover, compared with BMI, WC is more true to the biologically well-established mechanism that visceral fat has a greater association with insulin resistance than does subcutaneous fat (1).

Recently, the waist-to-height ratio (WHtR) was introduced as the hypothetically best abdominal obesity indicator of risk of type 2 diabetes mellitus because it is reasonable to think that short subjects generally will have more abdominal fat and associated cardiovascular risk factors than will tall subjects under the condition of a similar WC (2). Actually, it has been suggested that WHtR might be an effective screening tool for various diseases, including diabetes (3).

However, evidence for the superiority of WHtR in prediction of type 2 diabetes compared with other anthropometric indicators remains uncertain. The present meta-analysis aimed to summarize the risk of development of type 2 diabetes related to each anthropometric obesity indicator, including WHtR, and to compare the strength of the association among the obesity indicators.

MATERIALS AND METHODS

Data sources and study selection

We conducted an electronic search in MEDLINE (January 1950 to April 27, 2011) and EMBASE (January 1974 to April 27, 2011), with an additional manual search. Search terms used are shown in the Web Table 1 (available at http://aje.oxfordjournals.org/). Studies were included if 1) a prospective design was used; 2) type 2 diabetes was analyzed as a study endpoint; and 3) in addition to WHtR, at least 1 of the 3 obesity indicators (i.e., BMI, WC, or WHR) was analyzed as a continuous (i.e., relative risk per 1-unit increase) or categorical variable so that comparison of the strength of the association among the anthropometric indicators was possible. Even if a study did not indicate whether diabetes was type 1 or type 2, we considered the diabetes to be type 2 if it was adult onset. When multiple articles were available for a single observational study, the first priority for selection was the article describing the longest follow-up, and the second priority was the article with full cohort analysis covering the largest number of participants.

Data abstraction

From the included studies, 2 authors (S. K. and H. Sone) extracted data on study characteristics and risk measures. Discrepancies were solved by discussion. In addition to risk measures for diabetes, the following study characteristics were extracted: characteristics of the study population (sex, geographic region, ethnicity or race); methods for assessment of diabetes (definition of diabetes and instruments for ascertaining the endpoint); and model assumption (methods for representing associations of the obesity indicators with diabetes risk (i.e., categorical or continuous) and study-specific covariates). Study quality was assessed according to follow-up periods, percentage of subjects lost to follow-up, and extent of adjustment for covariates. When both unadjusted and adjusted risk estimates were reported in the same study, the most adjusted risk estimate was used.

Risk measures in an individual study were standardized into relative risks per 1-standard deviation increase in the obesity indicators. To make comparisons among the obesity indicators possible, we made 2 assumptions: 1) Frequency distributions of the obesity indicators were normal, and 2) a linear relation was observed between obesity measures and diabetes risk. If studies expressed relative risks based on categorical variables, they were regressed on the Z values for the mean or median value in each category. The standardized risk measure was estimated with the method of Berlin et al. (4) in a program developed by Orsini et al. (5). In summary, this program can calculate a weighted linear regression of a natural logarithm (log) of the relative risk across categories of obesity indicators, taking into account the covariance among risk measures if data on the adjusted RR and the number of participants and cases for each category are provided.

Data synthesis

Each log relative risk was pooled with the use of a univariate random-effects model (6). The pooled relative risk s ultimately were expressed as per 1-standard deviation increase in WHtR (RR_{WHtR}), BMI (RR_{BMI}), WC (RR_{WC}), and WHR (RR_{WHR}). For each pooled relative risk, between-study heterogeneity was assessed by I-squared (7). The possibility of publication bias was assessed by 2 formal tests (the Begg-adjusted rank correlation test (8) and Egger's regression asymmetry test (9)), as well as by visual inspection of a funnel plot.

Significance for differences was calculated between each pair of pooled relative risks by using a bivariate random-effects model that considered both within- and between-study correlations to estimate the standard error of the difference (10). In summary, when 2 parameters ($j = 1$ or 2) for $i = 1$ to n studies are examined, and the associated standard errors for each study's results are calculated as s_{ij} in a meta-analysis, the standard error for the difference between the pooled estimate of the 2 parameters (S_{diff}) can be calculated from the following formula:

$$\frac{1}{S^2_{\mathrm{diff}}} = \sum\nolimits_{i=1}^{n} \frac{1}{(s^2_{i1} + s^2_{i2} - 2\rho_{wi} s_{i1} s_{i2}) + (\tau^2_1 + \tau^2_2 - 2\rho_B \tau_1 \tau_2)},$$

where τ^2_j is the between-study variance and ρ_{wi} and ρ_B are the within- and between-study correlations, respectively. We used the "mvmeta" function provided by Stata software (StataCorp LP, College Station, Texas), which could calculate the between-study matrix and make it possible to estimate τ^2_i and ρ_B, if ρ_{wi} were known. Because the within-study correlation was generally unknown, we imputed the correlation coefficient on the basis of the between-study covariance matrix as the within-study correlation coefficient. According to the formula, when the results from the 2 parameters within each study are similar (i.e., ρ_{wi} and ρ_B are high), the statistical power for detecting the difference between the 2 results from each parameter is increased because S_{diff} is lowered.

Analyses were repeated for subgroups with similar study characteristics where we a priori stratified the included studies. Meta-regression analyses also were conducted to examine the impact of potential confounding factors on the strength of the association with diabetes risk within each obesity indicator. Data were analyzed in Stata software, version 11. Two-sided P values ≤ 0.05 were considered statistically significant, except for the test of publication bias, for which the level of significance was $P < 0.10$ (11).

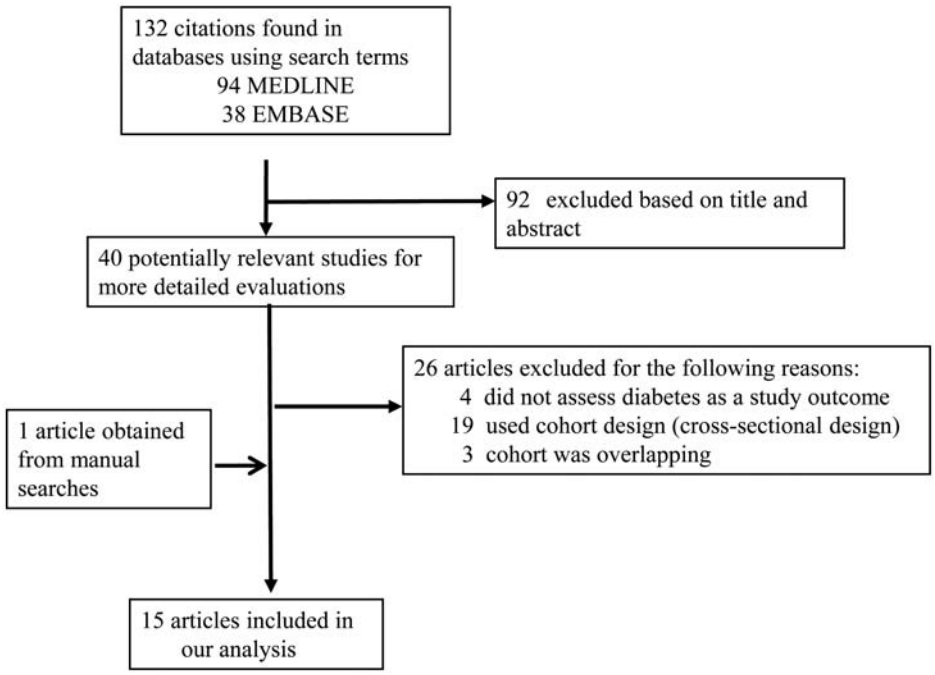

Figure 1. Study flow chart of the literature search in this meta-analysis.

RESULTS

Literature search

Figure 1 shows details of the literature search. Of the 132 citations that were retrieved by the electronic literature search, 14 studies (12–25) met the inclusion criteria. We added 1 article (26) obtained by a manual search of the reference lists in each of the 14 studies. Finally, 15 studies that included 120,102 participants (average length of follow-up, 6.0 years) were included in this meta-analysis. With the exception of the 1 study (12) that presented no data on the number of diabetes cases, the analyzed studies reported a total of 6,472 cases. Of the 15 studies, 4 (14–16, 20) had a single cohort. One study (18) consisted of 3 cohorts according to ethnicity, and 1 study (21) consisted of 2 United Kingdom cohorts. Six studies (17, 22–26) had 2 data sets according to sex. Additionally, 1 study (12) had 6 data sets (2 according to sex × 3 with intervention groups), and 2 studies (13, 19) had 4 data sets (2 according to sex × 2 cohorts). Consequently, a total of 35 data sets were generated on the basis of the published data in the 15 articles.

Study characteristics

Table 1 summarizes the characteristics of the 15 eligible studies. Averages of mean age, WHtR, BMI, WC, and WHR in each study population were 50 years, 0.55, 27.2, 89.3 cm, and 0.88, respectively. Participants in a major portion of the included studies were from the general population, although in 3 studies (12, 16, 18), participants were selected on the basis of being at high risk of diabetes. From the viewpoint of study quality, 4 studies (12, 19, 23, 24) had observational periods of 10 years or more. Participants who were lost to follow-up from their analysis were excluded in all but 3 studies (12, 17, 26) (lost to follow-up range, 0.2%–10%). Although all studies controlled risk measures for at least age, sex, and race or ethnicity, only 8 studies (13–15, 19, 21, 23–25) did so for 3 or more of the following main lifestyle and metabolic confounders: smoking, alcohol, physical activity, baseline fasting plasma glucose values or fasting glycemic status, systolic blood pressure or presence of hypertension, and triglyceride level. Other prespecified confounders were family history of diabetes (in 7 studies) (14–16, 18, 19, 23, 25), education (in 2 studies) (25, 26), and socioeconomic status (in 2 studies) (19, 21). Five studies (13, 17, 20, 21, 25) did not state whether diabetes was type 2 or not, although they did note that it was adult onset. Reports of the remaining 10 studies stated that study outcome was type 2 diabetes.

Overall absolute and relative contributions of each anthropometric indicator to the development of diabetes

Web Figure 1 shows a forest plot with relative risks for a 1-standard deviation increase in the 4 obesity indicators and their corresponding 95% confidence intervals in each study and overall. Overall, the incremental diabetes risk was 1.62 (95% confidence interval (CI): 1.48, 1.78) for RR_{WHtR}, 1.55 (95% CI: 1.43, 1.69) for RR_{BMI}, 1.63 (95%

Table 1. Summary of Characteristics of 15 Included Studies Included in the Meta-Analysis

Category	No. of Studies[a]	Range	Reference No.	No. of Data Sets	No. of Participants
Participants (total $n = 120,012$)		704–61,703			
Cases[b] (total $n = 6,472$)		51–2,991			
Geographic region					
Western	8		12, 17, 18, 22, 24	20	42,871
Non-Western	7		13–16, 19, 23, 25	15	77,231
Race					
>50% white	6		12, 17, 18, 21, 24, 26	16	40,168
>50% black	3		18–20	4	2,164
Other	8		13–16, 19, 22, 23, 25	15	77,770
Sex					
Men only	11		12, 13, 15, 17, 19, 21–26	15	69,754
Women only	11		12–14, 17, 19, 21–26	15	47,843
Bboth men and women	3		16, 18, 20	5	2,505
Percentage of men		21–78			
Mean age, years		40–73			
≥50	5		12, 13, 21, 24, 25	13	16,673
<50	8		12, 14–17, 19, 20, 23	15	75,629
Not described	3		18, 22, 26	7	27,800
Mean BMI[c,d]		23.0–34.0			
≥28	4		12, 16, 18, 22	11	6,162
<28	12		13–15, 17–21, 23–26	24	113,940
Mean WHtR[e]		0.49–0.65			
Mean WC[f,g]		79.3–107.5			
Mean WHR[f,g]		0.81–0.93			
Duration of follow-up, years		2.0–12.4			
≥10	4		13, 19, 23, 24	11	13,139
<10	12		12, 14–18, 20–22, 25, 26	24	106,963
Criteria for diabetes					
FPG ≥7.0 mmol/L or 2hPG ≥11.1 mmol/L	7		12, 14, 15, 17, 19, 20, 22	17	15,871
Other[h]	8		16, 18, 21, 23–26	18	104,231
Methods for ascertainment of diabetes					
Blood test only	8		12–18, 24, 25	22	21,780
Self-report or medical record	7		19–23, 26	13	98,322
Representation of risk estimates for obesity indicators					
Continuous	9		12, 13, 17–22, 24	26	24,898
Categorical	6		14–16, 23, 25, 26	9	95,204
Variables as study confounders: factors other than age, sex, and ethnicity					
Considered	10		13–15, 18, 19, 21, 23–26	23	112,125
Not considered	5		12, 16, 17, 20, 22	12	7,977

Table continues

CI: 1.49, 1.79) for RR_{WC}, and 1.52 (95% CI: 1.40, 1.66) for RR_{WHR}. For all 4 obesity indicators, study heterogeneity in the strength of association between each obesity indicator and diabetes was highly significant ($P<0.001$).

Because all 15 included studies assessed the risk of diabetes in relation to all 4 anthropometric indicators (i.e., WHtR, BMI, WC, and WHR), we compared the strength of the association with diabetes risk not only between WHtR and 1 of the

Table 1. Continued

Category	No. of Studies[a]	Range	Reference No.	No. of Data Sets	No. of Participants
Smoking					
Considered	6		13, 21, 23–26	14	102,454
Not considered	9		12, 14–20, 22	21	17,648
Alcohol					
Considered	5		13, 23–26	12	97,235
Not considered	10		12, 14–22	23	22,867
Physical activity					
Considered	5		21, 23–26	10	99,259
Not considered	10		12–20, 22	25	20,843
FPG or fasting glycemic status					
Considered	5		13–15, 19, 23	12	7,977
Not considered	10		12, 16–18, 20–22, 24–26	23	112,125
Systolic blood pressure or hypertension					
Considered	6		14, 15, 18, 19, 23, 25	13	74,405
Not considered	9		12, 13, 16, 17, 20–22, 24, 26	22	45,697
Triglycerides					
Considered	4		14, 15, 19, 23	7	70,301
Not considered	11		8, 12, 13, 16–18, 20–22, 25, 26	28	49,801
Multiple factors					
Considered	8		13–15, 19, 21, 23–25	18	105,833
Not considered	7		12, 16–18, 20–22	17	14,269
Family history of diabetes					
Considered	7		14–16, 18, 19, 23, 25	14	75,109
Not considered	8		12, 13, 17, 20–22, 24, 26	21	44,993
Socioeconomic factors or education					
Considered	4		19, 21, 25, 26	10	37,308
Not considered	11		12–18, 20, 22–24	25	82,794

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; 2hPG, 2-hour post-challenge glucose; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

[a] Total number of studies within a category heading does not necessarily equal the number of studies included (i.e., 15) because some studies have more than 1 subcategory.

[b] One study (12) (3,201 participants over a 3-year follow-up and a citation) did not have these data available.

[c] In 3 studies (18, 21, 26), BMI data were obtained from other articles (39–42) sharing the same study population as the original study.

[d] Weight (kg)/height $(m)^2$.

[e] Data were missing in 3 studies (18, 25, 26).

[f] In 1 study (18), WC and WHR data were obtained from another article (39) sharing the same study population as the original study.

[g] Data were missing in 2 studies (25, 26).

[h] Used either FPG ≥7.0 mmol/L or 2hPG ≥11.1 mmol/L or did not describe diabetes criteria.

remaining 3 obesity indicators but between 2 of the 3 indicators (i.e., BMI–WC, BMI–WHtR, or WC–WHtR). High within-study correlations (RR_{WHtR} vs. RR_{BMI}, $r = 0.96$; RR_{WHtR} vs. RR_{WC}, $r = 0.98$; RR_{WHtR} vs. RR_{WHR}, $r = 0.93$; RR_{BMI} vs. RR_{WC}, $r = 0.96$; RR_{BMI} vs. RR_{WHtR}, $r = 0.87$; RR_{WC} vs. RR_{WHtR}, $r = 0.92$) and between-study correlations (RR_{WHtR} vs. RR_{BMI}, $r = 0.97$; RR_{WHtR} vs. RR_{WC}, $r = 0.99$; RR_{WHtR} vs. RR_{WHR}, $r = 0.94$; RR_{BMI} vs. RR_{WC}, $r = 0.96$; RR_{BMI} vs. RR_{WHR}, $r = 0.89$; RR_{WC} vs. RR_{WHR}, $r = 0.93$) were observed. As a result of the high correlation coefficient, WHtR had a stronger association with the risk of diabetes than did BMI and WHR ($P<0.001$ for all comparisons). WC was also more strongly associated with diabetes risk than were BMI and WHR ($P<0.001$ for any comparisons). Nevertheless, the strength of association did not differ between RR_{WHtR} and RR_{WC} ($P = 0.69$) or between RR_{BMI} and RR_{WHR} ($P = 0.34$).

Funnel plots for each obesity indicator are presented in Web Figure 2. The 4 funnel plots were similar and

Table 2. Stratified Analyses of Pooled Relative Risk and Its Corresponding 95% Confidence Interval of Diabetes for +1-Standard Error Increment in 4 Obesity Indicators

Category and Subcategory	No. of Data Units	WHtR		BMI		WC		WHR		Difference[a]
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Country										
Western	20	1.74	1.51, 2.01	1.65	1.45, 1.89	1.74	1.51, 2.00	1.63	1.41, 1.88	1, 3 > 2, 4
Non-Western	15	1.47	1.36, 1.58	1.41	1.31, 1.52	1.48	1.36, 1.61	1.40	1.29, 1.52	1 > 4<3 > 2
Dominant race										
>50% white	16	1.78	1.49, 2.14	1.65	1.41, 1.94	1.77	1.49, 2.11	1.68	1.42, 1.99	1, 3 > 2
>50% black	5	1.62	1.26, 2.09	1.55	1.38, 1.74	1.62	1.27, 2.06	1.51	1.18, 1.94	1, 3 > 4
Others	14	1.43[b]	1.37, 1.49	1.44	1.33, 1.56	1.46	1.36, 1.57	1.37[c]	1.28, 1.47	3, 1 > 4
Sex										
Men	15	1.61	1.40, 1.85	1.55	1.34, 1.79	1.60	1.38, 1.85	1.54	1.34, 1.76	3 > 4<1 > 2
Women	15	1.64	1.41, 1.92	1.55	1.35, 1.77	1.66	1.42, 1.93	1.49	1.30, 1.71	3, 1 > 2, 4
Combined	5	1.61	1.41, 1.84	1.61	1.40, 1.84	1.65	1.42, 1.91	1.61	1.35, 1.93	N.S.
Mean age										
≥50 years	13	1.53	1.35, 1.72	1.48	1.33, 1.63	1.56	1.38, 1.77	1.44	1.26, 1.63	3 > 2, 4
<50 years	15	1.52	1.38, 1.67	1.46	1.32, 1.58	1.53	1.38, 1.69	1.44	1.32, 1.56	3, 1 > 2, 4
Not assessed	7	2.08[c]	1.53, 2.83	2.01[c]	1.57, 2.56	2.01[c]	1.49, 2.72	1.95[c]	1.41, 2.69	N.S.
Mean BMI[d] ≥28										
Yes	11	1.39	1.29, 1.51	1.37	1.22, 1.53	1.41	1.29, 1.54	1.31	1.23, 1.40	N.S.
No	24	1.74[c]	1.54, 1.97	1.65[c]	1.47, 1.84	1.74[c]	1.54, 1.97	1.59	1.42, 1.79	1, 3 > 2, 4
Duration ≥10 years										
Yes	11	1.55	1.40, 1.72	1.52	1.39, 1.66	1.56	1.41, 1.72	1.43	1.27, 1.60	3, 1 > 4
No	24	1.66	1.47, 1.89	1.57	1.39, 1.77	1.66	1.46, 1.90	1.58	1.40, 1.79	3, 1 > 4, 2
Use of both FPG and 2hPG as DM criteria										
Yes	17	1.51	1.38, 1.66	1.46	1.33, 1.60	1.51	1.38, 1.65	1.43	1.32, 1.55	3 > 2<1 > 4
No	18	1.73	1.48, 2.03	1.65	1.43, 1.90	1.75	1.49, 2.05	1.60	1.38, 1.87	3, 1 > 2, 4
Methods for ascertainment of DM										
Blood test only	22	1.48	1.37, 1.61	1.44	1.32, 1.57	1.51	1.39, 1.63	1.39	1.29, 1.50	3 > 2, 4
Other methods[e]	13	1.85[c]	1.56, 2.20	1.74[c]	1.48, 2.04	1.82[c]	1.52, 2.18	1.69[c]	1.44, 1.99	1, 3 > 2, 4
Representation of obesity indicators										
Continuous	26	1.56	1.44, 1.69	1.52	1.41, 1.63	1.57	1.45, 1.71	1.46	1.35, 1.58	1 > 4<3 > 2
Categorical	9	1.82	1.37, 2.01	1.65	1.25, 2.17	1.79	1.34, 2.40	1.69	1.19, 2.21	1, 3 > 4, 2
Study adjustment for minimum[f] adjustment										
Yes	12	1.48	1.33, 1.66	1.45	1.28, 1.65	1.51	1.35, 1.70	1.39	1.27, 1.53	3, 1 > 4
No	23	1.70	1.50, 1.93	1.61	1.43, 1.81	1.69	1.49, 1.92	1.59	1.49, 1.79	1, 3 > 2, 4

Table continues

asymmetrical, which suggests that the association between obesity and risk of incident diabetes tended toward a strong relation between obesity and risk of diabetes. However, Egger's test detected statistical evidence for publication bias only for WC ($P = 0.07$) and WHR ($P = 0.06$) but not for WHtR ($P = 0.18$) or BMI ($P = 0.26$), whereas Begg's test did not detect publication bias ($P > 0.2$ for each obesity indicator).

Relative contributions of each anthropometric indicator to the development of diabetes after stratification by several study characteristics

We stratified the risks of diabetes for a 1-standard deviation increase according to categories and subcategories of characteristics of the participants and study design. Table 2 shows the results of tests for significant differences among

Table 2. Continued

Category and Subcategory	No. of Data Units	WHtR		BMI		WC		WHR		Difference[a]
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Smoking										
Yes	14	1.82	1.47, 2.25	1.71	1.41, 2.07	1.84	1.50, 2.26	1.64	1.32, 2.03	3, 1 > 2, 4
No	21	1.53	1.41, 1.66	1.48	1.36, 1.61	1.53	1.41, 1.66	1.45	1.35, 1.57	3, 1 > 4
Alcohol										
Yes	12	1.69	1.38, 2.07	1.62	1.34, 1.96	1.70	1.40, 2.08	1.52	1.27, 1.83	1 > 4<3 > 2
No	23	1.59	1.45, 1.74	1.51	1.39, 1.64	1.59	1.45, 1.75	1.51	1.39, 1.65	3, 1 > 4, 2
Physical activity										
Yes	10	1.92	1.53, 2.41	1.74	1.42, 2.12	1.89	1.51, 2.38	1.70	1.40, 2.12	1, 3 > 2, 4
No	25	1.50[c]	1.40, 1.62	1.47	1.36, 1.59	1.52[c]	1.41, 1.64	1.43	1.33, 1.53	3 > 4
FPG values[g]										
Yes	12	1.47	1.35, 1.61	1.44	1.32, 1.56	1.50	1.37, 1.65	1.40	1.27, 1.55	3, 1 > 4
No	23	1.70	1.49, 1.94	1.61	1.42, 1.82	1.71	1.51, 1.94	1.60	1.40, 1.82	3, 1 > 2, 4
Systolic blood pressure values[h]										
Yes	13	1.53	1.40, 1.67	1.43	1.32, 1.55	1.50	1.37, 1.65	1.48	1.34, 1.63	3, 1 > 2
No	22	1.67	1.45, 1.91	1.61	1.42, 1.83	1.70	1.48, 1.94	1.53	1.34, 1.75	1 > 4<3 > 2
Triglycerides										
Yes	7	1.51	1.35, 1.69	1.43	1.31, 1.55	1.48	1.32, 1.66	1.45	1.29, 1.62	1 > 2
No	28	1.65	1.47, 1.86	1.58	1.42, 1.70	1.67	1.49, 1.88	1.55	1.37, 1.74	3, 1 > 2, 4
Multiple factors[i]										
Yes	18	1.65	1.43, 1.90	1.57	1.38, 1.80	1.65	1.43, 1.90	1.52	1.34, 1.73	1, 3 > 2, 4
No	17	1.59	1.42, 1.78	1.53	1.37, 1.70	1.61	1.43, 1.82	1.52	1.36, 1.70	1 > 2<3 > 4
Family history of DM										
Yes	14	1.52	1.40, 1.65	1.43	1.33, 1.55	1.51	1.38, 1.65	1.47	1.34, 1.62	1, 3 > 2
No	21	1.67	1.45, 1.93	1.62	1.42, 1.85	1.70	1.48, 1.95	1.54	1.34, 1.76	3, 1 > 2, 4
Education or socioeconomic factors										
Yes	10	1.95	1.55, 2.46	1.73	1.39, 2.14	1.91	1.53, 2.40	1.81	1.50, 2.18	3 > 2<1 > 4
No	25	1.49[c]	1.40, 1.59	1.48	1.37, 1.59	1.51[c]	1.41, 1.62	1.37[c]	1.29, 1.46	3, 1, 2 > 4

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; 2hPG, 2-hour post-challenge glucose; N.S., not significant; RR, relative risk; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio.

[a] Difference in RR among the 4 obesity indicators; " > " or "<" indicates that the difference is statistically significant ($P<0.05$).

[b] Data were based on fixed-effects model because between-study heterogeneity was not significant ($P = 0.14$).

[c] There was a significant difference ($P<0.05$) in RR value compared with the top of each strata detected by meta-regression analyses to explore the impact of study characteristics on the strength of associations between individual obesity indicators and DM risk.

[d] Weight (kg)/height $(m)^2$.

[e] Other methods include medical records and self-report.

[f] RR is adjusted only for age, sex, and ethnicity.

[g] Included fasting glycemic status, such as presence of impaired fasting glucose.

[h] Included presence of hypertension.

[i] Defined at least 3 of the following main lifestyle and metabolic factors: smoking, FPG/glucose status, systolic blood pressure/hypertension, alcohol, physical activity, and triglycerides.

the anthropometric obesity indicators within each subcategory. In general, WHtR and WC were similar in the strength of associations with diabetes risk within all strata of any study characteristic, and these associations were stronger than the association between WHR and diabetes risk. However, in studies that adjusted for blood pressure (or hypertension) or family history of diabetes, there were no significant differences in the strength of association between WHR and WHtR or WC.

The superiority of WHtR or WC to BMI in the strength of association with diabetes risk was observed between subgroups defined by geographic region, sex, and mean age. In studies of white-dominant populations, WHtR and WC had a stronger association than BMI ($P<0.001$ and

$P = 0.002$, respectively). However, in non-white-dominant populations, RR_{BMI}, RR_{WHtR}, and RR_{WC} were 1.47 (95% CI: 1.37, 1.57), 1.49 (95% CI: 1.40, 1.59), and 1.50 (95% CI: 1.40, 1.61), respectively, and there were no statistical differences among these values. Although RR_{WHtR} and RR_{WC} were also significantly higher than RR_{BMI} ($P<0.001$ and $P = 0.002$, respectively) in studies that targeted relatively less obese populations that had an average BMI less than 28, the differences between RR_{BMI} and RR_{WHtR} or RR_{WHR} were not significant in studies that targeted populations with a mean BMI of 28 or higher.

Methodological features, such as criteria for diabetes, methods for ascertainment of diabetes, and representation of the associations or the extent of adjustment for main lifestyle and metabolic confounders, had no influence on the overall superiority of WHtR or WC to BMI or WHR in the strength of associations with diabetes. The predictive superiority of WHtR or WC to BMI also was observed when studies were limited to those with a follow-up period less than 10 years. However, that superiority statistically disappeared in studies with follow-up periods of 10 years or more ($P = 0.40$ for BMI vs. WHtR; $P = 0.13$ for BMI vs. WC).

Influences of specified study characteristics on the absolute contributions of each anthropometric indicator to the development of diabetes

Table 2 also shows results of the test for significant differences in the strength of diabetes risk between subgroups within each subcategory for each anthropometric indicator using meta-regression. When the study targeted a population with a mean BMI of 28 or greater, the associations between obesity indicators and diabetes risk were significantly or borderline-significantly weakened compared with studies in which the mean BMI was less than 28 ($P = 0.02$ for RR_{WHtR}, $P = 0.04$ for RR_{BMI}, $P = 0.03$ for RR_{WC}, $P = 0.11$ for RR_{WHR}). Differences according to the mean BMI remained significant after adjustment for racial differences in the study population ($P = 0.001$ for RR_{WHtR}, $P = 0.007$ for RR_{BMI}, $P = 0.002$ for RR_{WC}, $P = 0.02$ for RR_{WHR}).

Higher risks for diabetes with incremental increases in obesity indicators were reported in studies where medical records or self-reports were included for ascertainment of diabetes than in studies that depended on the diagnosis of diabetes exclusively by blood tests ($P = 0.02$ for WHtR, $P = 0.03$ for BMI, $P = 0.045$ for WC, $P = 0.04$ for WHR). However, other methodological features, such as diabetes criteria (i.e., whether both fasting and 2-hour post-load glucose values were used), representation of obesity indicators (i.e., categorical or continuous), and follow-up duration, did not significantly influence the strength of the association between each obesity indicator and diabetes risk. The impact of study-specific covariates did not significantly influence the strength of the associations, except that a significantly or borderline-significantly stronger association was observed in studies with than without adjustment for physical activity ($P = 0.02$ for WHtR, $P = 0.07$ for BMI, $P = 0.02$ for WC, $P = 0.052$ for WHR) or socioeconomic factors ($P = 0.006$ for WHtR, $P = 0.08$ for BMI, $P = 0.02$ for WC, $P = 0.002$ for WHR).

DISCUSSION

The present meta-analysis indicated that WHtR and WC were more strongly associated with the development of diabetes than was BMI or WHR. This finding is inconsistent with a previous meta-analysis that indicated that BMI, WC, and WHR had similar associations with incident diabetes (27). The main reason for this inconsistency is the method of study selection. The aforementioned meta-analysis included not only articles that did not investigate WHtR but also studies with data on only 1 or more of the 3 indicators (i.e., BMI, WC, and WHR) with regard to the association with diabetes risk; the previous meta-analysis also failed to make head-to-head comparisons in the same population. This method is problematic and would distort the pooled estimate, especially under the condition that high correlations were observed among the results from 4 obesity indicators within 1 study, as in the present meta-analysis. For example, if some studies reported an extremely strong association between BMI and diabetes risk but presented no data on WC, the missing data would cause the pooled risk of diabetes for WC to be underestimated.

Although a meta-analysis of observational cohort studies can never prove a cause-effect relation, there is a plausible biologic mechanism for the present finding. WHtR or WC has been more strongly correlated with intra-abdominal visceral fat than has BMI or WHR (28). The accumulation of visceral fat stores affects insulin metabolism by releasing free fatty acids (29). Free fatty acids reduce the hepatic clearance of insulin, which could lead to insulin resistance and hyperinsulinemia (30). As a result, the present meta-analysis has confirmed the consistency between findings at the tissue- and whole-body levels.

Another main finding of this meta-analysis is that WHtR did not have a stronger association with risk of incident diabetes than WC, which suggests no additional benefit of measuring height in addition to WC alone. It is believed that WHtR is superior to WC because it corrects the WC for height of the individual. However, whether height affects the relation between WC and visceral fat is controversial (31, 32). It is possible that WHtR might not be a useful clinical tool for prediction of diabetes risk.

Although it can be concluded that WHtR or WHR is not superior to WC for prediction of future diabetes risk, measurement of height, hip circumference, or both could nevertheless be worthwhile. Previous reports have demonstrated that models for prediction of incident diabetes were improved substantially when height, hip circumference, or both were entered as separate terms in a model containing WC (33, 34). The development of methods for incorporating a height- or hip-adjusted WC level into risk-prediction tools could be a topic of further research.

Familial aggregation of visceral fat is well known (35). The results of the stratified analyses indicated that the superiority of WHtR or WC to WHR for prediction of diabetes risk disappeared after adjustment for a family history of diabetes. It is possible that persons with a family history of

diabetes have high levels of visceral fat and consequently are at high risk of incident diabetes.

It has long been assumed that the superiority of the waist element to the body weight element for prediction of diabetes risk depends on characteristics of the study population (e.g., race, ethnicity (36)). However, such characteristics have not been sufficiently clarified. The present stratified analyses suggested that WHtR and WC were more strongly associated with diabetes risk than BMI was in studies of white-dominant populations but not in studies of non-white-dominant populations. Also, in studies of populations with a relatively high BMI (≥28), no differences were observed in the strength of the association with diabetes among the obesity indicators. A plausible explanation for these results is difficult, but future studies are needed to determine population characteristics that would indicate whether measurement of WC is more important than that of body weight alone.

Several limitations in the present meta-analysis should be addressed. First, the linearity between anthropometric obesity indicators and diabetes risk is an a priori assumption. Actually, this is not the case, especially with the elderly, for whom being underweight is a predictor of diabetes (37). If underweight subjects had a higher risk of diabetes than those with normal weight across various study populations, the risk of diabetes for incremental increases in obesity could be underestimated. For example, the receiver operating characteristics curve and the area under the curve could provide more information than a linear regression on details of the dose-response relation between obesity and diabetes risk or on comparisons of diagnostic value among the anthropometric indicators. However, few of the studies (2, 20, 25) in this meta-analysis presented sufficient data for comparing the predictive value for diabetes among the anthropometric indicators (i.e., area under receiver operating characteristics curves and their corresponding 95% confidence intervals).

Second, the exclusion of many studies that did not observe diabetes risk related to WHtR could potentially cause a selection bias, although the exclusion of such studies was unavoidable for the head-to-head comparison of the predictive ability for diabetes risk among obesity indicators. Third, publication bias is inevitable under the condition that the association between WHtR and diabetes risk is not commonly recognized. Actually, the funnel plot for WHtR tended to favor a positive association. The present meta-analysis indicated that the bias was not statistically significant. Nevertheless, potential publication bias cannot be ruled out.

Fourth, adjustment for potential confounders is generally insufficient, which could distort the study result. According to the present meta-regression analyses, several confounders, such as physical activity or socioeconomic and educational factors, influenced the absolute strength of the association with diabetes risk. The present stratified meta-analyses did not indicate that the extent of the traditional metabolic and lifestyle risk factors for diabetes changed the superiority of WHtR or WC to BMI or WHR. Nevertheless, the influence of unknown residual confounders cannot be ignored.

Fifth, differences in the association of obesity indicators with diabetes risk by age could not be analyzed fully because only 1 study exclusively analyzed elderly people (24). That study found a weaker association between obesity and diabetes risk in participants 75 years of age or older than in those less than 75 years of age. Further research is needed to investigate the differences in anthropometric indicators according to age.

Lastly, length of the follow-up periods might have influenced study results. Actually, the present meta-analyses indicated that WC and WHtR did not have a significantly stronger association with diabetes than that of BMI in studies with a follow-up period of 10 or more years. A previous longitudinal study reported that over 10 years, total fat mass and fat mass other than subcutaneous fat increased, whereas body weight did not change (38). It is possible that many people tend to become abdominally obese (i.e., accumulate abdominal adiposity) during follow-up rather than become totally obese (i.e., gain weight), and the impact of baseline body fat distribution on diabetes risk is weakened with lengthening of the follow-up period. From the viewpoint of practical use in clinical settings, more frequent assessment of indicators of abdominal obesity is proposed. However, further research is needed on whether changes in WC or WHtR as simple obesity indicators are more closely associated with the development of diabetes than is BMI.

In conclusion, the present meta-analysis indicates that WHtR is a statistically but modestly better obesity indicator for prediction of future diabetes risk than is BMI or WHR. This finding is consistent with tissue-level biologic findings that abdominal adipose tissue plays an important role in the development of diabetes mellitus. However, there is no evidence that WHtR is superior to WC as a clinical tool for detecting persons at high risk of incident diabetes.

ACKNOWLEDGMENTS

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Drs. Sone and Kodama are recipients of a Grant-in-Aid for Scientific Research (grant 20300227) and Postdoctoral Research Fellowship (202965), respectively, both from the Japan Society for the Promotion of Science (JSPS). This work was also financially supported by the Japan Cardiovascular Research Foundation and Ministry of Health Labor and Welfare, Japan.

The authors thank Ms. Satomi Fukuya in the University of Tsukuba for her excellent secretarial work.

Conflict of interest: none declared.

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