

Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies

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Received 18 December 2006; revised 14 February 2007; accepted 23 February 2007; online publish-ahead-of-print 2 April 2007

KEYWORDS

Cardiovascular disease;
Abdominal obesity;
Systematic review;
Meta-regression

Aims The objectives of this study were to determine the association of waist circumference (WC) and waist-to-hip ratio (WHR) with the risk of incident cardiovascular disease (CVD) events and to determine whether the strength of association of WC and WHR with CVD risk is different.

Methods and results This meta-regression analysis used a search strategy of keywords and MeSH terms to identify prospective cohort studies and randomized clinical trials of CVD risk and abdominal obesity from the Medline, Embase, and Cochrane databases. Fifteen articles ($n = 258\,114$ participants, 4355 CVD events) reporting CVD risk by categorical and continuous measures of WC and WHR were included. For a 1 cm increase in WC, the relative risk (RR) of a CVD event increased by 2% (95% CI: 1–3%) overall after adjusting for age, cohort year, or treatment. For a 0.01 U increase in WHR, the RR increased by 5% (95% CI: 4–7%). These results were consistent in men and women. Overall risk estimates comparing the extreme quantiles of each measure suggested that WHR was more strongly associated with CVD than that for WC (WHR: RR = 1.95, 95% CI: 1.55–2.44; WC: RR = 1.63, 95% CI: 1.31–2.04), although this difference was not significant. The strength of association for each measure was similar in men and women.

Conclusion WHR and WC are significantly associated with the risk of incident CVD events. These simple measures of abdominal obesity should be incorporated into CVD risk assessments.

Introduction

Abdominal obesity is increasingly recognized as a major risk factor for cardiovascular disease (CVD). Compared with body mass index (BMI), anthropometric measures of abdominal obesity [e.g. waist circumference (WC), waist-to-hip ratio (WHR), sagittal abdominal diameter] appear to be more strongly associated with metabolic risk factors,^{1,2} incident CVD events, and death.^{3–7} The cardio-metabolic risk associated with abdominal obesity is attributed to the presence of visceral adipose tissue (VAT), which promotes insulin resistance, dyslipidaemia, and hypertension.^{8–10} VAT stores can be measured by computerized axial tomography, magnetic resonance imaging, and dual energy x-ray absorptiometry, but these techniques are not feasible and too expensive for everyday use. WC and WHR are the most common proxy measures of VAT. Both measures are correlated with VAT; however, WC is more strongly associated with VAT.^{11–13} Despite this, WHR may be a better predictor of CVD risk as hip circumference is inversely associated with the development of

cardio-metabolic risk factors and CVD.^{14–19} Opinion is divided as to which is a more appropriate measurement.

We performed a systematic review and meta-regression analysis of all available prospective cohort studies and randomized clinical trials (RCTs) of CVD that measured WC or WHR. The objectives of this study were to (1) determine the association of each measure with the relative risk (RR) of incident CVD events in men and women and (2) determine whether the strength of association differs between the two measures.

Methods

Search strategy

We identified studies of abdominal obesity and cardiovascular outcomes by searching in the Cochrane Library (inception of database to issue no. 4, 2006), EMBASE (1980 to week 45, 2006), and MEDLINE (1966 to November week 1, 2006). We used a combination of keywords [e.g. waist, WHR, abdominal obesity, myocardial infarction (MI), stroke, angina] and medical subject headings (e.g. heart arrest, cerebrovascular accident, myocardial ischaemia, myocardial revascularization) to maximize our search sensitivity (see Supplementary material online). Searches were performed using the OVID search engine (release 10.0.0) by de Koning and Pierroz, and

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articles were evaluated for inclusion by de Koning and Merchant. Bibliographies of studies that met inclusion criteria were manually searched for relevant articles. Authors were contacted for additional details (e.g. outcome definitions) or if results were presented in an incompatible format.

Inclusion criteria

English language prospective cohort studies or RCTs that reported RR estimates (or the data to calculate them) for incident CVD events were eligible for inclusion in our review. CVD was defined as fatal and non-fatal CHD and stroke events. CHD events included MI, ischaemic heart disease (angina), and coronary interventions (coronary artery bypass surgery or coronary angioplasty) according to ICD-9 codes 410–414. Stroke events included ischaemic and haemorrhagic stroke according to ICD-9 codes 430–438. Studies that recorded any other CVD endpoints (e.g. congestive heart failure) were excluded. Any method to verify CVD outcomes was permissible, provided it was verified by a physician, hospital record, or death certificate. We allowed any measurement method for WC or WHR to be used, including self-report.

Studies were included if they reported sex-stratified RR estimates in at least three quantiles of WC or WHR or as beta-coefficients for dichotomous outcomes (e.g. RR per 1 U increase of WC or WHR). We allowed any method (e.g. Mantel-Haentzel, Cox proportional hazard models, logistic regression) to be used in the calculation of RR estimates, as the results of most methods converge when disease outcomes are rare.²⁰

Articles were excluded if all participants had an existing metabolic risk factor (e.g. diabetes) or if any participants had diagnosed or suspected CVD. These criteria insured that only low-risk individuals who had suffered their first CVD episode were included in our analysis.

Information on disease endpoint definitions, mean follow-up, mean age of participants, ethnicity of participants, number of participants, waist measure quantile ranges, risk estimates, standard errors, and covariates in multivariate models were extracted from each study and tabulated in a Microsoft Excel spreadsheet. To assess inter-rater agreement on the inclusion of studies, we calculated the kappa statistic, which provides a measure of observed agreement compared with agreement by chance alone.²¹

Statistical analysis

We stratified our analyses by sex and the numbers of covariates that risk estimates were adjusted for in each study. 'Minimally adjusted' estimates were adjusted for age, cohort year, and drug treatment if the study was an RCT. 'Moderately adjusted' estimates were additionally adjusted for confounders (e.g. smoking) but not biological mediators (e.g. diabetes, dyslipidaemia) of the effect of abdominal obesity on CVD risk. 'Maximally adjusted' estimates were additionally adjusted for biological mediators or BMI.

Determining the association of waist circumference and waist-to-hip ratio with cardiovascular disease

We used weighted-least-squares (WLS) regression in studies that reported risk estimates by quantiles of WC or WHR. Values corresponding to the cut-points for extreme quantiles and median values for intermediate quantiles were used as the predictor. The outcome was the natural logarithm of CVD risk in each quantile. Beta-coefficients represented the change in log CVD risk for a 1 U increase in WC or WHR. We used the inverse quasi-variance of risk estimates as regression weights in order to include the reference category in the regression. Quasi-variances are variance estimates that summarize all the covariances between levels of a categorical variable and, unlike standard variance estimates, are assigned to each level.²² The sum of two quasi-variances is approximately equal to the variance of a comparison of the two levels.²² We used the web-based QV-calculator to derive quasi-variances from variances in log RR for categories of WC and WHR and estimates

of their covariances.²³ As none of the included studies reported covariances between WC and WHR categories, we generated an estimate of their covariance using correlations of log CVD risk in WC and WHR categories from the Heart Outcomes Prevention Evaluation Trial (HOPE).²⁴ Correlation coefficients from the HOPE trial and variances in log RR for categories of WC and WHR were used to estimate covariances using the equation: $\text{cov}_{1,2} = \text{corr}_{1,2} * \text{var}_1 * \text{var}_2$.

Heterogeneity in beta-coefficients was explored using a random effects meta-regression model ('metareg' module, Stata ver 8.2). We included predictors for mean age, mean follow-up, and the type of data (categorical or continuous) used to derive beta-coefficients, with beta-coefficients as the outcome. Beta-coefficients were weighted by their inverse variances and pooled using the DerSimonian and Laird random effects model to allow for differences between studies ('meta' module, Stata ver 8.2).²⁵ Cochran's Q was used to assess heterogeneity among the beta-coefficients. Pooled beta-coefficients with 95% confidence intervals were exponentiated and plotted to assess the statistical significance of the estimates. Risk estimates for WC were evaluated for a 1 cm increase, and estimates for WHR were evaluated for a 0.01 U increase. We calculated the predicted changes in WC and WHR for an equivalent increase in CVD risk to give WHR a meaningful interpretation.

Testing for differences in the association of waist circumference and waist-to-hip ratio with cardiovascular disease risk

In an effort to compare the strength of association of WC and WHR with CVD risk, we pooled risk estimates comparing the highest vs. the lowest quantiles of WC and WHR. Exponentiated risk estimates and 95% confidence intervals were plotted to test for significant differences.

Assessing publication bias: funnel plots

Beta-coefficients and their standard errors were plotted to identify possible publication biases. In the absence of publication bias, beta-coefficients are expected to form a funnel-shaped distribution. We plotted moderately and maximally adjusted beta-coefficients to maximize the number of studies included in the assessment. Moderately adjusted beta-coefficients were plotted if both levels of adjustment were reported in the same study.

Results

Study characteristics

Figure 1 shows study assessment, exclusion and inclusion of studies in this review. Our search identified 3368 articles, which were reduced to 94 studies after excluding duplicates, articles with inappropriate study designs, non-English articles, and articles on unrelated topics (references available on request). Of the 94 articles, 79 were excluded as detailed in Figure 1. The kappa statistic for inter-rater agreement on inclusion or exclusion of potential studies was 0.98.

Fifteen studies (12 with primary outcome of CHD, three with primary outcome of stroke), comprising 258 114 participants (35.7% men) and over 1 520 864 person-years of follow-up were included.^{26–40} The mean age of participants was 57 years. Table 1 summarizes features of the 15 studies. During a mean weighted follow-up of 5.9 years, 4355 CVD events were recorded. A subgroup analysis was performed on CHD events after eliminating three studies on stroke,^{27,38,39} reducing the total number of participants to 226 395 (27.2% male) and over 1 328 747 person-years. During a mean follow-up of 5.9 years, 3727 CHD events were recorded. The mean age of participants was 57 years.

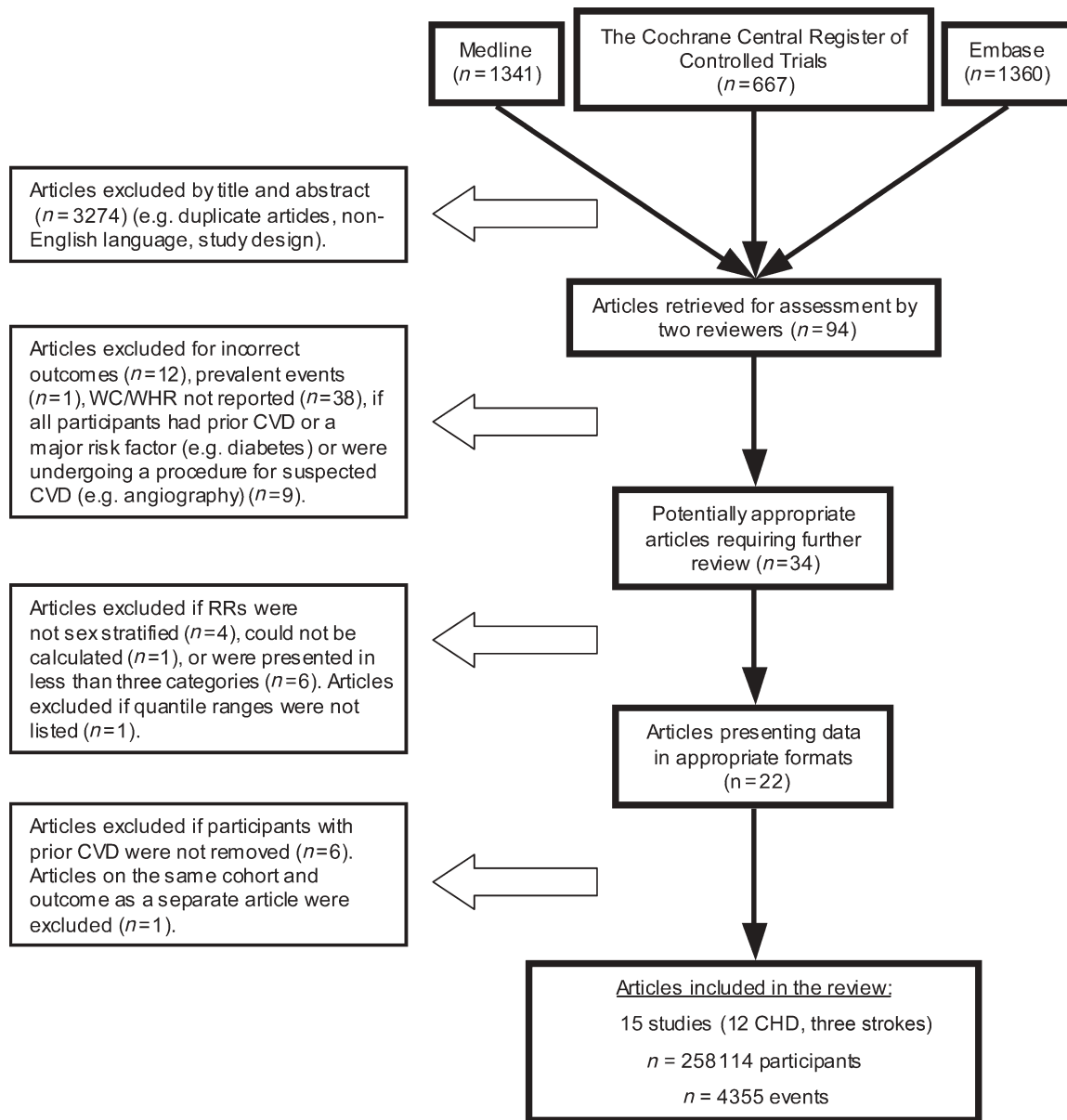


Figure 1 Flow chart of systematic review.

Associations of waist circumference and waist-to-hip ratio with cardiovascular disease risk

Beta-coefficients and the covariates that risk estimates were adjusted for in the included studies are listed in a table of the Supplementary material. Meta-regression of study level predictors (mean age, mean follow-up, type of data) did not account for significant heterogeneity in beta-coefficients (data not shown). We therefore pooled beta-coefficients using the random effects model to allow for differences between studies.

WC and WHR were positively associated with CVD risk after minimal adjustment (Figure 2). Moderately and maximally adjusted estimates were inconsistently associated with CVD risk. Only WHR was significantly associated with increased CVD risk among all adjustment levels for the men and women subgroup. Risk estimates were highest in the moderately adjusted subgroup. Women had higher risk estimates than men in the moderately adjusted

subgroup and the maximally adjusted subgroup for WC. However, confidence intervals overlapped across subgroups and, therefore, it is not possible to determine whether observed risk differences represent true differences in risk.

Table 2 shows changes in WC and WHR for an equivalent increase in risk and was derived from risk estimates shown in Figure 2. For example, a 10% increase in risk (RR = 1.1) is associated with a 5.04 cm increase in WC or a 0.02 U increase in WHR for men and women using minimally adjusted data.

Pooled risk estimates for the comparison of extreme quantiles of WC and WHR are shown in Figure 3. Estimates were higher for WHR within each level of adjustment and were slightly higher in women than in men. However, these estimates were not significantly different.

Publication bias did not appear to be present for studies that reported risk estimates for WC (Figure 4). There was a potential bias against studies that found a weak relationship between WHR and CVD risk.

Table 1 Features of included studies

Author	Sample size (n)	Men (%)	Mean age (years)	Mean follow-up (years)	Measures reported	Outcome	Events
Bengtsson <i>et al.</i> ²⁶	1450	0	49	20	WHR	CHD (fatal)	26
Dey <i>et al.</i> ²⁷	2287	46	70	15	WC	Stroke (fatal+non-fatal)	453
Dey and Lissner ²⁸	1597	46	70	15	WC	CHD (fatal+non-fatal)	684
Folsom <i>et al.</i> ²⁹	14 040	44	55	6.2	WHR	CHD (fatal+non-fatal)	398
Folsom <i>et al.</i> ³⁰	31 702	0	62	11.5	WC, WHR	CHD (fatal)	438
Lakka <i>et al.</i> ³¹	2682	100	51	10.6	WC, WHR	CHD (fatal+non-fatal)	123
Lawlor <i>et al.</i> ³²	3589	0	70	4.4	WC, WHR	CHD (fatal+non-fatal)	194
Nicklas <i>et al.</i> ³³	2503	51	75	4.6	WC	CHD (fatal+non-fatal)	116
Rexrode <i>et al.</i> ³⁴	44 702	0	53	8	WC, WHR	CHD (fatal+non-fatal)	320
Rexrode <i>et al.</i> ³⁵	16 164	100	62	3.9	WC, WHR	CHD (fatal+non-fatal)	552
Rimm <i>et al.</i> ³⁶	29 122	100	58	3	WC, WHR	CHD (fatal+non-fatal)	420
Silventoinen <i>et al.</i> ³⁷	11 510	47	45	8	WC, WHR	CHD (fatal+non-fatal)	386
Walker <i>et al.</i> ³⁸	28 643	100	58	5	WHR	Stroke (fatal+non-fatal)	118
Welin <i>et al.</i> ³⁹	789	100	54	18.5	WHR	Stroke (fatal +non-fatal)	57
Zhang <i>et al.</i> ⁴⁰	67 334	0	55	2.5	WC, WHR	CHD (fatal +non-fatal)	70

WC, waist circumference; WHR, waist-to-hip ratio; CHD, coronary heart disease.

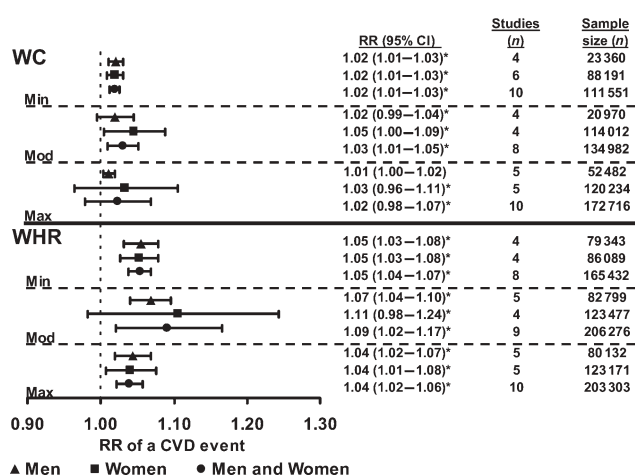


Figure 2 Pooled exponentiated beta-coefficients and 95% confidence intervals plotted by sex and level of adjustment. Waist circumference was evaluated per 1 cm increase, and waist-to-hip ratio was evaluated per 0.01 U increase. Asterisks indicate significant heterogeneity among beta-coefficients from included studies ($P_{\chi^2} < 0.05$). Comparisons cannot be made between beta-coefficients for waist circumference and waist-to-hip ratio in this figure due to differences in scaling.

Discussion

Using data pooled from 15 prospective studies that included 258 114 individuals, we demonstrated that the risk of incident CVD increases in men and women with elevations in WC or WHR. Specifically, a 1 cm increase in WC is associated with a 2% increase and a 0.01 increase in WHR is associated with a 5% increase in risk of future CVD after adjusting for age and cohort characteristics.

In an effort to understand the causal pathway that relates abdominal obesity to CVD risk, we examined adjusted risk estimates. We tried to determine whether adjustment for confounders such as smoking (i.e. moderately adjusted data) would strengthen the association of abdominal obesity with CVD, and whether adjustment for factors in the causal pathway between abdominal obesity and CVD, such as blood

lipids (i.e. maximally adjusted data), would attenuate the association. However, no changes in associations were identified. This supports prior investigations which demonstrate that abdominal obesity is an independent risk factor for CVD over and above other abdominal obesity correlates.

To explore whether CVD risk differed between men and women, we stratified our analyses by sex. We found a sex difference in the moderately adjusted subgroup analysis of beta-coefficients, in the maximally adjusted subgroup analysis of beta coefficients for WC, and within all adjustment subgroup analyses of extreme quantiles. However, these differences were not statistically significant. We expected that a sex-related difference might exist because metabolic risk factors appear in women at lower WC and WHR thresholds than in men.⁴¹ However, our data suggest that increases in WC or WHR are associated with similar risk of CVD in men and women.

WHR has been suggested to be a superior predictor of CVD risk because it includes a measurement of hip circumference, which is inversely associated with dysglycaemia, dyslipidaemia, diabetes, hypertension, CVD, and death.^{14–19} The protective association of hip circumference with cardio-metabolic risk is possibly related to its correlation with other anthropometric features. Increased hip circumference is associated with increased hip subcutaneous fat, gluteal muscle, and total leg muscle mass.^{42,43} Leg muscle mass may represent a proxy measure of physical activity, which is inversely related to cardio-metabolic risk.^{14,44} In our data, the RR for WHR was greater than WC for comparisons of extreme quantiles, which supports WHR as being superior to WC as a measure of CVD risk. However, these associations were not significantly different.

Although there may be advantages of the WHR over the WC, WHR is more difficult to perform and a less reliable measure than WC. Intra-class correlation (ICC) for repeat measures and Pearson's correlations between self-report and clinical measurement are lower for WHR (WHR: ICC = 0.68–0.85, $r = 0.69–0.85$; WC: ICC = 0.89–0.96, $r = 0.89–0.97$).^{45,46} Furthermore, WHR may be inappropriate to

Table 2 Changes in waist circumference and waist-to-hip ratio for an equivalent increase in cardiovascular disease risk

% Increase in risk	WC (cm)			WHR (U)		
	Men	Women	Men and women	Men	Women	Men and women
Minimally adjusted						
10	4.71	5.08	5.04	0.02	0.02	0.02
20	9.02	9.72	9.65	0.03	0.04	0.03
30	12.98	13.99	13.88	0.05	0.05	0.05
40	16.64	17.95	17.80	0.06	0.07	0.06
50	20.06	21.63	21.46	0.08	0.08	0.08
Moderately adjusted						
10	5.00	2.13	3.20	0.01	0.01	0.01
20	9.56	4.07	6.12	0.03	0.02	0.02
30	13.76	5.86	8.81	0.04	0.03	0.03
40	17.64	7.52	11.30	0.05	0.03	0.04
50	21.26	9.06	13.62	0.06	0.04	0.05
Maximally adjusted						
10	8.46	2.99	4.26	0.02	0.02	0.02
20	16.18	5.72	8.15	0.04	0.05	0.05
30	23.28	8.23	11.73	0.06	0.07	0.07
40	29.86	10.55	15.05	0.08	0.08	0.09
50	35.98	12.72	18.13	0.09	0.10	0.10

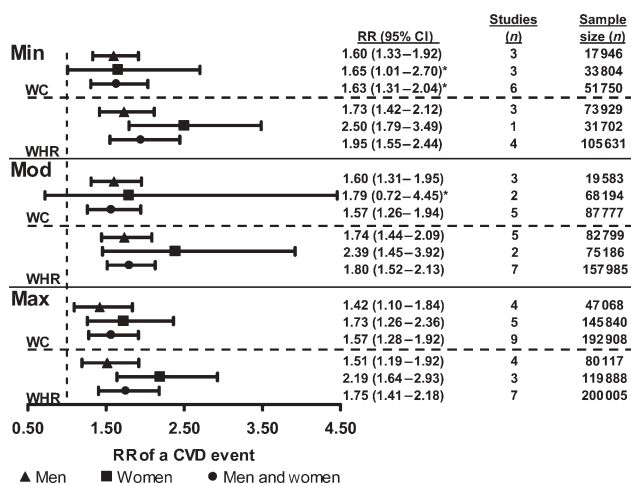


Figure 3 Pooled relative risk estimates and 95% confidence intervals representing comparisons of the lowest vs. the highest quantiles of waist circumference and waist-to-hip ratio. Asterisks indicate significant heterogeneity among beta-coefficients from included studies ($P_{\text{hetero}} < 0.05$).

assess obesity or weight loss. A non-obese and an obese individual could theoretically have the same WHR, which could remain constant during weight change.⁴⁷ Furthermore, patients may show reluctance to allow hip measurements to be taken, as this usually requires disrobing.⁴⁸ Thus the choice to use WC or WHR may depend on the setting, as in a physicians' office it is more feasible to measure WC, whereas in research studies, it appears to be more informative to measure WHR.

We were unable to examine the association of abdominal obesity with CVD risk by ethnic group. Most participants were white Caucasians, and only one article studied an exclusively non-white population.⁴⁰ Given that non-white ethnic groups appear to develop metabolic risk factors at different BMI cut-points, it is possible that the risk of CVD

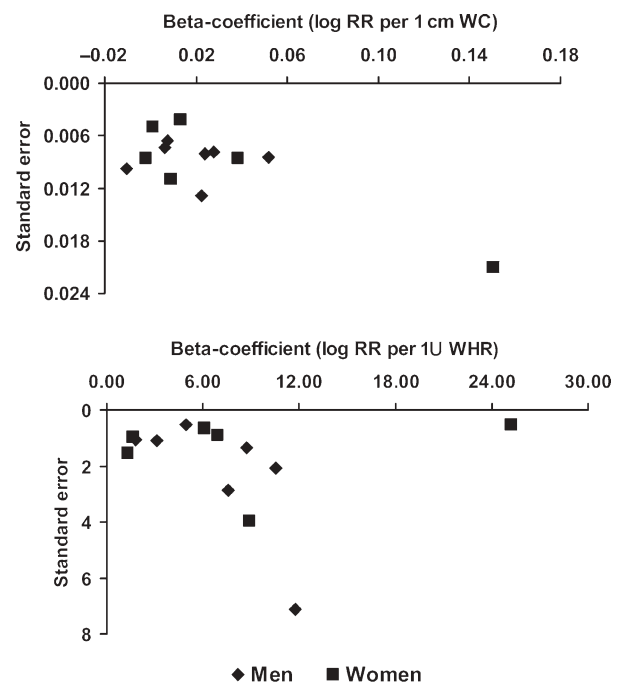


Figure 4 Funnel plots of moderately and maximally adjusted beta-coefficients.

associated with increasing WC and WHR differs between ethnic groups.^{40,48,49} Recently, the INTERHEART study, the world's largest case-control study of MI, showed that WC and WHR were positively associated with the risk of incident MI and that the strength of association differed significantly between ethnic groups.⁵⁰

Our study has several strengths. The first is clearly the number of participants assessed by the included articles. Over 250 000 participants were followed for nearly 6 years, and there were over 4000 CVD events. Secondly, we included only prospective studies in order to minimize

potential biases associated with retrospective study designs. Thirdly, we included studies of healthy individuals who later suffered their first CVD episode in order to make our findings generalizable to healthy populations. Finally, we tried to utilize all available data in the literature and employed a novel technique to include the reference category in WLS meta-regression.

Our study has some limitations. The first is that we did not include studies that used a WC or WHR cut-point to denote abdominal obesity. Secondly, we could not evaluate the standardized linear associations of WC and WHR with CVD because standard deviations of each measure were not consistently reported in all articles. However, we attempted to address this problem by pooling risk estimates representing the comparison of extreme quantiles for each measure. Thirdly, studies were adjusted for different covariates, which contributed to heterogeneity among the moderate and maximally adjusted subgroups. Finally, the small number of studies and significant heterogeneity limited our ability to detect small differences in risk.

Conclusions

Abdominal obesity as measured by WC and WHR is significantly associated with the risk of incident CVD events. A 1 cm increase in WC is associated with a 2% increase in risk of future CVD and a 0.01 increase in WHR is associated with a 5% increase in risk. These simple measures of abdominal obesity should be incorporated in CVD risk assessments.

Declaration of Helsinki and Ethics approval

This study complies with the Declaration of Helsinki. It did not require ethics approval.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

L.D. designed the study, performed literature searches, assessed studies for inclusion, analyzed data, and wrote the manuscript. A.M. assisted in literature searches, assessed studies for inclusion, and assisted in writing the manuscript. J.P. assisted with statistical analysis and editing of the manuscript. S.A. conceived of the original idea for this study and assisted in writing the manuscript. We thank Lehana Thabane for statistical advice, Sarah Pierroz for assisting in the literature search, and Salim Yusuf for his critical reading of the manuscript. This study was supported by L.D.'s scholarships from the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research. S.A. is a recipient of a CIHR clinician scientist (Phase 2) award.

Conflict of interest: none declared.

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