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REVIEW ARTICLE

Association between neck circumference and lipid profile: a systematic review and meta-analysis of observational studies

Nafiseh Shokri-Mashhadi [1], Sajjad Moradi [2], Hamed Mohammadi [3], Abed Ghavami [3], and Mohammad Hossein Rouhani [4]*

[1]Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, 2348569, Iran; [2]Student Research Committee, School of Nutrition and Food Science, Department of Clinical Nutrition, Isfahan University of Medical Sciences, Isfahan, 2348569, Iran; [3]Student Research Committee, School of Nutrition and Food Science, Department of Community Nutrition, Isfahan University of Medical Sciences, Isfahan, 2348569, Iran; and [4]Department of Community Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, PO Box 81745, Isfahan, 2348569, Iran

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Aims Previous studies suggested that neck circumference (NC) as a new, simple, and valuable tool for the measuring obesity. However, the results of studies regarding the relationship between blood lipids and neck circumference were inconsistent. Therefore, we aimed to perform a systematic review and meta-analysis to summarize the association between NC and lipid profiles in adults.

Methods and results PubMed and Scopus electronic databases were searched until 30 June 2018 to find articles that reported the association between NC and blood lipids. Mean serum lipids and variables contributed to heterogeneity were extracted. Sources of inter-study heterogeneity were determined by subgroup analysis. Of 2490 publications identified, 33 studies were included in the qualitative and quantitative synthesis. We found an inverse correlation between NC and high-density lipoprotein cholesterol [HDL-C; overall Fisher's $Z = -0.18$; 95% confidence interval (CI): -0.21, -0.15]. Furthermore, we found positive associations between NC and total cholesterol (TC; overall Fisher's $Z = 0.11$; 95% CI = 0.06, 0.16), low-density lipoprotein cholesterol (LDL-C; overall Fisher's $Z = 0.1$; 95% CI = -0.04, 0.16), and triglyceride (TG; overall Fisher's $Z = 0.21$; 95% CI = 0.17, 0.25) in men. Neck circumference was directly correlated to TC (overall Fisher's $Z = 0.1$; 95% CI = 0.01, 0.19) and LDL-C (overall Fisher's $Z = 0.16$; 95% CI = 0.12, 0.20) in healthy and unhealthy women, respectively. There was no correlation between NC and serum concentration of TC (overall Fisher's $Z = 0.01$; 95% CI = -0.02, 0.03) and LDL-C (overall Fisher's $Z = 0.09$; 95% CI = 0.02, 0.16) in unhealthy and healthy women, respectively.

Conclusion Higher NC in unhealthy men was strongly indirectly associated with HDL-C, and directly related to LDL-C, TG, and TC. In unhealthy women, higher NC was inversely associated with HDL and directly related to LDL-C.

Keywords LDL-C • HDL-C • TC • TC • Neck circumference • Meta-analysis

Implications of practice

- Neck circumference (NC) could be a predictor of dyslipidaemia in men.
- Neck circumference is inversely related to cardiovascular protective factors.
- The predictor effect of NC could be affected by gender.
- In women with comorbidity, NC is a good predictor triglyceride levels.

* Corresponding author. Tel: +98 313 792 3151, Fax: +98 313 668 2509, Email: sm_rouhani@nutr.mui.ac.ir

Introduction

Obesity, as a growing public health problem, is currently prevalent in many countries.[1] Increased fat accumulation causes severe illness and is associated with reduced life expectancy in obese subjects. Studies have shown that excessive adipose tissue has adverse effects on the cardiovascular system and could be related to hypertension,[2] type 2 diabetes mellitus,[3] and respiratory disorders.[4] Moreover, dyslipidaemia [elevated serum concentration of low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and free fatty acids, and decreased level of high-density lipoprotein cholesterol (HDL-C)] is an obesity-related disorder which can link obesity to cardiovascular diseases.[5]

Several methods are employed to evaluate whole-body fat, central obesity, and distribution of body fat.[6] Anthropometric indices, such as body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR), are commonly used to measure obesity and body fat distribution.[7] Although BMI has been extensively used in clinical practices, it has intrinsic limits to estimate body fat mass.[8] Some limitations also should be considered in the application of WC and WHR. For instance, they are appropriate only for healthy subjects, has variations during the day, and do not reflect upper-body subcutaneous fat.[9]

Neck circumference (NC) is a new, simple, valuable, and low-cost obesity measurement tool, reflecting upper-body fat distribution.[10] However, the association between NC and total cholesterol (TC) indicated inconsistent results.[11] Also, there was no significant correlation between NC and HDL-C.[12] Therefore, present systematic review and meta-analysis were conducted to summarize inconsistent findings regarding the association between NC and blood lipids. We also tried to evaluate the strengths and limitations of studies that reported the relation between NC and lipid profiles.

Methods

Literature search and selection

We conducted a systematic review and meta-analysis in conformity with the guidelines of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE).[13] A systematic literature review was followed through the PubMed (www.ncbi.nlm.nih.gov/pubmed) and Scopus (www.scopus.com) databases until 30 June 2018. The search strategy was completed using subject headings, abstract, and keywords. No language and date restrictions were applied. The following terms were used in an electronic systematic search to determine studies regarding the correlation between NC and lipid profiles: ('Neck Circumference' [Title/Abstract]) AND ('Lipid Profile' [MeSh] OR 'low Density Lipoprotein Cholesterol' [Title/Abstract] OR 'Free Fatty Acids' [MeSh] OR 'High Density Lipoprotein Cholesterol' [MeSh] OR 'Total Cholesterol' [Title/Abstract] OR 'Triglycerides' [Title/Abstract] OR 'Triacylglycerol' [Title/Abstract] OR 'Very low density lipoprotein' [Title/Abstract] OR 'Lipoprotein' [Title/Abstract] OR 'VLDL' [Title/Abstract] OR 'LDL' [Title/Abstract] OR 'HDL' [Title/Abstract] OR 'TC' [Title/Abstract] OR 'TG' [Title/Abstract] OR 'TAG' [Title/Abstract]. We also searched references listed in retrieved articles manually. After excluding duplicates, two researchers (S.M. and N.S.-M.) independently screened the title and abstract of all records and determined potentially relevant articles for further assessment. Studies that did not meet the eligibility criteria were removed using a screen form, using a classified approach according to study design, population, exposure, and outcome. Any differences of opinion in this regard have been discussed and resolved.

Eligibility criteria

Articles were met inclusion criteria if they: (i) conducted on adults (>18 years); (ii) were designed as a cohort or a cross-sectional study; (iii) used NC as the independent variable; (iv) reported correlation coefficients (Pearson or Spearman) between NC and blood lipids. If there were more than one report from one dataset, the paper with the largest sample size was included. Studies were excluded if they: (i) were review articles, case reports, conference reports, or letters; (ii) enrolled children or adolescents.

Data collection

Two reviewers separately extracted data for selected studies, using a standard data extraction form.[14] In case of discrepancies, we discussed the eligibility of data with the third author until consensus. Following information was obtained from eligible studies: (i) study details (name of the first author, year of the publication, name of the study, geographical area, and sample size); (ii) population characteristics (age range or mean age, sex, race, and ethnicity); (iii) details of exposure and outcome (methods of measuring NC, methods of evaluation of lipid profile, adjusted covariates, and main findings).

Quality assessment for individual studies

The quality of selected studies was assessed by two reviewers using the Newcastle-Ottawa scale (adapted for cross-sectional studies). This scale brings up a maximum of 10 stars for each study: Five stars for the selection (representative of the sample, sample size, non-respondents, and determination of the exposure), two stars regarding comparability (controls for the effect or factors), and three stars for the property of outcome (evaluation of the outcome and statistical test). Studies were categorized as high (≥9 stars), medium (7–9 stars), or low (<7 stars) quality.

Statistical analysis

Correlation coefficients (reported for the relationship between NC and blood lipids) were used for meta-analysis. The Fisher's $Z \pm SE$ was calculated using the correlation coefficient and sample size. According to the method of DerSimonian and Laird, effects sizes were pooled by applying the random-effects model. Subgroup analysis was applied to discover the possible sources of heterogeneity among studies. We performed subgroup analysis according to gender (men, women, and both), the region of study (Eastern and Western, Europe, Middle East), and type of correlation coefficient (Pearson and Spearman). Furthermore, subgroup heterogeneity was evaluated for all subgroups. The overall consequence was identified by sensitivity analysis for evaluating the statistical outcome validity. Begg's test and Egger's test were conducted to evaluate publication bias ($P < 0.05$ was considered representative of the statistical significance). All statistical tests for this meta-analysis were performed with STATA version 14.0 (Stata Corporation, College Station, TX, USA).

Results

As shown in *Figure 1*, a systematic literature search produced a total number of 2490 publications, excluding duplications. After screening articles, we excluded 1525 publications because they did not meet eligibility criteria, and therefore, 167 articles remained for full-text

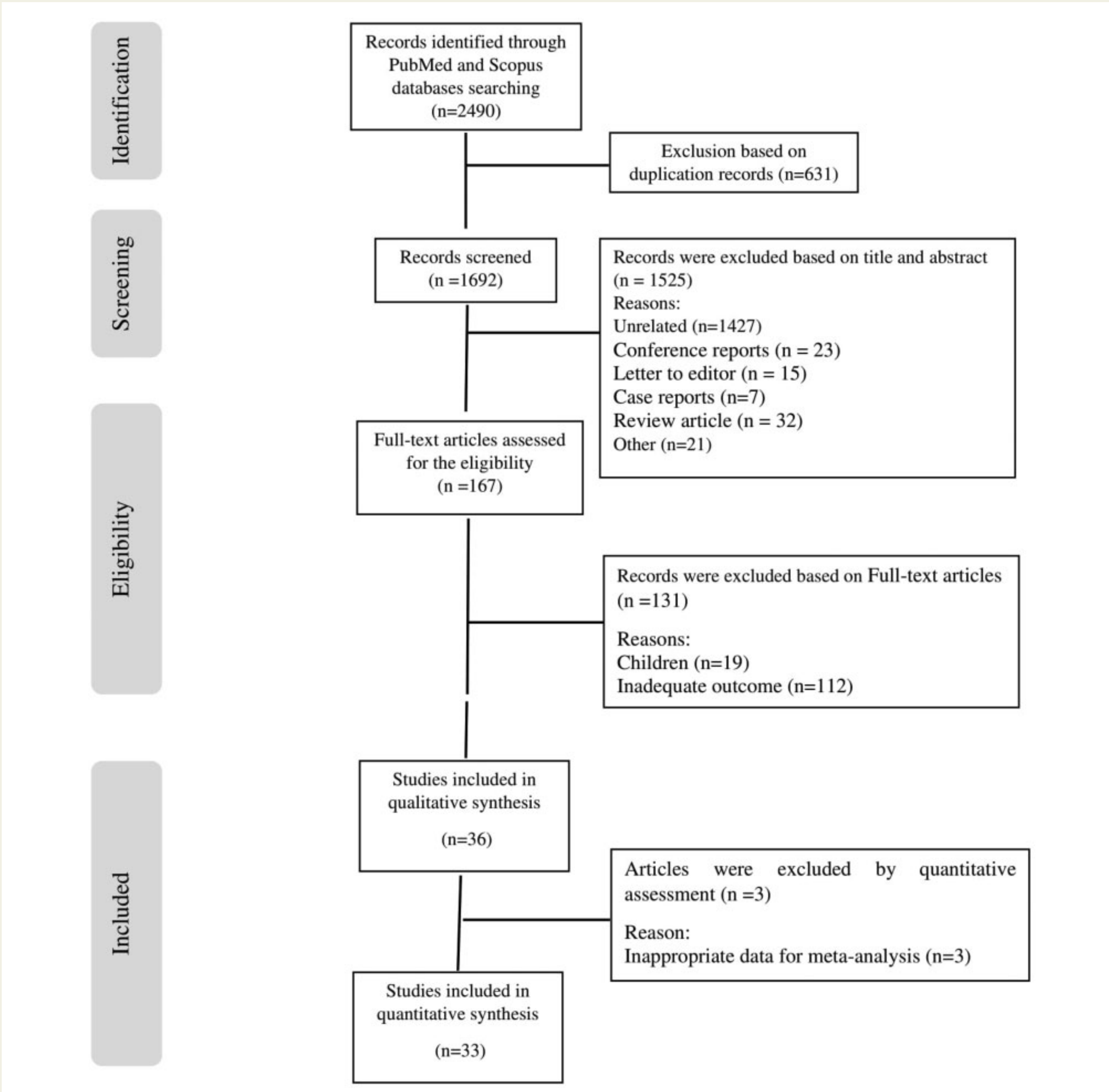

Figure 1 PRISMA flow diagram of study selection process.

assessment. Finally, 33 studies were included in the qualitative and quantitative synthesis.[5,9–12,15–42] The characteristics of the included studies were summarized in *Table 1*. All studies were used cross-sectional data and were published between 2003 and 2018. Studies were conducted in the USA[12,15–17,37] Brazil,[11,20,21] Middle East,[9,20–23] Asia,[5,11,16,23–30] and Europe.[31–34] Four studies[21,25,28,35] enrolled women, and 29 studies conducted in both genders. Participants of eight studies were unhealthy (having obesity, overweight, dyslipidaemia, or being HIV-infected adults), and other studies enrolled healthy subjects (without mentioned absolute disease). Approximately many studies measured NC at the mid-neck level just below the laryngeal prominence or Adam's apple, and there were no differences in measuring NC.

Correlation between neck circumference and total cholesterol

Correlation between NC and TC were pooled using a random-effects model. Results indicated a significant correlation between NC and TC [overall Fisher's $Z = 0.01$; 95% confidence interval (CI) = 0.06, 0.14]. High heterogeneity was found across the studies ($I^2 = 94.6\%$, $P < 0.001$). A subgroup analysis based on the gender (male or female), the region of study (Europe, Asia, Middle East, USA, or Brazil), and

Table 1 Description of the studies included in systematic review

First author (year)	Main study/ country	Subjects (M/F)	Race or ethnicity	Mean neck circumference ± SD (cm)	Reported or extracted data	Main findings
Androutsos (2011)	-/Greece	*N* = 324 (167/157)	European	30.7 ± 2.54/30.5 ± 2.25	Pearson correlation	NC: TC, HDL PC: LDL, TG Null: -
AOI (2014)	-/Japan	*N* = 64 (-/64)	Asian	33 ± 1.6	Pearson correlation	NC: TC, HDL PC: LDL, TG Null:-
AOI (2016)	-/Japan	*N* = 63 (-/63)	Asian	33 ± 1.9	Pearson correlation	NC: TC, HDL, LDL PC: TG Null:-
Assyov (2016)	-/Bulgaria	*N* = 255 (102/153)	European	41 ± 4//38 ± 3	Pearson correlation	NC: HDL PC: LDL, TG, TC Null: -
Stabe (2012)	-/Brazil	*N* = 8726 (3810/4916)	Brazil	37.4 ± 2.46/32.4 ± 2.24	Pearson correlation	NC: HDL PC: TG
Ben-Noun (2006)	-/Israel	*N* = 431 (187/244)	Middle east	38.9 ± 2.4/33.4 ± 2.3	Pearson correlation	NC: HDL PC: LDL, TG, TC Null: -
Ben-Noun (2003)	-/Israel	*N* = 561 (231/330)	Middle east	38.2 ± 2.734.2 ± 2.5	Pearson correlation	NC: HDL PC: LDL, TG, TC Null: -
Cho (2015)	-/Korea	*N* = 3521 (1784/1737)	Asian	37.6 ± 2/32.9 ± 1.8	Pearson correlation	NC: HDL PC: TG
Fantin (2017)	-/Italy	*N* = 95 (NR)	European	40.2 ± 4.14	Pearson correlation	NC: TC, HDL PC: LDL, TG Null:-
Gomez (2016)	-/Estonia	*N* = 669 (318/351)	European	11.52 ± 1.16/11.52 ± 1.16	Pearson correlation	NC: HDL PC: TG
Fitch (2011)	-/Massachusetts	*N* = 154 (NR)	USA	36.4 ± 0.3	Pearson correlation	NC: TC, HDL PC: LDL, TG Null:-
Goncalve (2014)	-/Brazil	*N* = 303 (152/151)	Brazil	44 ± 6/39 ± 7	Pearson correlation	NC: TC, HDL PC: LDL, TG Null:-
HE (2016)	/-Chinese	*N* = 255 (NR)	Asian	31.0 ± 3.0	Pearson correlation	PC: TG
Joshipura (2016)	-/USA	*N* = 1206 (-/1206)	USA	42.0 ± 4.8/36.1 ± 2.9	Pearson correlation	NC: HDL PC: TG
Küçük (2016)	-/Turkey	*N* = 100 (NR)	Middle east	39.4 ± 2.39	Pearson correlation	NC: LDL, HDL PC: TC, TG Null:-
Ya-Fang (2008)	-/Turkey	*N* = 1192 (934/978)	Middle east	38.8 ± 2.9/34.8 ± 2.75	Pearson correlation	NC: LDL, HDL PC: TC Null:-
Liu (2015)	-/Taiwan	*N* = 177 (125/52)	Asian	40 ± 3.3/35.6 ± 2.9	Pearson correlation	NC: HDL PC: LDL, TG, TC Null: -
Kurtoglu (2012)	-/Turkey	*N* = 164 (125/52)	Middle east	36 ± 5/34 ± 5.5	Pearson correlation	NC: HDL PC: TG
Lee (2017)	-/USA	*N* = 2756 (1501/1255)	Asian	34.08 ± 2.16/30.92 ± 2.25	Pearson correlation	NC: LDL, TG, TC, HDL
Li (2015)	-/China	*N* = 1905 (435/1470)	Asian	34.08 ± 2.16/30.92 ± 2.25		NC: HDL

Continued

Table 1 *Continued*

First author (year)	Main study/ country	Subjects (M/F)	Race or ethnicity	Mean neck circumference ± SD (cm)	Reported or extracted data	Main findings
					Pearson correlation	PC: LDL, TG, TC Null: -
Liang (2015)	-/China	N = 1905 (1008/701)	Asian	32.66 ± 2.3/37.71 ± 2.49	Pearson correlation	PC: TG, TC
Luo (2016)	-/China	N = 1160 (-/1160)	Asian	33.6 ± 2.4	Pearson correlation	NC: HDL PC: TG
Onat (2008)	-/Turkey	N = 1912 (934/978)	Middle east	38.8 ± 2.9/34.8 ± 2.75	Pearson correlation	PC: TG, TC
Ozkaya (2017)	-/Turkey	N = 164 (130/134)	Asian	40.6 ± 4.2/41.0 ± 4.6	Pearson correlation	NC: HDL PC: TG
Pokharel (2014)	-/Texas	N = 845 (NR)	USA	17 ± 1	Pearson correlation	NC: HDL PC: TG
Preis (2010)	/-Massachusetts	N = 3307 (1718/1589)	USA	40.5 ± 2.9/34.2 ± 2.8	Pearson correlation	NC: TC, HDL PC: LDL, TG Null:-
Lin (2018)	-/China	N = 1473 (569/904)	Asian	38.2 ± 2.7/34.2 ± 2.5	Pearson correlation	NC: HDL PC: LDL, TG, TC Null:-
Silva (2014)	-/Brazil	N = 109 (50/59)	Brazil	30.6 ± 4.0/32.8 ± 3.8	Pearson correlation	NC: TC, HDL PC: TG Null:-
Wang (2015)	/-China	N = 1047 (383/664)	Asian	39.7 ± 2.9/35.9 ± 2.8	Pearson correlation	NC: HDL
Selvan (2017)	-/India	N = 451 (258/193)	Asian	36.9 ± 7.5/34.1 ± 2.1	Pearson correlation	NC: HDL PC: LDL, TG, TC Null:-
Zhao (2018)	-/China	N = 9366 (3938/5428)	Asian	35.5 ± 17/32 ± 19	Pearson correlation	NC: HDL PC: LDL, TG, TC Null:-
Zhong (2017)	-/China	N = 2074 (965/1109)	Asian	37.81 ± 2.81/34.35 ± 2.75	Pearson correlation	PC: TG, TC
Zhou (2013)	-/China	N = 2074 (965/1109)	Asian	37.40 ± 2.46/32.46 ± 2.24	Pearson correlation	NC: HDL PC: LDL, TG, TC Null:-

NC, negative correlation; NR, not reported; Null, not correlation; PC, positive correlation; SD, standard deviation.

health status (healthy or unhealthy) was undertaken to detect potential sources of heterogeneity. As shown in *Figure 2A*, NC was positively correlated to TC in healthy (overall Fisher's $Z = 0.11$; 95% CI = 0.06, 0.17) and unhealthy (overall Fisher's $Z = 0.12$; 95% CI = 0.09, 0.15) men. Although between-study heterogeneity was significant in the healthy men ($I^2 = 92.6\%$, $P < 0.001$), it was attenuated in the unhealthy men ($I^2 = 0.0$; $P = 0.96$). Also, between subgroup heterogeneity was high ($P < 0.001$). Further subgroup analysis showed that NC was correlated to TC in the healthy women (overall Fisher's $Z = 0.10$; 95% CI = 0.01, 0.19). In contrast, there was no correlation between NC and TC in the unhealthy women (overall Fisher's $Z = 0.01$; 95% CI = -0.02, 0.03) (*Figure 2B*). However, heterogeneity was high in the healthy women ($I^2 = 96.9\%$, $P < 0.001$), but it was not significant in unhealthy women subgroup ($I^2 = 0.0$; $P = 0.47$). Also, between subgroup heterogeneity was high ($P < 0.001$). More subgroup analysis could not detect sources of heterogeneity (*Table 2*).

Correlation between neck circumference and low-density lipoprotein

The correlation between NC and LDL were pooled using a random-effects model. Results indicated a significant positive correlation

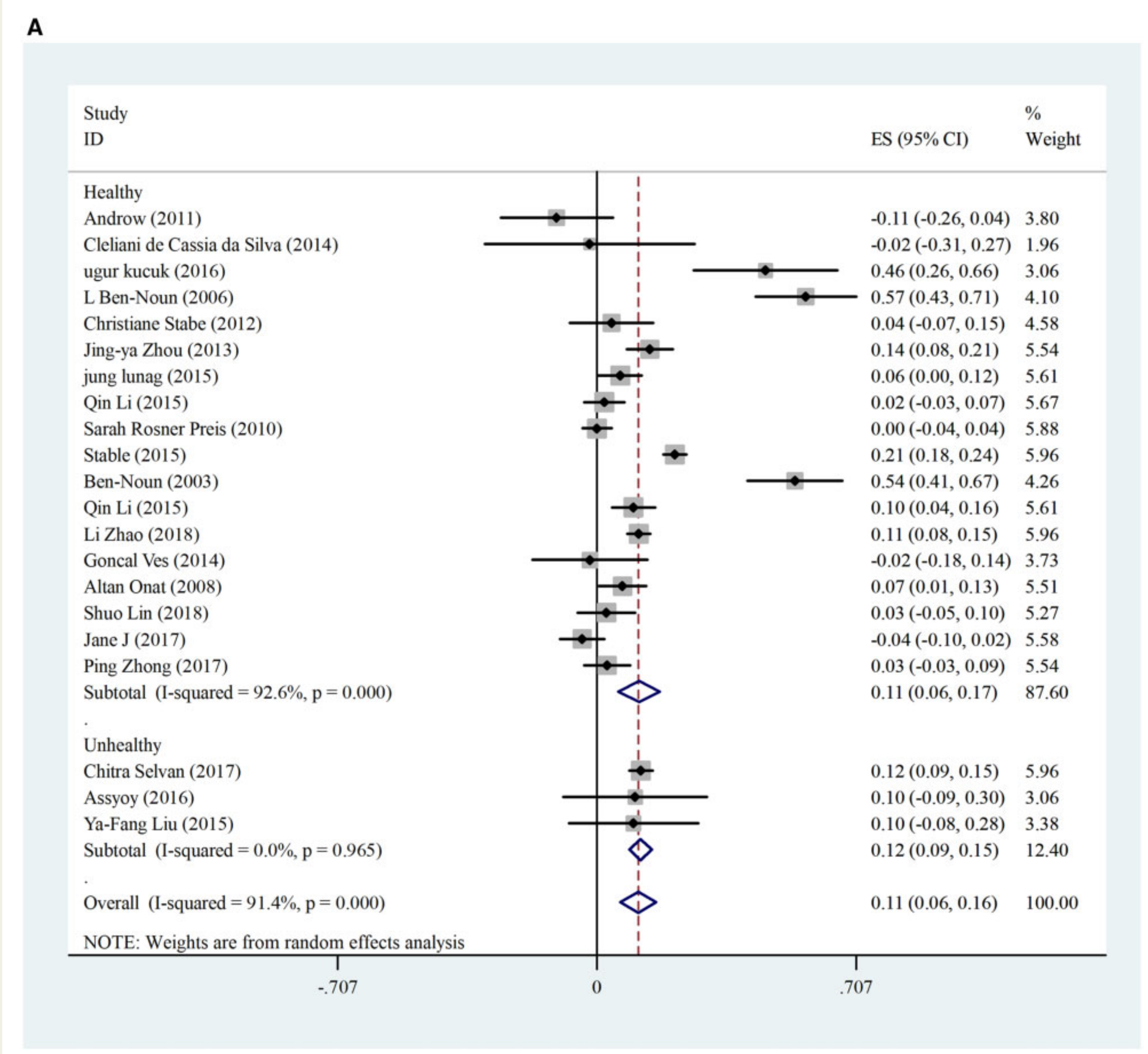

Figure 2 (*A*) Correlation between neck circumference and total cholesterol in men stratified by health status of subjects. (*B*) Correlation between neck circumference and total cholesterol in women stratified by health status of subjects.

between NC and LDL (overall Fisher's $Z = 0.08$; 95% CI = 0.03, 0.13). High heterogeneity was established among the studies ($I^2 = 94.6$; $P < 0.001$). A subgroup analysis based on the gender (male or female), the region of study (Europe, Asia, Middle East, USA, or Brazil), and the health status (healthy or unhealthy) was undertaken to detect potential sources of heterogeneity. As shown in *Figure 3A*, NC was positively correlated to LDL in healthy (overall Fisher's $Z = 0.09$; 95% CI = 0.02, 0.16) and unhealthy (overall Fisher's $Z = 0.1$; 95% CI = 0.04, 0.16) men. Significant heterogeneity was observed in the healthy men subgroup ($I^2 = 92.2\%$, $P < 0.001$). However, it was attenuated in the unhealthy men subgroup ($I^2 = 0.0$; $P = 0.73$). Also, between subgroup heterogeneity was high ($P < 0.001$). Further subgroup analysis showed that NC was not correlated to LDL in healthy women (overall Fisher's $Z = 0.05$; 95% CI = -0.7, 0.17). In contrast, there was a direct correlation between NC and LDL in unhealthy women subgroup (overall Fisher's $Z = 0.09$; 95% CI = 0.07, 0.11) (*Figure 3B*). Although a high between-study heterogeneity was found in the healthy women subgroup ($I^2 = 97.1\%$, $P < 0.001$), there

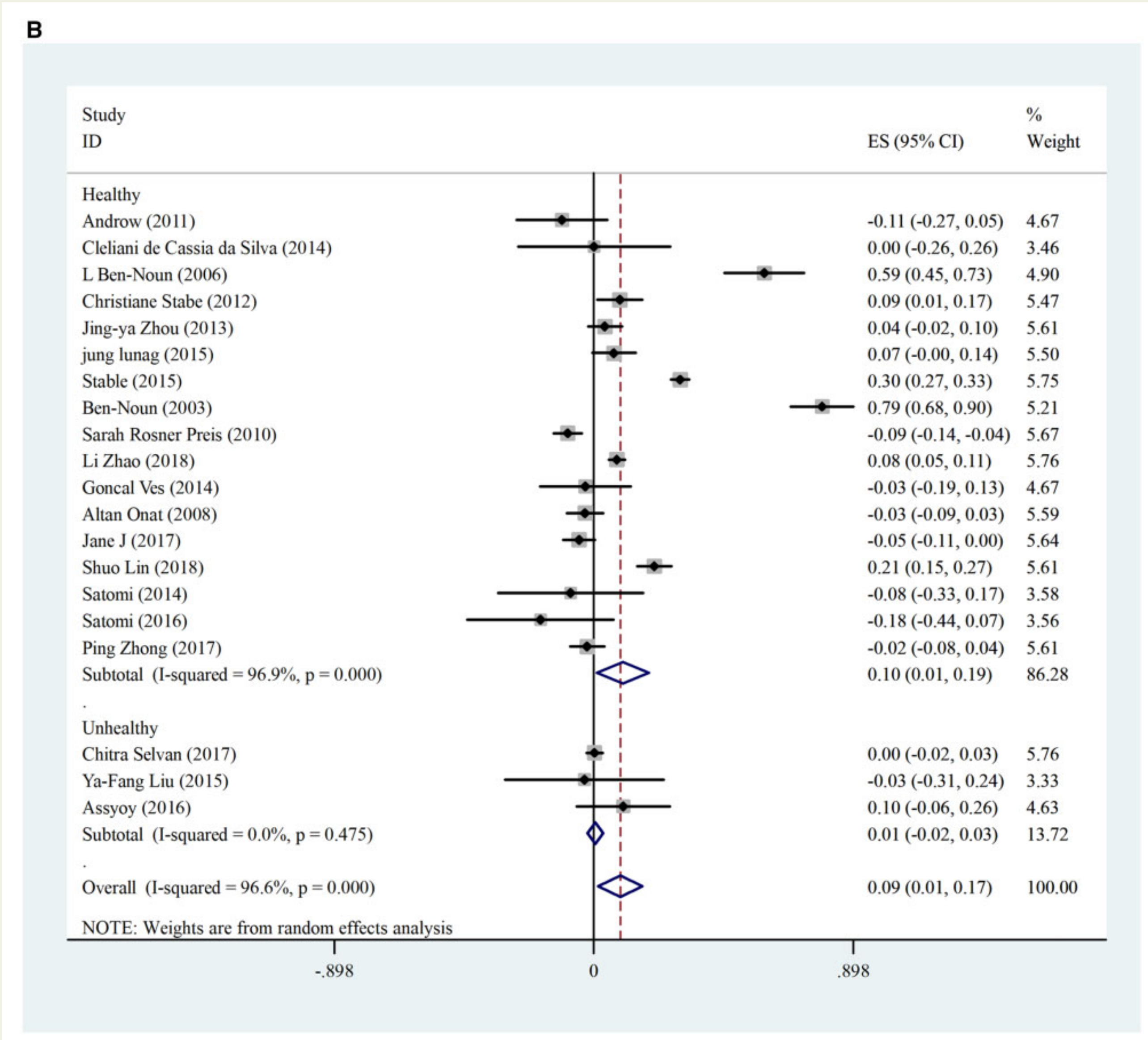

Figure 2 Continued.

was no heterogeneity in the unhealthy women subgroup ($I^2 = 0.0$; $P = 0.78$), also, between subgroup heterogeneity was high ($P < 0.001$). More subgroup analysis could not detect sources of heterogeneity (*Table 2*).

Correlation between neck circumference and high-density lipoprotein cholesterol

Reported correlations were pooled to examine the relationship between NC and HDL in adults. There was an overall significant relationship between NC and HDL in adults (overall Fisher's $Z = -0.18$; 95% CI: -0.21, -0.15). Significant heterogeneity was observed among the studies ($I^2 = 89.2$; $P < 0.001$). Therefore, we run a subgroup analysis according to the gender, health status, and the region of study to diminish observed heterogeneity. As shown in *Figure 4A*, pooled results showed that NC had an inverse correlation with HDL in the healthy (overall Fisher's $Z = -0.16$; 95% CI: -0.21, -0.11) and the unhealthy (overall Fisher's $Z = -0.32$; 95% CI: -0.36, -0.29) men. Heterogeneity was high in the healthy men subgroup ($I^2 = 91.2\%$; $P < 0.001$). In contrast, it was not significant in the unhealthy men subgroup ($I^2 = 0.0$; $P = 0.63$). Also, between subgroup heterogeneity was

Table 2 Subgroup analysis based on different potential sources of heterogeneity

Subgroup			Number of study	Effect size	I^2 (%)	P heterogeneity	P between subgroup heterogeneity
TC	—	—	49	0.01 (0.06, 0.14)	94.6	0.00	——
Overall (mg/dL)							
TC	Healthy/unhealthy	Healthy	18	0.11 (0.06, 0.17)	92.6	0.00	<0.001
Men (mg/dL)		Unhealthy	3	0.12 (0.09, 0.15)	0.0	0.965	
	Region	European	2	-0.11 (-0.22, 0.02)	64.9	0.09	<0.001
		Middle East	4	0.41 (0.11, 0.71)	96.0	0.000	
		Brazil	4	0.07 (-0.07, 0.22)	83.0	0.001	
		Asian	9	0.07 (0.03, 0.11)	79.3	0.000	
		USA	2	0.03 (0.03, 0.11)	67.2	0.081	
TC	Healthy/unhealthy	Healthy	17	0.10 (0.01, 0.19)	96.9	0.00	<0.001
Women (mg/dL)		Unhealthy	3	0.01 (-0.02, 0.03)	0.0	0.475	
	Region	European	2	-0.11 (-0.21, 0.2)	70.8	0.064	<0.001
		Middle East	3	0.45 (-0.12, 1.02)	0.99	0.00	
		Brazil	4	0.11 (-0.07, 0.28)	92.6	0.000	
		Asian	9	0.03 (-0.03, 0.08)	87.9	0.000	
		USA	2	-0.01 (-0.17, 0.14)	96.6	0.000	
TG	—	—	49	0.21 (0.17, 0.25)	94.6	0.000	—
Overall (mg/dL)							
TG	Healthy/unhealthy	Healthy	18	0.2 (0.13, 0.28)	96.0	0.000	<0.001
Men (mg/dL)		Unhealthy	5	0.34 (0.27, 0.41)	27.2	0.240	
TG	Region	European	3	0.14 (0.05, 0.24)	20.8	0.283	<0.001
Women (mg/dL)		Middle East	5	0.40 (0.27, 0.52)	62.7	0.030	
		Brazil	3	0.03 (-0.06, 0.12)	0.0	0.500	
		Asian	10	0.21 (0.10, 0.31)	97.8	0.000	
		USA	2	0.28 (0.21, 0.35)	70.9	0.000	
	Healthy/unhealthy	Healthy	17	0.23 (0.18, 0.28)	89.4	<0.001	<0.001
		Unhealthy	5	0.21 (0.1, 0.33)	67.9	<0.05	
	Region	European	3	0.14 (-0.01, 0.30)	73.1	0.024	<0.001
		Middle East	4	0.23 (-0.02, 0.49)	91.3	0.000	
		Brazil	3	0.02 (-0.21, 0.25)	85.6	0.001	
		Asian	10	0.25 (0.19, 0.13)	92.2	0.000	
		USA	2	0.36 (0.25, 0.47)	82.9	0.016	
LDL-C	—	—	35	0.08 (0.03.0.13)	94.6	0.000	—
Overall (mg/dL)							
LDL-C	Healthy/unhealthy	Healthy	5	-3.44 (-11.12, 4.23)	62.3	0.03	0.004
Men (mg/dL)		Unhealthy	3	-3.89 (-12.31, 4.53)	85.4	0.001	
	Region	European	2	0.02 (-0.12, 0.15)	30.1	0.232	<0.001
		Middle East	3	0.25 (-0.18, 0.69)	98.3	0.000	
		Brazil	2	-0.01 (-0.14, 0.13)	0.0	0.665	
		Asian	8	0.07 (0.04, 0.10)	54.1	0.033	
LDL-C	Healthy/unhealthy	Healthy	4	-3.18 (-11.30, 4.95)	77.3	0.004	<0.001
Women (mg/dL)		Unhealthy	2	0.09 (-7.47, 7.65)	75.1	0.04	
	Region	European	2	-0.05 (-12.39, 0.15)	30.1	0.232	<0.001
		Middle East	3	0.25 (-0.18, 0.69)	98.3	0.00	
		Brazil	2	-0.01 (-0.14, 0.13)	0.0	0.665	
		Asian	10	0.07 (0.04, 0.10)	54.1	0.033	

Continued

Table 2 *Continued*

Subgroup			Number of study	Effect size	I^2 (%)	P heterogeneity	P between subgroup heterogeneity
HDL-C Overall (mg/dL)	—	—	51	-0.18 (-0.21, -0.15)	89.2	0.000	—
HDL-C Men (mg/dL)	Healthy/unhealthy	Healthy	19	3.36 (-0.96, 7.68)	91.2	0.000	<0.001
		Unhealthy	5	-3.17 (-2.24, -8.58)	0.0	0.632	
	Region	European	3	-0.11 (-0.28, 0.05)	73.3	0.024	<0.001
		Middle East	6	-0.17 (-0.28, -0.06)	74.6	0.001	
		Brazil	4	-0.31 (-0.34, -0.28)	0.1	0.391	
		Asian	10	-0.17 (-0.24, -0.10)	92.5	0.000	
		USA	1	-0.29 (-0.33, -0.25)	—	—	
HDL-C Women (mg/dL)	Healthy/unhealthy	Healthy	19	-0.15 (-0.20, -0.10)	88.7	0.00	0.005
		Unhealthy	5	-0.27 (-0.36, -0.17)	86.7	0.00	
	Region	European	3	-0.04 (-0.12, 0.04)	0.0	0.499	<0.001
		Middle East	5	-0.16 (-0.23, -0.09)	41.3	0.164	
		Brazil	4	-0.25 (-0.28, -0.22)	0.0	0.899	
		Asian	10	-0.2 (-0.27, -0.14)	85.6	0.000	

high ($P < 0.001$). In women, NC was inversely correlated to HDL in the healthy (overall Fisher's $Z = -0.15$; 95% CI: -0.20, -0.10) and unhealthy (overall Fisher's $Z = -0.27$; 95% CI: -0.36, -0.17) subgroups (*Figure 4B*). Subgroup analysis could reduce the degree of heterogeneity in the unhealthy subgroup ($I^2 = 41.7$; $P = 0.14$) but not in the healthy subgroup ($I^2 = 88.7$; $P < 0.001$). Also, between subgroup heterogeneity was high ($P < 0.001$). Subgroups analysis based on the region of study suggested that studies conducted in the Middle East (overall Fisher's $Z = -0.16$; 95% CI: -0.23, -0.09) and Asian (overall Fisher's $Z = -0.2$; 95% CI: -0.27, -0.14) regions reported an indirect association between NC and HDL concentration (*Figure 4C*). In contrast, studies conducted in European countries reported an insignificant correlation coefficient between NC and HDL (overall Fisher's $Z = -0.04$; 95% CI: -0.12, 0.04). Between-study heterogeneity was attenuated in all subgroups except for Asia. Also, between subgroup heterogeneity was high ($P < 0.001$). More subgroup analysis could not detect sources of heterogeneity (*Table 2*).

Correlation between neck circumference and triglyceride

The correlation between NC and TG were pooled using a random-effects model. The pooled data revealed a significant correlation between NC and TG (overall Fisher's $Z = 0.21$; 95% CI = 0.17, 0.25). High heterogeneity was recognized among the studies ($I^2 = 94.6$; $P < 0.001$). Subgroup analysis was performed according to health status, region, and gender to identify the source of heterogeneity. As shown in *Figure 5*, there was a significant correlation between NC and TG in the healthy (overall Fisher's $Z = 0.20$; 95% CI: 0.13, 0.28) and unhealthy (overall Fisher's $Z = 0.34$; 95% CI: 0.27, 0.41) men. However, a high degree of heterogeneity was observed in the healthy men subgroup ($I^2 = 96\%$; $P < 0.001$), and it was attenuated in unhealthy men subgroup ($I^2 = 27.2$; $P = 0.24$). We could not found other sources of heterogeneity by further subgroup analysis (*Table 2*).

Sensitivity analysis and publication bias

According to the sensitivity analysis, the results of the study were not impressed by any article. There were no evidences of publication bias for studies examining the association between NC, LDL ($P = 0.317$ for Begg's test and $P = 0.669$ for Egger's test), HDL ($P = 0.922$ for Begg's test and $P = 0.03$ for Egger's test), TC ($P = 0.563$ for Begg's test and $P = 0.944$ for Egger's test), and TG ($P = 0.859$ for Begg's test and $P = 0.993$ for Egger's test).

Discussion

The current meta-analysis indicated that there was an inverse correlation between NC and HDL-C. Furthermore, we found positive associations between NC and TC, LDL-C, and TG in men. NC was directly correlated to TC and LDL-C in healthy and unhealthy women, respectively. There was no correlation between NC, and serum concentration of TC and LDL-C in unhealthy and healthy women, respectively. To the best of our knowledge, this is the first systematic review and meta-analysis, which provided a quantitative estimate of the correlation between NC and lipid profile by control of between-study heterogeneity.

Recently, published systematic review and meta-analysis reported an association between NC and metabolic syndrome components, including dyslipidaemia.[43] Although the results of the mentioned

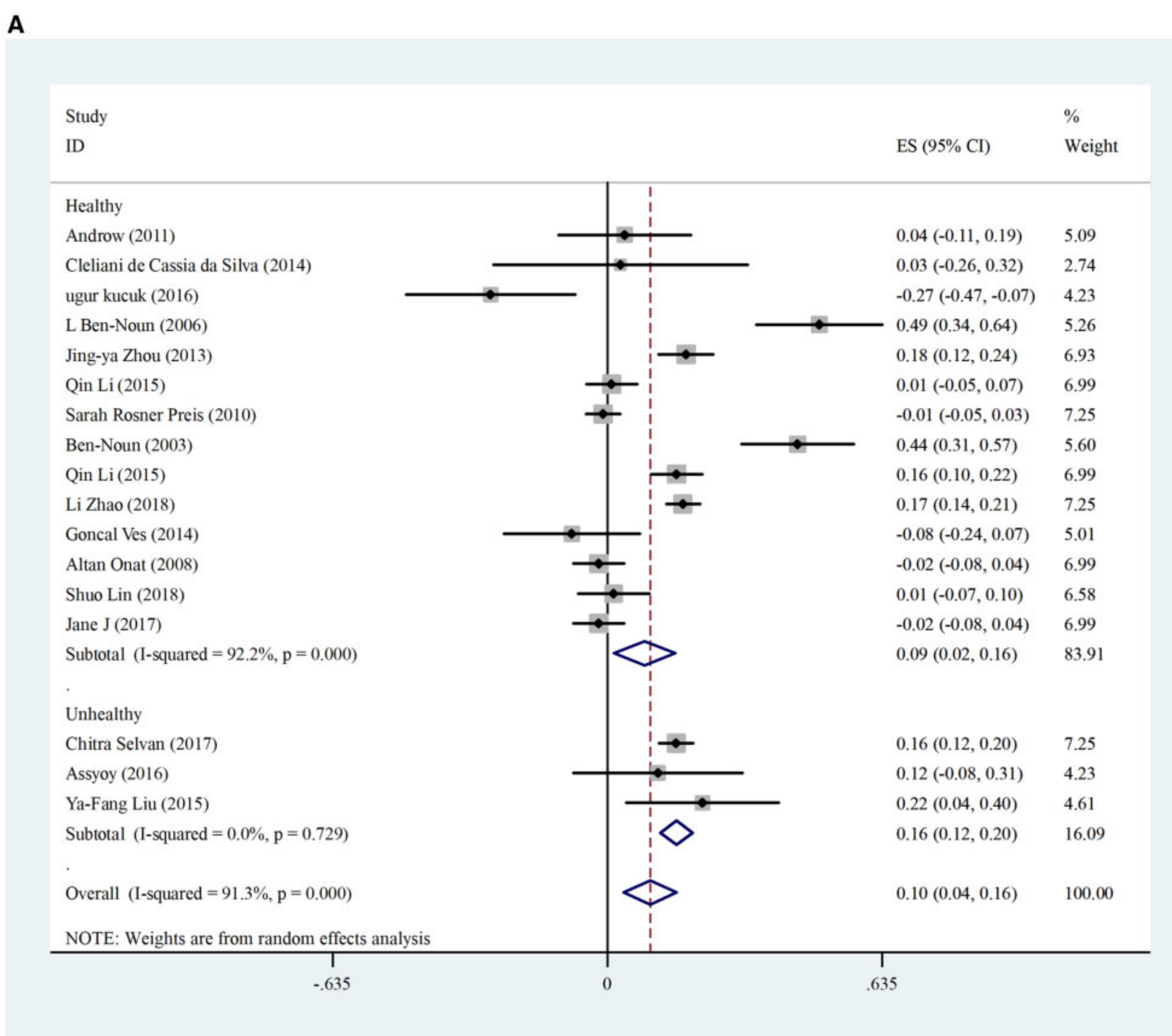

Figure 3 (*A*) Correlation between neck circumference and low-density lipoprotein cholesterol in men stratified by health status of subjects. (*B*) Correlation between neck circumference and low-density lipoprotein cholesterol in women stratified by health status of subjects.

study were partially similar to our findings, the quality of results was suffering from several limitations. The most important limitation was publication bias due to missing several studies.[6,8,21,22,25,27,32,33,42] Moreover, potential sources of heterogeneity did not detect. In contrast, we conducted a comprehensive subgroup analysis to find sources of heterogeneity and observed that gender and health status were two significant sources of heterogeneity.

Although we found that NC was indirectly associated with HDL-C in both genders, the correlation was more robust among unhealthy subjects compared than healthy individuals. Accumulation of adipose tissue in the upper body is associated with the risk of cardiovascular disease, insulin resistance, and type 2 diabetes mellitus.[44] Furthermore, fat accumulation in the lower body (gluteofemoral obesity) showed an opposite association with the risk of cardiovascular disease and type 2 diabetes.[45] Therefore, we suggest that future studies focus on upper to lower body fat ratio to evaluate body fat distribution.

Although region was a heterogeneity source between studies that reported the association between NC and HDL-C among women, subgroup analysis based on the region could not attenuate heterogeneity between men's studies. Evidence has shown that low HDL-C concentration is more prevalent in the Middle East than Europe.[46]

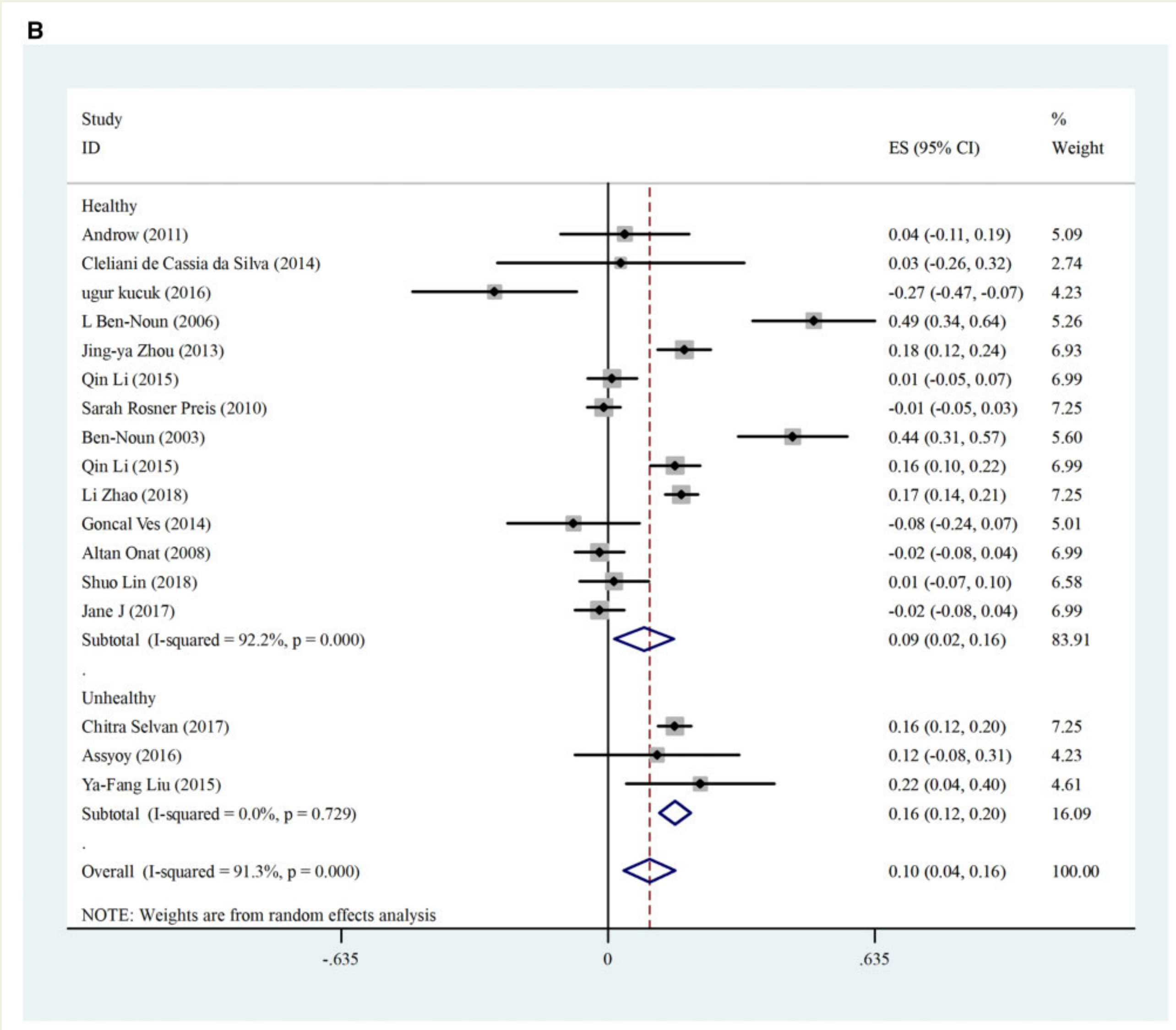

Figure 3 Continued.

Therefore, genetic variation influences on HDL-C concentration. In addition to the region, sex-related genetic variation may effect on HDL-C level.[47] Reports from different regions showed that women had a higher concentration of HDL-C than men.[32]

Furthermore, the response of men and women to treatment of dyslipidaemia is different and, the prevalence of low HDL-C in obese women was higher compared with obese men.[48] Therefore, HDL-C concentration may be affected by an interaction between gene, sex, and obesity. Also, we found that the NC was inversely related to HDL-C in Middle East women. In contrast, this relationship was not significant in European women. Therefore, the pattern of the association between NC and HDL-C may be different in various populations. So, it is assumed that NC cut-off point for cardiovascular disease may differ across various populations.

We established a significant relationship between LDL-C and NC. The association was stronger among unhealthy subjects compared with healthy individuals in both genders. It is well known that, NC is positively related to central obesity,[49] and the prevalence of central obesity in insulin-resistant conditions is higher than the general population.[50] Furthermore, in central obesity-induced insulin-resistant, dyslipidaemia is characterized by a different composition and distribution of LDL particles, results in an increased concentration of small and dense LDL.[51] This mechanism links upper-body obesity to cardiovascular disease indicators, such as LDL. Nevertheless, we recommend that the relationship between NC and other components of

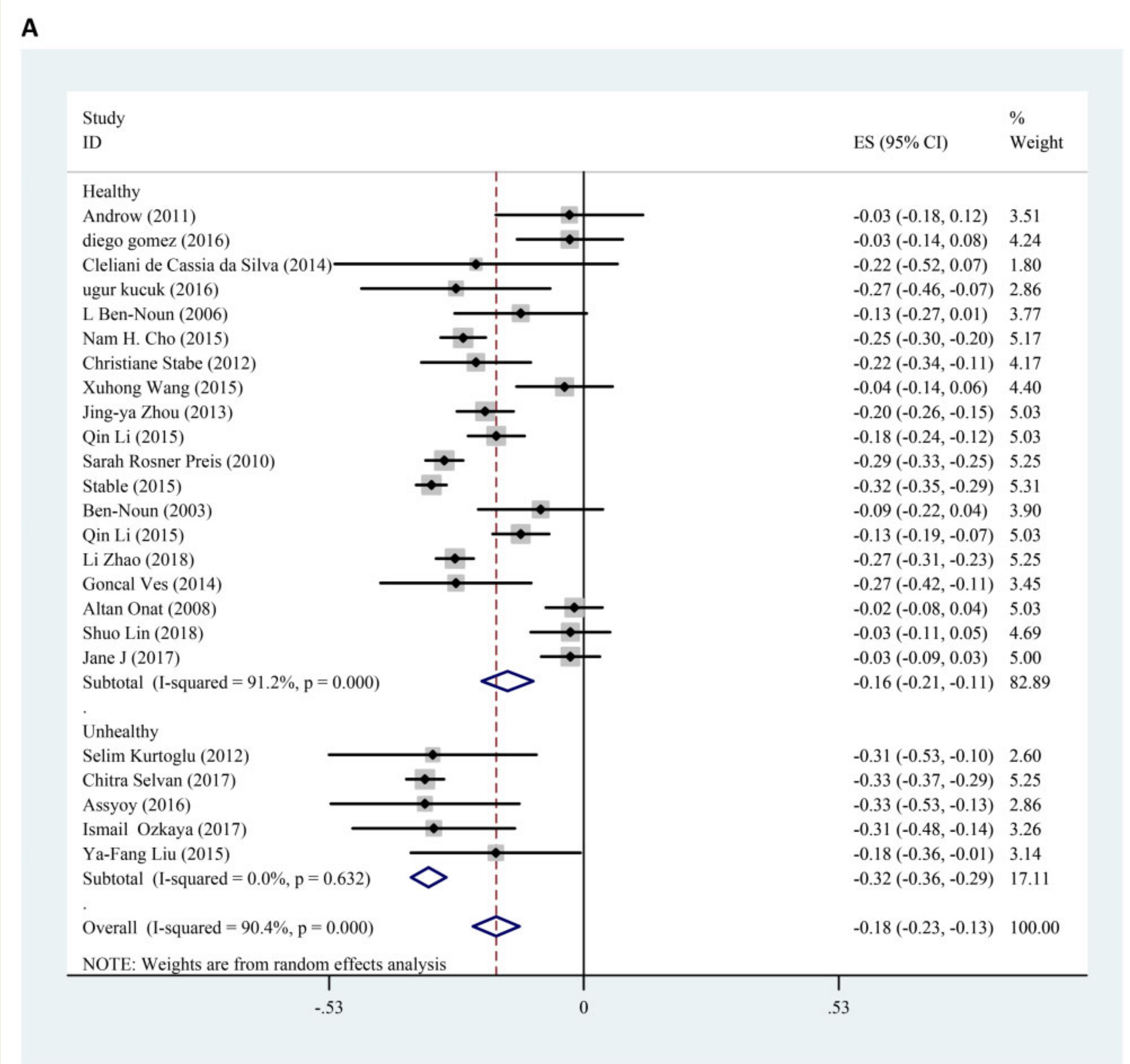

Figure 4 (*A*) Correlation between neck circumference and high-density lipoprotein cholesterol in men stratified by health status of subjects. (*B*) Correlation between neck circumference and high-density lipoprotein cholesterol in women stratified by health status of subjects. (*C*) Correlation between neck circumference and high-density lipoprotein cholesterol in women stratified by residential region.

cardiovascular diseases, such as endothelial dysfunction and blood pressure will be measured in other systematic reviews.

We demonstrated that NC was closely correlated to TC in unhealthy men compared with healthy men. Higher NC is positively correlated to metabolic syndrome factors due to impaired fatty acid utilization in these patients.[52] However, these findings highlight the importance of anthropometric assessment in subjects with a high risk of coronary artery disease to identify those who might benefit from clinical interventions.

The association between NC and TC levels in unhealthy women was different from the unhealthy men. Therefore, gender can be a factor that affects the association between NC and TC. On the other hand, it appears that TC to HDL-C ratio may a better risk factor than TC or HDL in women.

B

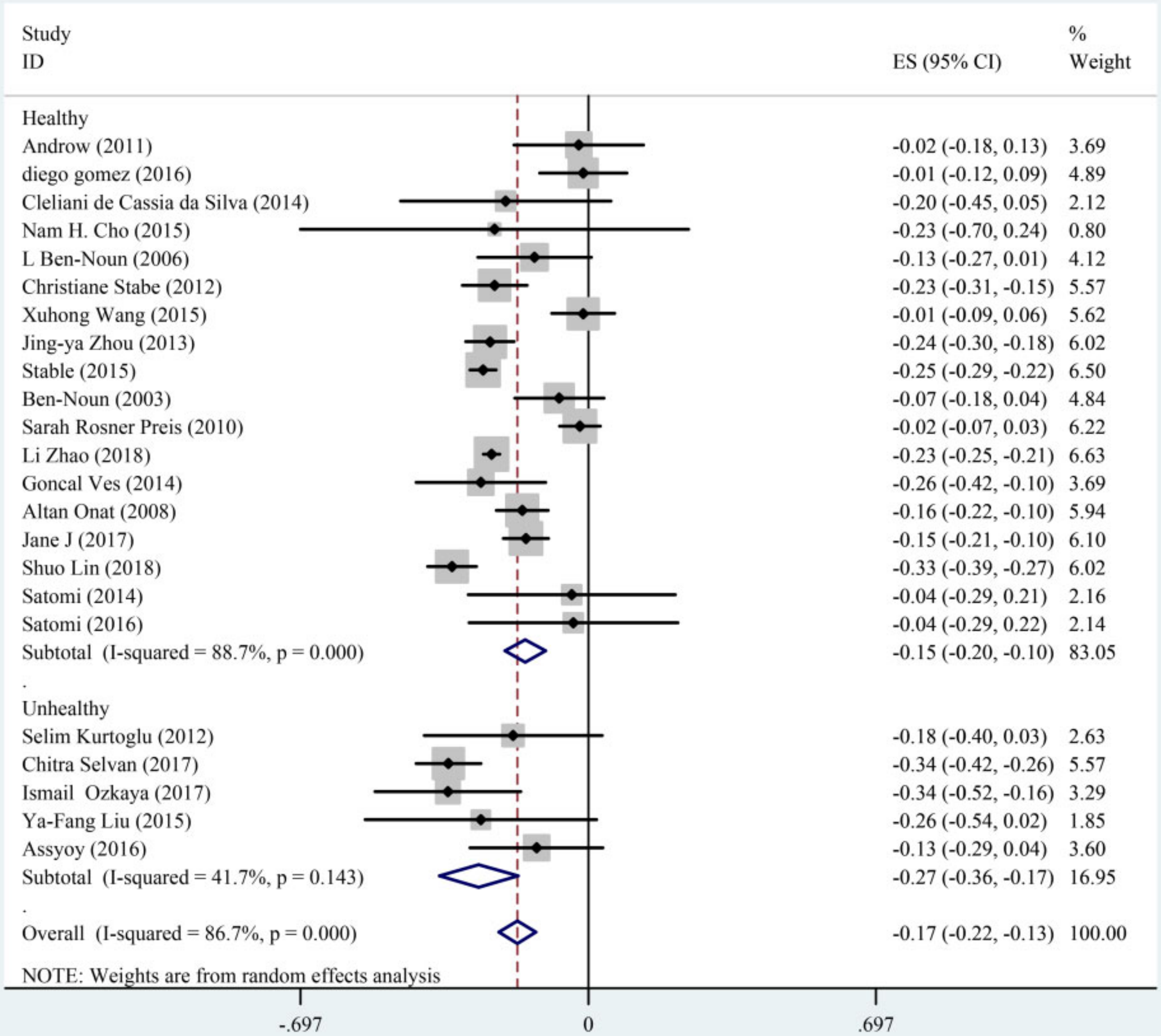

Figure 4 Continued.

Although our study findings revealed a significant correlation between NC and TG, this relationship was stronger among unhealthy men compared with healthy men. Previous studies declared that upper body adipose tissue is more closely associated with high fasting TG and insulin levels, and with low HDL cholesterol in men.[53] Therefore, NC as an indicator of upper body adipose tissue, can be a predictor of dyslipidaemia, especially in men. This relationship between NC and TG did not observe in women. Since both premenopausal and menopausal women were included in our study, hormonal changes could affect findings. A large population study that enrols both premenopausal and menopausal women is needed to investigate these relationships accurately.

It should be noted that neck adipose tissue's precise biological mechanisms on metabolic abnormality are not fully understood. However, previous studies indicated a positive correlation of NC with visceral fat accumulation (using computed tomography and magnetic resonance imaging assessment) closely related to clustering cardiometabolic risk factors.[54,55] Additionally, it is supposed that the neck fat tissue as an ectopic fat can

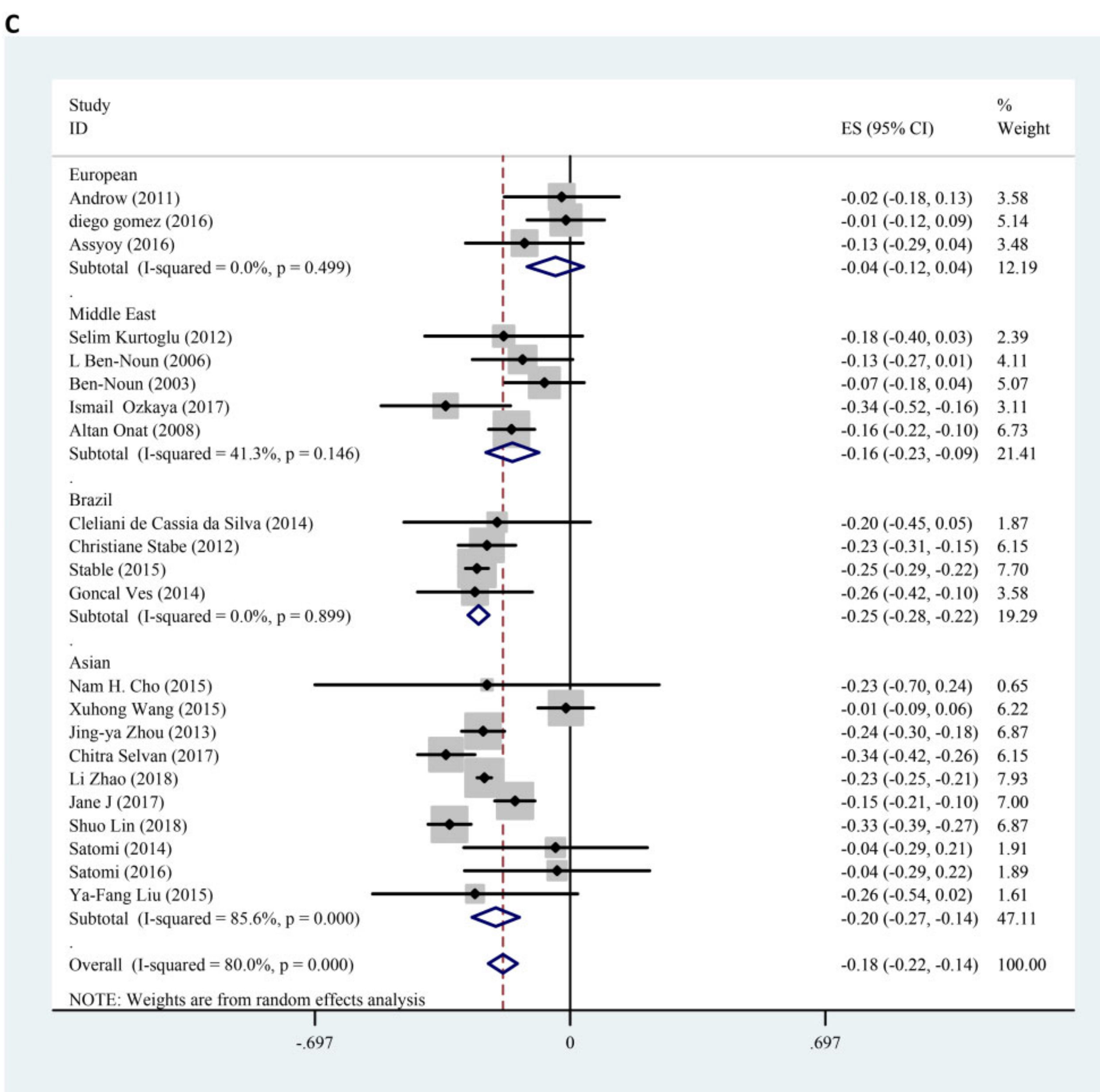

Figure 4 Continued.

secrete various adipokines, leading to metabolic stimulation abnormality.[56]

Some limitations of the present meta-analysis should be discussed. (i) A significant statistical heterogeneity was observed between the studies. However, we run a comprehensive subgroup analysis to find the potential sources of heterogeneity. (ii) Although several studies reported a correlation between NC and lipid profile, heterogeneity was considerably high and was not attenuated after subgroup analysis in a healthy population. (iii) There are few studies to determine the association between NC and lipid profiles in different diseases. (iv) Since this study is not an original article, we typically applied the previously reported data of the eligible studies. And, they did not determine the cut-off point, and consequently, we could not identify the cut-off for neck circumference regarding association with lipid profile. Finally, evaluating the association of the neck circumference ratio with lipid profiles could identify cardiovascular disease risk. Also, the cut-off point for the novel use of this index, neck circumference, should be further investigated.

Conclusion

Higher NC in unhealthy men was strongly indirectly associated with HDL-C and directly related to LDL-C, TG, and TC. In unhealthy

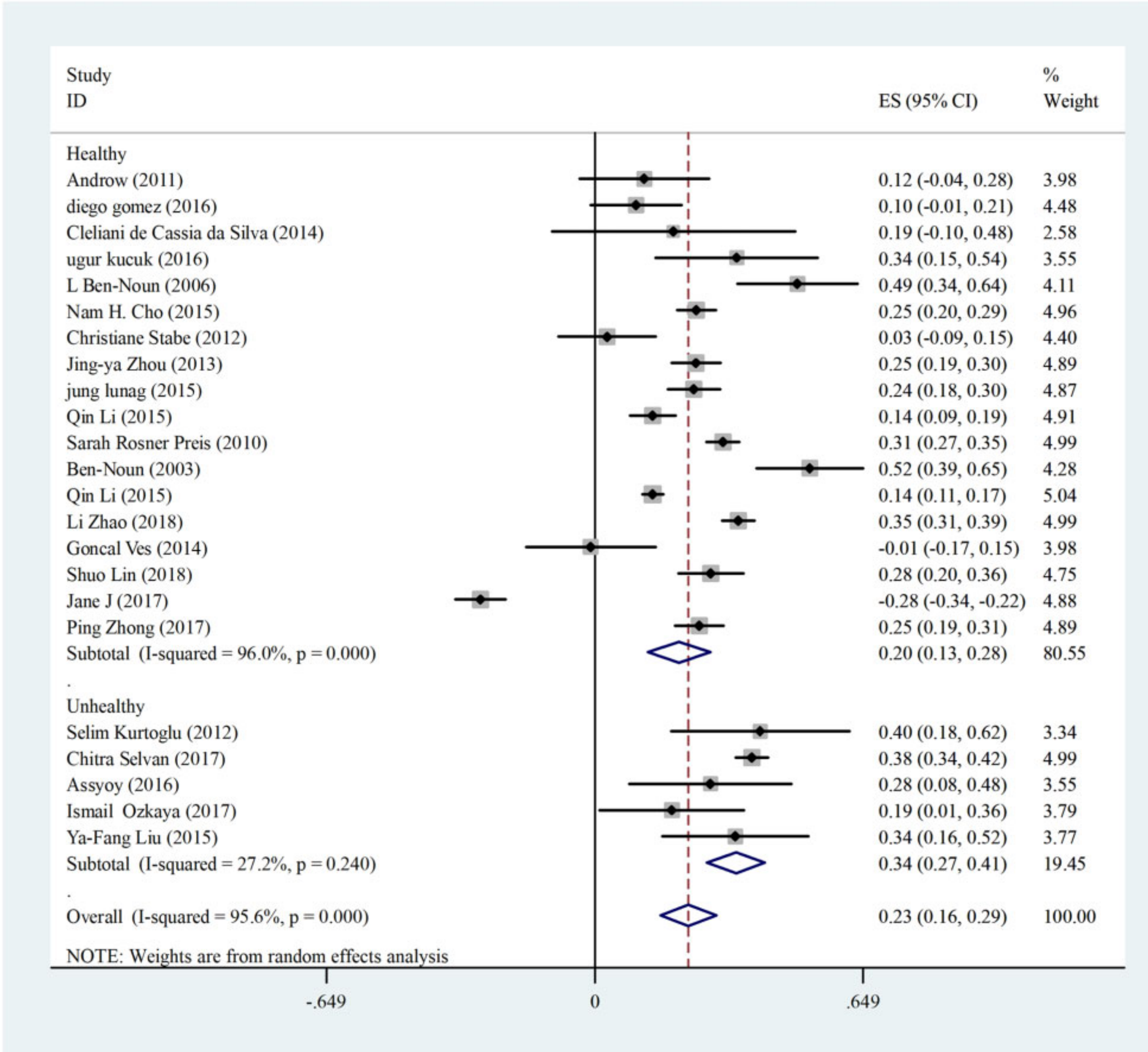

Figure 5 Correlation between neck circumference and triglyceride in men stratified by health status of subjects.

women, higher NC was inversely associated with HDL and directly related to LDL-C.

Conflict of interest: none declared.

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