doi: 10.1111/obr.12003

Etiology and Pathophysiology

Obesity and C-reactive protein in various populations: a systematic review and meta-analysis

J. Choi[1], L. Joseph[1,2] and L. Pilote[1,2,3]

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada; [2]Division of Clinical Epidemiology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada; [3]Division of General Internal Medicine, McGill University Health Centre, McGill University, Montreal, Quebec, Canada

Received 11 September 2012; revised 9 October 2012; accepted 16 October 2012

Address for correspondence: Dr L Pilote, Division of Clinical Epidemiology, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.
E-mail: louise.pilote@mcgill.ca

Summary

Obesity has been associated with elevated levels of C-reactive protein (CRP), a marker of inflammation and predictor of cardiovascular risk. The objective of this systematic review and meta-analysis was to estimate the associations between obesity and CRP according to sex, ethnicity and age. MEDLINE and EMBASE databases were searched through October 2011. Data from 51 cross-sectional studies that used body mass index (BMI), waist circumference (WC) or waist-to-hip ratio (WHR) as measure of obesity were independently extracted by two reviewers and aggregated using random-effects models. The Pearson correlation (*r*) for BMI and ln(CRP) was 0.36 (95% confidence interval [CI], 0.30–0.42) in adults and 0.37 (CI, 0.31–0.43) in children. In adults, *r* for BMI and ln(CRP) was greater in women than men by 0.24 (CI, 0.09–0.37), and greater in North Americans/Europeans than Asians by 0.15 (CI, 0–0.28), on average. In North American/European children, the sex difference in *r* for BMI and ln(CRP) was 0.01 (CI, –0.08 to 0.06). Although limited to anthropometric measures, we found similar results when WC and WHR were used in the analyses. Obesity is associated with elevated levels of CRP and the association is stronger in women and North Americans/Europeans. The sex difference only emerges in adulthood.

Keywords: C-reactive protein, meta-analysis, obesity, sex differences.

obesity reviews (2012)

Introduction

The obesity epidemic affects approximately a third of all North Americans and has become a leading health concern due to its link to cardiovascular disease (CVD) in both children and adults (1). Numerous pathophysiological mechanisms linking obesity and cardiovascular risk have been postulated (2). Recently, inflammation has been understood to be a key pathogenic mechanism in the initiation and progression of CVD (3), and great attention has been given to inflammatory markers for their ability to predict CVD risk (4). Among these, C-reactive protein (CRP) has emerged as a powerful marker. In an individual participant meta-analysis, every 1-SD increase in CRP was shown to increase vascular risk by more than 60% (5).

Obesity has been linked to CRP in a large number of cross-sectional studies as well as a narrative review (6). Varying degrees of association between obesity and CRP have been noted in populations of different sex, ethnicity and age. To date, no systematic review or meta-analysis has accumulated the evidence to assess such association according to population characteristics. In this systematic review and meta-analysis, we aim to determine and assess the association between obesity and CRP in the general adult and child populations and the subpopulations of males, females, North Americans/Europeans and Asians.

Methods

Data sources and searches

In 5 October 2011 we searched MEDLINE and EMBASE for cross-sectional studies of obesity and CRP, using the text words and MeSH terms 'C-reactive protein', 'CRP', 'body mass index', 'BMI', 'waist circumference', 'WC', 'waist-hip ratio', 'WHR', 'overweight' and 'obesity'. Searches in Google Scholar and references of retrieved articles were also conducted. We limited our search to studies written in English, and published between 1966 and 2011 (Appendix Table A1).

Study selection

We included studies if they met all of the following criteria (i) cross-sectional study; (ii) primary objective is to assess association between obesity and CRP; (iii) observe the general population; (iv) use at least one of body mass index (BMI), waist circumference (WC) or waist-hip ratio (WHR) as measure of obesity and (v) provide correlation coefficients or odds ratios (ORs) as effect measure. For those studies that presented analyses on a common database, only one study with the largest sample size and highest quality was included for review (Fig. 1).

Data extraction and quality assessment

The final set of articles was assessed independently by two reviewers. Disagreements were resolved by consensus, or, when necessary, by a third reviewer. Reviewers extracted information on author's names, year of publication, study design, study setting, and number of male and female participants. Extracted baseline participant characteristics included sex, age, ethnicity, mean BMI, WC, WHR, CRP, prevalence of obesity and prevalence of elevated CRP. Outcomes data presented as Pearson or Spearman correlation coefficients or ORs were also extracted. Sex-specific data were collected wherever available. Information on logarithmic transformation of CRP ($\log_{10}$, $\log_e$ or unknown), measurement of high-sensitivity CRP (yes, no or unknown) and type of assay used were also collected. Quality assessment was conducted using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies (7) to reduce the risk of bias of individual studies. Studies that failed to meet any of the checklist items were excluded from analysis (Fig. 1).

Data synthesis and analysis

We conducted separate reviews for the eligible studies grouped according to effect measure (OR, Pearson or Spearman coefficient), measure of obesity (BMI, WC or WHR), sex (male or female), age group (children or adults) and ethnicity (North American/European or Asian). For studies reporting ORs, we further grouped studies of similar cut-off values for elevated CRP levels and obesity. For studies reporting Pearson or Spearman correlation coefficients, we further grouped studies according to the logarithmic transformation of the CRP variable ($\log_{10}$, $\log_e$ or unknown).

We synthesized the results of included studies using random-effects meta-analyses, and results are presented as correlation coefficients with corresponding 95% confidence intervals (CIs). Meta-regression models of Pearson coefficients assessed the association between each of BMI, WC and WHR with CRP by including sex (male or female) and ethnicity (North American/European or Asian) of study subjects as categorical moderators. In addition to meta-regression, we conducted subgroup analyses in sex and ethnicity-specific subgroups with at least three studies.

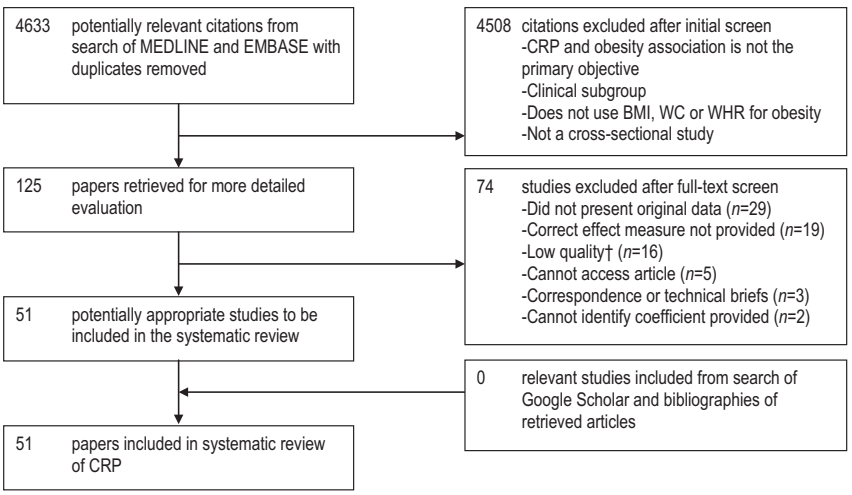

Figure 1 Study selection process and reasons for exclusion of studies. BMI, body-mass index; CRP, C-reactive protein; WC, waist circumference; WHR, waist-to-hip ratio. †Low quality studies defined as failing to meet the following STROBE criteria: data sources/measurements ($n = 5$), objectives ($n = 4$), statistical methods ($n = 3$), participants ($n = 2$), main results ($n = 1$), limitations ($n = 1$).

Fisher's r-to-z transformation of Pearson coefficients was conducted to obtain variance-stabilized correlation coefficients. The transformed Pearson coefficients were used in meta-regression and subgroup analysis. Pooled correlation coefficients were transformed back to the raw scale for presentation. Meta-analysis for Spearman coefficients was not possible because their sampling variances could not be deduced from the data provided in studies.

We reported effect measures in tables as part of our systematic review. We classified non-adjusted ORs and ORs adjusting exclusively for age and/or sex as 'least adjusted'. In contrast, ORs adjusting for any other cardiovascular risk factor were classified as 'most adjusted'. All statistical analyses were conducted using R software version 2.14 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Search results and study inclusion

A total of 4,633 potentially relevant abstracts were identified in our initial literature search (Fig. 1). Of these abstracts, the full-length papers of 125 studies were retrieved and assessed for eligibility. A total of 51 studies met our inclusion criteria and were included in our review. The remaining 74 studies were excluded either because they did not present original data ($n = 29$), did not provide one of our predetermined effect measures ($n = 19$), were low quality according to STROBE criteria ($n = 16$), were not accessible ($n = 5$), were correspondences or technical briefs ($n = 3$) or did not identify the correlation coefficient reported as Pearson or Spearman ($n = 2$). Studies that did not meet STROBE criteria were either lacking description of data sources or methods of variable measurement ($n = 5$), study objectives ($n = 4$), statistical methods ($n = 3$), eligibility criteria or methods used for participant selection ($n = 2$), main study results ($n = 1$) or study limitations ($n = 1$). No additional studies were identified through our search of Google Scholar and references of retrieved studies.

Appendix Table A2 summarizes the study population characteristics from all included studies. Studies were published since 1999 and had sample sizes ranging from 83 to 27,158. Of the 51 studies, 45 used BMI, 25 used WC and 15 used WHR as measure of obesity to assess the association with CRP. Many studies followed specific subpopulations, accounting for much of the variability. In particular, 34 studies provided sex-specific effect measures of 51,777 males and 84,601 females, 24 studies observed 78,444 North American/Europeans (American, Australian, Canadian, Dutch, French, German, Greek, Italian, Spanish and Welsh), 19 studies observed 59,040 Asians (Chinese, Filipino, Indian, Japanese, Korean, Mongolian, Siberian and Taiwanese) and 12 studies focused on 14,687 children.

High-sensitivity CRP was measured in all studies using an immunoassay test. Nineteen studies used immunonephelometry, 19 used immunoturbidimetry, 9 used enzyme-linked immunosorbent assay, 3 used chemi-illuminescence immunoassay and 1 used immunoradiometry. Of the 34 studies reporting correlation coefficients, all but two studies logarithmically transformed CRP to obtain a normal distribution (30 studies performed $\log_e$ transformation) (8,9). In this review, the association between obesity and CRP was reported using Pearson coefficients in 25 studies, ORs in 21 studies and Spearman coefficients in 11 studies, with some studies reporting more than one type of effect measure.

Obesity and C-reactive protein

In all studies, each measure of obesity was associated with CRP, regardless of age, sex and ethnicity of participants. In adults, the random-effects summary correlation coefficient between BMI and ln(CRP) was strong (Pearson coefficient [r] = 0.36; 95% CI = 0.30 to 0.42). Obesity and overweight, defined as BMI $\geq$ 30 kg m^{-2} and $\geq$25 kg m^{-2}, respectively, were strongly associated with increased odds of elevated CRP (Table 2). Similarly, the random-effects summary correlations between ln(CRP) with WC ($r = 0.40$; 95% CI = 0.31 to 0.48) and WHR ($r = 0.23$; 95% CI = 0.16 to 0.29) in adults were strong. Studies in children also showed strong associations between both BMI and WC with CRP, with the exception of inconclusive ORs reported by two studies in young Indians and Filipinos (Table 2) (10,11). The random-effects summary correlation between BMI and ln(CRP) in children was strong ($r = 0.37$; 95% CI = 0.31 to 0.43).

Sex

Using meta-regression, subgroup analysis and qualitative review of data, we assessed the potential impact of sex in the association between obesity and CRP in adults. Results from meta-regression models including sex and ethnicity moderators showed that the correlation was stronger in women than men. Upon adjusting for ethnicity, the correlation coefficients between BMI and ln(CRP) in women were greater by 0.24 (0.09 to 0.37) (r [95% CI]) than men on average. Correlation coefficients between WC and ln(CRP) were not found to be significantly higher in women than men with an average difference of 0.18 (–0.01 to 0.36). Specifically, WC and ln(CRP) were more strongly correlated in women than men in both North Americans/Europeans (men: $r = 0.44$ [0.24 to 0.64]; women: $r = 0.62$ [0.49 to 0.76]) and Asians (men: $r = 0.09$ [–0.07 to 0.25]; women: $r = 0.27$ [0.12 to 0.43]). We found no sex difference (difference in $r = 0$; 95% CI = –0.04 to 0.03) for the

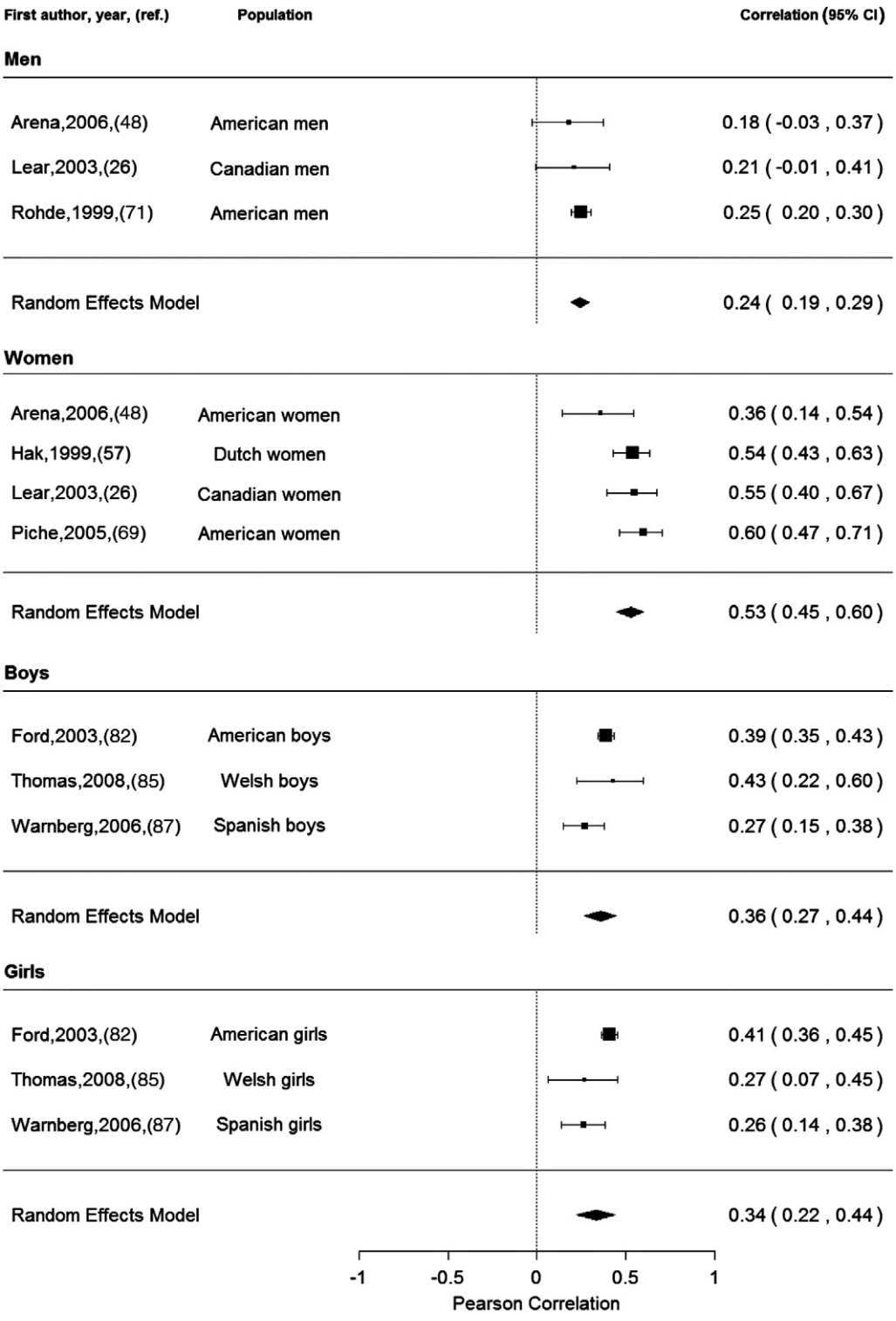

Figure 2 Pooled Pearson correlation coefficients from studies linking BMI and ln(CRP) in North Americans/Europeans. Error bar indicates 95% CIs.

correlation between WHR and ln(CRP) using the same meta-regression model. Subgroup analyses, conducted where possible, confirmed a sex difference as the summary correlation between BMI and ln(CRP) was greater in women ($r = 0.53$; 95% CI = 0.45 to 0.60) compared with men ($r = 0.24$; 95% CI = 0.19 to 0.29) in North American/European adult populations (Fig. 2). The association between obesity and CRP was stronger in women than men

from qualitatively reviewing the included studies. With the exception of one study (12), we found larger Pearson coefficients, Spearman coefficients and ORs for the association between BMI and WC with CRP in women (Tables 1 and 2). Sensitivity analyses including one study (13) that reported Pearson coefficients adjusted for an unusually high number of variables did not alter our conclusions in meta-regression and subgroup analysis.

Ethnicity

Meta-regression and qualitative review of data showed the association between obesity and CRP to be different between North Americans/Europeans and Asians, regardless of sex. In meta-regression models including sex and ethnicity moderators, the correlations between BMI, WC and WHR with ln(CRP) were significantly greater in North Americans/Europeans by 0.15 (0 to 0.28), 0.34 (0.16 to 0.49) and 0.16 (0.06 to 0.27), respectively. Due to the insufficient number of studies in Asian subgroups, we were not able to compare ethnic differences through subgroup analyses. However, we found the median values of Pearson and Spearman coefficients to be consistently higher in North Americans/Europeans than Asians across each measure of obesity (data not shown). Sensitivity analyses including the one study (13) with Pearson coefficients adjusting for additional variables did not alter our conclusions.

Children

BMI and WC were strongly associated with CRP in children; however, the sex difference observed in adults was not found in children. Subgroup analyses in male and female children of North Americans/Europeans revealed no sex difference in the correlation between BMI and ln(CRP) (Fig. 2). The pooled Pearson coefficient from meta-analyzing the sex difference within these three studies on children was –0.01 (–0.08 to 0.06) (Appendix Fig. A1). Qualitative assessment of all effect measures for studies in children showed varying conclusions to a potential sex difference between obesity and CRP (Tables 1 and 2).

Discussion

In our systematic review and meta-analysis, obesity was strongly associated with elevated levels of CRP in all populations observed. Meta-regression, subgroup analyses and qualitative review of data revealed stronger associations between obesity and CRP in women compared with men and in North Americans/Europeans compared with Asians. In children, subgroup analyses showed BMI and CRP to be equivalently correlated in male and female children of North American/European countries.

The pathophysiological mechanisms linking obesity to elevated levels of CRP are well recognized (6,14–16). Adipose tissue is an active endocrine organ that releases a variety of hormones and cytokines that contributes to CRP elevation (2). In obesity, the accumulation of free fatty acid intermediates activates proinflammatory serine kinase cascades, such as IκB kinase and c-JunN-terminal kinase (16). These cascades promote the secretion of cytokines, such as interleukin-6 (IL-6), which in turn trigger the hepatic synthesis of CRP. The liver is known to play a central role in the expression and release of CRP as it drains visceral adipose tissue, circulating triacylglycerol and free fatty acids to yield elevated cytokine secretion and promote an inflammatory milieu (6). More recently, a study in severely obese patients has found gene polymorphisms to explain the inter-individual variability in CRP (17).

In our study, we observed a greater magnitude of the association between obesity and CRP in women compared with men. However, the pathophysiological mechanisms for a sex difference remain unclear. Several theories can be postulated. First, sex differences in the metabolic activity of adipose tissues may be linked to increased CRP production in women (18,19). In a previous study, a greater proportion of the variance in IL-6 levels has been found to be explained by measures of obesity in women (20). Second, sex differences in the association between obesity and CRP may be mediated by leptin levels (21–23). Leptin is an adipocyte-specific hormone that has been positively correlated with elevated CRP (24). Furthermore, higher levels of leptin have been associated with increased body fat, earlier onset of puberty and the female sex (25). The observed sex difference in the non-linear association between CRP and fat mass has been found to disappear upon adjusting for leptin (19). Third, anthropometric indices of obesity are indirect measures of body fat, and the sex difference may be partially explained by women having a higher percent body fat, thus pronounced CRP synthesis, compared with men at any given BMI, WC or WHR (18,20,26).

Our finding of a difference in the magnitude of the association between obesity and CRP between ethnic groups adds to only a few studies that have examined ethnic differences (26–28). In the National Health and Nutrition Examination Survey study, the association between BMI and CRP was found to be similar between Caucasian Americans, African–Americans and Hispanic Americans (27). However, a recent study of Chinese, Malay and Asian-Indian residents of Singapore has found BMI and CRP to be associated differently according to ethnicity (28). Thus, lifestyle may be playing an important role in modifying the association. For instance, elevated CRP levels have been associated with diets high in glycaemic loads (29). There is already evidence that the Western diet plays a major role in the development of atherosclerosis (30). Further studies comparing ethnic differences, particularly between North

Table 1 Studies reporting correlation coefficients for obesity and CRP

First author, year (Reference)	log	Population	*n*	CRP (mg L^{-1})	BMI (kg m^{-2})	Correlation coefficient		WC (cm)	Correlation coefficient		WHR	Correlation coefficient	
						r	rho		r	rho		r	rho
Asian adults													
Choi, 2006 (51)	ln	Korean men	560	0.60*	24.0	–	0.20	84.0	–	0.22	–	–	–
		Korean women	486	0.40*	22.9	–	0.34	78.1	–	0.28	–	–	–
Jeemon, 2011 (60)	ln	Indian	600	1.10*/1.20*	23.0	0.55	–	80.3	0.47	–	–	–	–
Kim, 2008 (61)	ln	Korean	160	0.06*	25.4	0.44	–	–	–	–	0.90	0.43	–
Lee, 2009 (62)	ln	Korean men	2,248	0.76	24.7	0.27	–	–	–	–	–	–	–
		Korean women	2,675	0.49	23.2	0.39	–	–	–	–	–	–	–
Lim, 2006 (63)	ln	Korean men	4,611	1.88	24.2	0.13	–	83.7	0.15	–	0.90	0.15	–
		Korean women	5,162	1.75	24.9	0.23	–	81.8	0.21	–	0.87	0.14	–
Nakamura, 2008 (12)	ln	Japanese men	262	0.40	–	–	–	82.0	–	0.38	–	–	–
		Japanese women	366	0.30	–	–	–	76.7	–	0.28	–	–	–
Nakanishi, 2005 (68)	ln	Japanese men	715	0.53*	23.6	–	0.23	–	–	–	–	–	–
		Japanese women	988	0.32*	22.0	–	0.36	–	–	–	–	–	–
Ryu, 2005 (72)	ln	Korean	202	1.90	24.3/24.9	0.18	–	–	–	–	–	–	–
Saito, 2003 (73)	ln	Japanese	1,053	1.00/0.80	23.2/23.8	0.19	–	–	–	–	–	–	–
Snodgrass, 2007 (75)	log	Siberian men	56	1.72	23	0.26	–	82.2	0.27	–	–	–	–
		Siberian women	85	1.34	24.7	0.49	–	78.4	0.49	–	–	–	–
North American/European adults													
Arena, 2006 (48)	ln	American men	90	1.88	25.0	0.18	–	–	–	–	–	–	–
		American women	75	2.36	25.5	0.36	–	–	–	–	–	–	–
Festa, 2001 (46)	ln	American men	700	2.73	28.6	–	0.34	97.2	–	0.41	0.94	–	0.34
		American women	859	5.24	30.2	–	0.45	90.5	–	0.45	0.83	–	0.24
Frohlich, 2000 (55)	ln	West German	1,703	3.15	25.0	–	0.32	–	–	–	–	–	–
Garcia-Lorda, 2006 (56)	ln	Spanish	1,157	1.61	26.4	0.32	–	86.8	0.34	–	–	–	–
Hak, 1999 (57)	ln	Dutch women	186	0.68*	24.9	0.54	–	81.5	0.55	–	0.77	0.33	–
Hoekstra, 2005 (58)	ln	Dutch elderly men	315	2.40*	25.4	–	0.09	–	–	–	–	–	–
		Dutch elderly women	290	2.10*	26.5	–	0.39	–	–	–	–	–	–
Lear, 2003 (26)	ln	Canadian men	83	0.48*	24.4	0.21	–	84.5	0.28	–	0.87	0.28	–
		Canadian women	99	0.44*	25.2	0.55	–	78.5	0.59	–	0.78	0.27	–
Marsland, 2010 (65)	ln	American	645	1.65	27.2	0.48	–	91.0	0.41	–	–	–	–
Panagiotakos, 2005 (13)	ln	Greek men	1,514	1.70	27.4	0.21	–	98.0	0.30	–	–	0.48	–
		Greek women	1,528	1.30	25.3	0.22	–	84.0	0.34	–	–	0.52	–
Piche, 2005 (69)	ln	American women	112	2.32	28.6	0.60	–	92.0	0.61	–	–	–	–
Rohde, 1999 (71)	ln	American men	1,172	2.00	–	0.25	0.24	–	–	–	–	–	–
Yudkin, 1999 (79)	ln	American	107	1.35*	25.9	0.41	–	–	–	–	0.86	0.32	–
Other adults													
Araujo, 2004 (47)	ln	Brazilian men	295	1.40	26.2	–	0.39	–	–	–	–	–	–
	ln	Brazilian women	389	1.70	26.2	–	0.44	–	–	–	–	–	–
Aronson, 2004 (49)	ln	Israeli	1,929	–	–	0.39	–	–	–	–	–	–	–
Connelly, 2003 (52)	log	Aboriginal men	223	2.07*	26.7	–	0.37	99.1	–	0.44	0.97	–	0.46
		Aboriginal women	289	3.89*	29.1	–	0.62	104	–	0.56	0.96	–	0.23
Doumatey, 2010 (53)	ln	West African	247	0.42/0.54	25.9/29.0	0.35	–	–	–	–	0.89/0.86	0.22	–
		African–American	315	0.54/0.81	29.0/30.6	0.45	–	–	–	–	0.91/0.85	0.18	–
Rogowski, 2010 (70)	ln	Israeli men	7,760	–	–	–	–	–	0.35	–	–	–	–
		Israeli women	4,312	–	–	–	–	–	0.41	–	–	–	–
Children													
Ford, 2003 (82)	ln	American boys	1,479	1.40	–	0.39	–	–	–	–	–	–	–
	ln	American girls	1,367	1.70	–	0.41	–	–	–	–	–	–	–
Lazarou, 2010 (8)	–	Cypriot children	83	1.00*	–	–	0.39	–	–	0.29	–	–	–
Thomas, 2008 (85)	ln	Welsh boys	75	1.07	20.8	0.43	–	69.8	0.54	–	–	–	–
	ln	Welsh girls	89	1.24	21.1	0.27	–	65.2	0.31	–	–	–	–
Vikram, 2003 (11)	ln	Indian children	331	0.50*	–	–	–	–	–	–	0.82	0.11	–
Warnberg, 2006 (87)	ln	Spanish boys	248	1.17*	20.1*	0.27	–	72.6*	0.23	–	0.81*	0.11	–
	ln	Spanish girls	224	0.83*	20.4*	0.27	–	68.9*	0.22	–	0.75*	0.004†	–
Wu, 2003 (9)	–	Taiwanese boys	410	0.30*	21.0	–	0.27	68.4	–	0.28	0.78	–	0.21
	–	Taiwanese girls	425	0.19*	20.6	–	0.30	63.1	–	0.27	0.71	–	0.19
Yoshida, 2006 (88)	ln	Japanese boys	340	1.08	–	0.49	–	–	–	–	–	–	–
	ln	Japanese girls	228	0.82	–	0.36	–	–	–	–	–	–	–

Studies are listed in alphabetical order. Numbers separated by a slash denotes values in males/females in total population.

*Median values.

†Not significant; –, not applicable/not reported.

BMI, body-mass index; CRP, C-reactive protein; r, Pearson coefficient; rho, Spearman coefficient; WC, waist circumference; WHR, waist-hip ratio.

Table 2 Studies reporting odds ratios for obesity and CRP

First author, year (Reference)	Population	*n*	CRP cut-off	Odds ratio (95% CI)		
				Least adjusted	Most adjusted	Incremental odds ratio[§]
Cut-off: BMI ≥ 30 kg m^{-2}						
Adults						
Hung, 2008 (59)	Australian men	1,761	3.00	4.58 (3.28–6.39)	3.49 (2.43–5.01)	–
	Australian women	2,248	3.00	8.71 (6.68–11.37)	7.83 (5.78–10.59)	–
Visser, 1999 (77)	American men	7,938	2.20	–	2.13 (1.56–2.91)	1.38 (1.22–1.55) per 5 kg m^{-2}
	American women	8,678	2.20	–	6.21 (4.94–7.81)	2.04 (1.89–2.20) per 5 kg m^{-2}
Children						
Al-Isa, 2010 (80)	Kuwaiti children	774	0.9	32 (17.3–58.8)	25.3 (13.6–47.2)	–
Caserta, 2010 (81)	Italian boys	288	3.0	–	9.1 (2.5–32.4)	–
	Italian girls	287	3.0	–	7.6 (1.3–44.5)	–
Kong, 2008 (83)	Chinese boys	958	1T v 3T[†]	7.06 (4.42–11.3)	3.65 (2.1–6.35)	–
	Chinese girls	1,144	1T v 3T[†]	10.5 (5.62–19.7)	6.28 (3.12–12.6)	–
Cut-off: BMI ≥ 25 kg m^{-2}						
Jeemon, 2011 (60)	Indian adults	600	2.60	6.80 (4.50–10.2)	3.90 (2.34–6.44)	–
Saito, 2003 (73)	Japanese adults	1,053	1.50	–	2.50 (1.09–5.75)	–
Saito, 2007 (74)	Japanese men	5,213	1.66	–	1.48 (1.27–1.72)	–
	Japanese women	7,071	1.17	–	2.42 (2.12–2.76)	–
Cut-off: BMI other[‡]						
Adults						
Gentile, 2010 (38)	Italian women	390	1.50	–	3.55 (1.94–6.49)	–
Mora, 2006 (67)	American women	27,158	4.20	–	10.79 (9.63–12.08)	–
Yamada, 2001 (78)	Japanese adults	6,107	0.11	–	–	1.52 (1.40–1.64) per 1 SD[†]
Lin, 2010 (64)	Taiwanese men	807	Top quartile[†]	1.36 (0.98–1.88)	1.25 (0.87–1.77)	1.12 (0.93–1.33) per 1 SD[†]
	Taiwanese women	862	Top quartile[†]	2.68 (1.97–3.66)	2.11 (1.51–2.95)	1.65 (1.39–1.97) per 1 SD[†]
Thompson, 2011 (76)	Mongolian adults	2,589	Top quartile[†]	–	–	1.31 (1.19–1.45) per 3.5 kg m^{-2}
Children						
Lambert, 2008 (84)	Canadian boys	907	3.0	–	2.8 (1.5–5.3)	–
	Canadian girls	975	3.0	–	5.2 (2.7–9.7)	–
Lazarou, 2010 (8)	Cypriot children	83	1.0*	–	7.35 (1.7–31.7)	–
Vikram, 2003 (11)	Indian boys	331	2.1	–	2.10 (0.90–4.79)	1.30 (0.90–1.80) per 3 kg m^{-2}
	Indian girls	46	2.1	–	3.40 (0.50–23.60)	1.90 (0.80–4.50) per 3 kg m^{-2}
Visser, 2001 (86)	American boys	1,725	2.2	–	3.74 (1.66–8.43)	1.65 (1.26–2.16) per 4 kg m^{-2}
	American girls	1,787	2.2	–	3.17 (1.60–6.28)	1.60 (1.25–2.05) per 4 kg m^{-2}
Cut-off: WC male 102 cm, male 88 cm						
Assoumou, 2011 (50)	French elderly	921	2.80	2.88 (1.90–4.37)	1.75 (1.05–2.91)	–
Dupuy, 2007 (54)	French elderly men	655	3.05	3.06 (1.82–5.14)	2.81 (1.66–4.77)	–
	French elderly women	1,054	3.05	7.04 (4.79–10.34)	5.80 (3.87–8.68)	–
Cut-off: WC male 90 cm, female 80 cm						
Adults						
Lin, 2010 (64)	Taiwanese men	807	Top quartile[†]	1.47 (1.05–2.05)	1.19 (0.83–1.70)	1.18 (0.98–1.41) per 1 SD[†]
	Taiwanese women	862	Top quartile[†]	3.04 (2.21–4.18)	2.37 (1.67–3.35)	1.76 (1.48–2.12) per 1 SD[†]
McDade, 2009 (10)	Filipino	1,648	3.0	0.95 (0.90–1.01)	0.96 (0.90–1.01)	–
Cut-off: WC other[‡]						
Adults						
Gentile, 2010 (38)	Italian women	390	1.50	–	3.11 (1.71–5.66)	–
Thompson, 2011 (76)	Mongolian adults	2,589	3.00	–	1.65 (1.30–2.10)	1.41 (1.27–1.56) per 9.59 cm
Jeemon, 2011 (60)	Indian adults	600	2.60	3.42 (2.31–5.07)	1.62 (1.02–2.60)	–
McDade, 2008 (66)	Filipino women	1,875	3.00	–	–	2.22 (1.94–2.53) per 1 SD[†]
Children						
Lazarou, 2010 (8)	Cypriot children	83	1.0*	–	7.81 (1.45–42.03)	–
Cut-off: WHR other[‡]						
Lin, 2010 (64)	Taiwanese men	807	Top quartile[†]	1.47 (1.07–2.01)	1.06 (0.76–1.50)	1.09 (0.90–1.31) per 1 SD[†]
	Taiwanese women	862	Top quartile[†]	2.73 (1.94–3.84)	2.07 (1.45–2.97)	1.40 (1.19–1.66) per 1 SD[†]
Visser, 1999 (77)	American men	7,938	2.20	–	–	1.41 (1.17–1.69) per 0.1
	American women	8,678	2.20	–	–	1.21 (1.07–1.37) per 0.1
Yamada, 2001 (78)	Japanese adults	6,107	0.11	–	–	1.29 (1.13–1.46) per 1 SD[†]

Studies are listed in alphabetical order. Numbers separated by a slash denotes values in males/females in total population. Non-adjusted odds ratios and odds ratios adjusted exclusively for age and/or sex were classified as 'Least adjusted'; Odds ratios adjusting for any cardiovascular risk factor were classified as 'most adjusted'.

*Median values reported.

[†]Exact value not reported.

[‡]Studies that did not use a common obesity cut-off value: Gentile (2010) (38) used BMI 19–25 vs. 29–42 kg m^{-2} and WC 66–84 vs. 94–118 cm, Mora (2006) (67) used <21.9 vs. >29.3 kg m^{-2}, Lin (2010) (64) used BMI 24 kg m^{-2} and WHR 0.90/0.85, and Thompson (2011) (76) used WC 85/80 cm, Lambert (2008) (84) used 21 kg m^{-2} (9 years), 25.2 kg m^{-2} (13 years), 27.6 kg m^{-2} (16 years), Vikram (2003) (11) used 23.10 kg m^{-2}, Visser (2001) (86) used 23.66/24.52 kg m^{-2}, otherwise studies did not report a cut-off value.

[§]Reflective of an incremental increase in measure of obesity.

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; WC, waist circumference; WHR, waist-hip ratio.

Americans/Europeans and Asians, in the association between obesity and CRP are needed to elucidate the pathophysiological mechanisms leading to our observed ethnic differences.

Our results suggest that young, obese children experience increased levels of CRP compared with children who are not obese, and that there is no discernible sex difference in this association. Childhood obesity is associated with increased morbidity and mortality in adulthood (31). Recently, body fatness in childhood was found to be a major predictor of CRP in young adulthood (32). Although we found no study that specifically examined sex differences in children, our results may be reflective of a parallel inflammatory response to obesity in boys and girls which subsequently diverge upon the onset of puberty. Changes in body composition and endocrine function that accompany puberty, such as an increased body fat and oestrogen secretion in females, may explain the lack of sex difference among our prepubertal populations. Oestrogen, for example, has been implicated in the transcriptional control, clearance and cytokine regulation of CRP (33,34). Further research is needed to understand the mechanisms responsible for exacerbating inflammation in obese boys and girls.

There is growing interest in interventions that can lower CRP levels in overweight and obese people. In a systematic review, researchers have found for every 1 kg loss of weight in adults obtained through surgical, lifestyle, dietary or exercise interventions the mean change in CRP level was -0.13 mg L^{-1} (35). Weight loss could directly lead to reductions in CRP levels by reducing the excess lipids stored in adipocytes, which are hypertrophied in obesity (36). The independent effect of physical activity has also been systematically examined, in which chronic physical activity has been associated with reduced CRP even after adjusting for measures of obesity. Multiple mechanisms have been suggested, including modification of cytokine production from skeletal muscles, endothelial and blood mononuclear cells, improved endothelial function and insulin sensitivity, and an antioxidant effect (37).

Our review has a number of potential limitations. First, the cross-sectional design of included studies prevents us from drawing causal inferences about the association between obesity and CRP levels. We are aware of only one prospective study which found an independent association between longitudinal estimates of weight gain and elevated CRP (38). However, recent reciprocal Mendelian randomization studies have shown promising evidence that adiposity causally influences circulating CRP levels and not vice versa (39,40). Second, our ethnic comparisons may be biased due to documented differences in BMI, WC and WHR between American/European and Asian populations. However, our comparison of associations, in which magnitudes depend on both the measure of obesity and level of CRP, should be minimally affected from the different BMI, WC and WHR between ethnic groups. Third, anthropometric measures of obesity have limited diagnostic capacity for body fatness in both adults and children, and may result in the misclassification of patients with high CRP levels (41–45). However, the ease of measuring BMI, WC or WHR and the lack of reliable methods for measuring body composition (6) leave us with BMI, WC and WHR as the predominant measures of obesity in research (32). Studies that use bioelectrical impedance, dual energy X-ray absorptiometry scanning and magnetic resonance imaging methods to measure body composition, however, have reported associations between obesity and CRP that are consistent with our conclusions (18,25,46). Fourth, the limited numbers of studies in each subgroup analyses, which have restricted our scope of sex and ethnic comparisons, may also underestimate the between-study variance of our pooled estimates. However, we achieved a high degree of homogeneity within subgroups by grouping studies according to measure of obesity, sex, ethnicity, logarithmic transformation of CRP and type of correlation coefficient. Finally, measures of publication bias could not be reasonably estimated due to the limited amount of studies in each subgroup analyses. Publication bias is an inherent limitation to virtually all meta-analyses.

Conclusion

Obesity is associated with elevated levels of CRP. This association is stronger in women than in men and in North Americans/Europeans compared with Asians. The implementation of sex-specific CRP cut-offs might be considered for improving CVD risk assessment conducted in North American or European populations. We further recommend that current CVD risk prediction models that are considering the incorporation of CRP to provide risk assessment methods that account for the sex-specific associations between measures of obesity and CRP. In addition, we did not find the association between obesity and CRP to be different between male and female children. Currently, the pathophysiology leading to sex and ethnicity differences in the association between obesity and CRP in adults are not well understood. The absence of such sex difference in childhood and its emergence in adulthood could indicate a hormonal role.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgement

The authors thank Sylvie Leung for help with data abstraction.

Funding

This project was supported in part by the Heart and Stroke Foundation of Canada in Quebec, Ontario, British Columbia and Yukon, Alberta, and Nova Scotia. JC received a student fellowship from the Research Institute of the McGill University Health Centre. Dr Pilote is funded by a James McGill Chair at McGill University and the Fonds de la Recherche en Santé du Québec.

Authors' contributions

Conception and Design: Choi, Pilote.
Analysis and interpretation of the data: Choi, Joseph, Pilote.
Drafting of the article: Choi.
Critical revision of the article for important intellectual content: Joseph, Pilote.
Final approval of the article: Choi, Joseph, Pilote
Statistical expertise: Choi, Joseph, Pilote.
Administrative, technical, or logistic support: Choi, Joseph, Pilote.
Collection and assembly of data: Choi.

References

1. Poirier P, Giles TD, Bray GA *et al*. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation* 2006; **113**: 898–918.
2. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006; **444**: 875–880.
3. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009; **54**: 2129–2138.
4. Pearson TA, Mensah GA, Alexander RW *et al*. Markers of inflammation and cardiovascular disease. *Circulation* 2003; **107**: 499–511.
5. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010; **375**: 132–140.
6. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. *Am J Cardiol* 2010; **106**: 56–61.
7. von Elm E, Altman DG, Egger M *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.
8. Lazarou C, Panagiotakos DB, Chrysohoou C *et al*. C-reactive protein levels are associated with adiposity and a high inflammatory foods index in mountainous Cypriot children. *Clin Nutr* 2010; **29**: 779–783.
9. Wu DM, Chu NF, Shen MH *et al*. Plasma C-reactive protein levels and their relationship to anthropometric and lipid characteristics among children. *J Clin Epidemiol* 2003; **56**: 94–100.
10. McDade TW, Rutherford JN, Adair L *et al*. Population differences in associations between C-reactive protein concentration and adiposity: comparison of young adults in the Philippines and the United States. *Am J Clin Nutr* 2009; **89**: 1237–1245.
11. Vikram NK, Misra A, Dwivedi M *et al*. Correlations of C-reactive protein levels with anthropometric profile, percentage of body fat and lipids in healthy adolescents and young adults in urban North India. *Atherosclerosis* 2003; **168**: 305–313.
12. Nakamura H, Ito H, Egami Y *et al*. Waist circumference is the main determinant of elevated C-reactive protein in metabolic syndrome. *Diabetes Res Clin Pract* 2008; **79**: 330–336.
13. Panagiotakos DB, Pitsavos C, Yannakoulia M *et al*. The implication of obesity and central fat on markers of chronic inflammation: the ATTICA study. *Atherosclerosis* 2005; **183**: 308–315.
14. Bastard JP, Maachi M, Lagathu C *et al*. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006; **17**: 4–12.
15. Ferrante AW. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med* 2007; **262**: 408–414.
16. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol* 2009; **6**: 399–409.
17. Faucher G, Guénard F, Bouchard L *et al*. Genetic contribution to C-reactive protein levels in severe obesity. *Mol Genet Metab* 2012; **105**: 494–501.
18. Khera A, Vega GL, Das SR *et al*. Sex differences in the relationship between C-reactive protein and body fat. *J Clin Endocrinol Metab* 2009; **94**: 3251–3258.
19. Rossi I, Bochud M, Bovet P *et al*. Sex difference and the role of leptin in the association between high-sensitivity C-reactive protein and adiposity in two different populations. *Eur J Epidemiol* 2012; **27**: 379–384.
20. Thorand B, Baumert J, Döring A *et al*. Sex differences in the relation of body composition to markers of inflammation. *Atherosclerosis* 2006; **184**: 216–224.
21. Abdullah SM, Khera A, Leonard D *et al*. Sex differences in the association between leptin and CRP: results from the Dallas Heart Study. *Atherosclerosis* 2007; **195**: 404–410.
22. Bochud M, Marquant F, Marques-Vidal P-M *et al*. Association between C-Reactive protein and adiposity in women. *J Clin Endocrinol Metab* 2009; **94**: 3969–3977.
23. Dullaart RPF, De Vries R, Dikkeschei LD *et al*. Higher plasma leptin largely explains increased C-reactive protein levels in women. *Eur J Clin Invest* 2007; **37**: 231–233.
24. Viikari LA, Huupponen RK, Viikari JSA *et al*. Relationship between leptin and C-reactive protein in young finnish adults. *J Clin Endocrinol Metab* 2007; **92**: 4753–4758.
25. Vettor R, De Pergola G, Pagano C *et al*. Gender differences in serum leptin in obese people: relationships with testosterone, body fat distribution and insulin sensitivity. *Eur J Clin Invest* 1997; **27**: 1016–1024.
26. Lear SA, Chen MM, Birmingham CL *et al*. The relationship between simple anthropometric indices and C-reactive protein: ethnic and gender differences. *Metabolism* 2003; **52**: 1542–1546.
27. Wee CC, Mukamal KJ, Huang A *et al*. Obesity and C-reactive protein levels among White, Black, and Hispanic US adults. *Obesity (Silver Spring)* 2008; **16**: 875–880.
28. Khoo CM, Sairazi S, Taslim S *et al*. Ethnicity modifies the relationships of insulin resistance, inflammation, and adiponectin with obesity in a multiethnic Asian population. *Diabetes Care* 2011; **34**: 1120–1126.
29. Liu S, Manson JE, Buring JE *et al*. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr* 2002; **75**: 492–498.
30. Gaziano JM, Manson JE. Diet and heart disease. The role of fat, alcohol, and antioxidants. *Cardiol Clin* 1996; **14**: 69–83.
31. Gunnell D, Frankel S, Nanchahal K *et al*. Childhood obesity and adult cardiovascular mortality: a 57-year follow-up study based on the Boyd Orr cohort. *Am J Clin Nutr* 1998; **67**: 1111–1118.

32. Toprak D, Toprak A, Chen W *et al*. Adiposity in childhood is related to C-reactive protein and adiponectin in young adulthood: from the Bogalusa Heart Study. *Obesity (Silver Spring)* 2011; **19**: 185–190.
33. Baumann H, Gauldie J. The acute phase response. *Immunol Today* 1994; **15**: 74–80.
34. Tuck CH, Holleran S, Berglund L. Hormonal regulation of lipoprotein(a) levels: effects of estrogen replacement therapy on lipoprotein(a) and acute phase reactants in postmenopausal women. *Arterioscler Thromb Vasc Biol* 1997; **17**: 1822–1829.
35. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med* 2007; **167**: 31–39.
36. Forsythe LK, Wallace JMW, Livingstone MBE. Obesity and inflammation: the effects of weight loss. *Nutr Res Rev* 2008; **21**: 117–133.
37. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol* 2005; **45**: 1563–1569.
38. Gentile M, Panico S, Rubba F *et al*. Obesity, overweight, and weight gain over adult life are main determinants of elevated hs-CRP in a cohort of Mediterranean women. *Eur J Clin Nutr* 2010; **64**: 873–878.
39. Welsh P, Polisecki E, Robertson M *et al*. Unraveling the directional link between adiposity and inflammation: a bidirectional mendelian randomization approach. *J Clin Endocrinol Metab* 2010; **95**: 93–99.
40. Timpson NJ, Nordestgaard BG, Harbord RM *et al*. C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization. *Int J Obes* 2011; **35**: 300–308.
41. Frankenfield DC, Rowe WA, Cooney RN *et al*. Limits of body mass index to detect obesity and predict body composition. *Nutrition* 2001; **17**: 26–30.
42. Freedman DM, Ron E, Ballard-Barbash R *et al*. Body mass index and all-cause mortality in a nationwide US cohort. *Int J Obes* 2006; **30**: 822–829.
43. Gallagher D, Visser M, Sepúlveda D *et al*. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996; **143**: 228–239.
44. Gomez-Ambrosi J, Silva C, Galofre JC *et al*. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *Int J Obes* 2012; **36**: 286–294.
45. Rothman KJ. BMI-related errors in the measurement of obesity. *Int J Obes (Lond)* 2008; **32**(Suppl. 3): S56–S59.
46. Festa A, D'Agostino R Jr, Williams K *et al*. The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes* 2001; **25**: 1407–1415.
47. Araujo F, Pereira AC, Latorre MDRDO *et al*. High-sensitivity C-reactive protein concentration in a healthy Brazilian population. *Int J Cardiol* 2004; **97**: 433–438.
48. Arena R, Arrowood JA, Fei DY *et al*. The relationship between C-reactive protein and other cardiovascular risk factors in men and women. *J Cardiopulm Rehabil* 2006; **26**: 323–329.
49. Aronson D, Bartha P, Zinder O *et al*. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. *Int J Obes* 2004; **28**: 674–679.
50. Assoumou HGN, Barthelemy JC, Garet M *et al*. Increased waist circumference is the component of metabolic syndrome the most strongly associated with elevated C-Reactive protein in elderly. *Metab Syndr Relat Disord* 2011; **9**: 281–285.
51. Choi EY, Park EH, Cheong YS *et al*. Association of C-reactive protein with the metabolic risk factors among young and middle-aged Koreans. *Metabolism* 2006; **55**: 415–421.
52. Connelly PW, Hanley AJ, Harris SB *et al*. Relation of waist circumference and glycemic status to C-reactive protein in the Sandy Lake Oji-Cree. *Int J Obes* 2003; **27**: 347–354.
53. Doumatey AP, Lashley KS, Huang H *et al*. Relationships among obesity, inflammation, and insulin resistance in African–Americans and West Africans. *Obesity (Silver Spring)* 2010; **18**: 598–603.
54. Dupuy AM, Jaussent I, Lacroux A *et al*. Waist circumference adds to the variance in plasma C-reactive protein levels in elderly patients with metabolic syndrome. *Gerontology* 2007; **53**: 329–339.
55. Frohlich M, Imhof A, Berg G *et al*. Association between C-reactive protein and features of the metabolic syndrome. *Diabetes Care* 2000; **23**: 1835–1839.
56. Garcia-Lorda P, Bullo M, Balanza R *et al*. C-reactive protein, adiposity and cardiovascular risk factors in a Mediterranean population. *Int J Obes* 2006; **30**: 468–474.
57. Hak AE, Stehouwer CD, Bots ML *et al*. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. *Arterioscler Thromb Vasc Biol* 1999; **19**: 1986–1991.
58. Hoekstra T, Geleijnse JM, Schouten EG *et al*. Relationship of C-reactive protein with components of the metabolic syndrome in normal-weight and overweight elderly. *Nutr Metab Cardiovasc Dis* 2005; **15**: 270–278.
59. Hung J, Knuiman MW, Divitini ML *et al*. Prevalence and risk factor correlates of elevated C-reactive protein in an adult Australian population. *Am J Cardiol* 2008; **101**: 193–198.
60. Jeemon P, Prabhakaran D, Ramakrishnan L *et al*. Association of high sensitive C-reactive protein (hsCRP) with established cardiovascular risk factors in the Indian population. *Nutr Metab* 2011; **8**: 19–27.
61. Kim K, Valentine RJ, Shin Y *et al*. Associations of visceral adiposity and exercise participation with C-reactive protein, insulin resistance, and endothelial dysfunction in Korean healthy adults. *Metabolism* 2008; **57**: 1181–1189.
62. Lee YJ, Lee JH, Shin YH *et al*. Gender difference and determinants of C-reactive protein level in korean adults. *Clin Chem Lab Med* 2009; **47**: 863–869.
63. Lim S, Jang HC, Lee HK *et al*. The relationship between body fat and C-reactive protein in middle-aged Korean population. *Atherosclerosis* 2006; **184**: 171–177.
64. Lin CC, Kardia SL, Li CI *et al*. The relationship of high sensitivity C-reactive protein to percent body fat mass, body mass index, waist-to-hip ratio, and waist circumference in a Taiwanese population. *BMC Public Health* 2010; **10**: 579–587.
65. Marsland AL, McCaffery JM, Muldoon MF *et al*. Systemic inflammation and the metabolic syndrome among middle-aged community volunteers. *Metabolism* 2010; **59**: 1801–1808.
66. McDade TW, Rutherford JN, Adair L *et al*. Adiposity and pathogen exposure predict C-reactive protein in filipino women. *J Nutr* 2008; **138**: 2442–2447.
67. Mora S, Lee IM, Buring JE *et al*. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA* 2006; **295**: 1412–1419.
68. Nakanishi N, Shiraishi T, Wada M. C-reactive protein concentration is more strongly related to metabolic syndrome in women than in men – the Minoh study. *Circ J* 2005; **69**: 386–391.
69. Piche ME, Lemieux S, Weisnagel SJ *et al*. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. *Am J Cardiol* 2005; **96**: 92–97.

70. Rogowski O, Shapira I, Bassat OKB *et al*. Waist circumference as the predominant contributor to the micro-inflammatory response in the metabolic syndrome: a cross sectional study. *J Inflamm* 2010; **7**: 1–7.
71. Rohde LEP, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol* 1999; **84**: 1018–1022.
72. Ryu SY, Lee YS, Park J *et al*. Relations of plasma high-sensitivity C-reactive protein to various cardiovascular risk factors. *J Korean Med Sci* 2005; **20**: 379–383.
73. Saito I, Yonemasu K, Inami F. Association of body mass index, body fat, and weight gain with inflammation markers among rural residents in Japan. *Circ J* 2003; **67**: 323–329.
74. Saito I, Sato S, Nakamura M *et al*. A low level of C-reactive protein in Japanese adults and its association with cardiovascular risk factors: the Japan NCVC-Collaborative Inflammation Cohort (JNIC) Study. *Atherosclerosis* 2007; **194**: 238–244.
75. Snodgrass JJ, Leonard WR, Tarskaia LA *et al*. Anthropometric correlates of C-reactive protein among indigenous Siberians. *J Physiol Anthropol* 2007; **26**: 241–246.
76. Thompson AM, Zhang Y, Tong W *et al*. Association of obesity and biomarkers of inflammation and endothelial dysfunction in adults in Inner Mongolia, China. *Int J Cardiol* 2011; **150**: 247–252.
77. Visser M, Bouter LM, McQuillan GM *et al*. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999; **282**: 2131–2135.
78. Yamada S, Gotoh T, Nakashima Y *et al*. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. *Am J Epidemiol* 2001; **153**: 1183–1190.
79. Yudkin JS, Stehouwer CD, Emeis JJ *et al*. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; **19**: 972–978.
80. Al-Isa AN, Thalib L, Akanji AO. Circulating markers of inflammation and endothelial dysfunction in Arab adolescent subjects: reference ranges and associations with age, gender, body mass and insulin sensitivity. *Atherosclerosis* 2010; **208**: 543–549.
81. Caserta CA, Pendino GM, Alicante S *et al*. Body mass index, cardiovascular risk factors, and carotid intima-media thickness in a pediatric population in Southern Italy. *J Pediatr Gastroenterol Nutr* 2010; **51**: 216–220.
82. Ford ES. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the National Health and Nutrition Examination Survey 1999–2000. *Circulation* 2003; **108**: 1053–1058.
83. Kong APS, Choi K-C, Ko GTC *et al*. Associations of overweight with insulin resistance, beta-cell function and inflammatory markers in Chinese adolescents. *Pediatr Diabetes* 2008; **9**: 488–495.
84. Lambert M, Delvin EE, Levy E *et al*. Prevalence of cardiometabolic risk factors by weight status in a population-based sample of Quebec children and adolescents. *Can J Cardiol* 2008; **24**: 575–583.
85. Thomas NE, Baker JS, Graham MR *et al*. C-reactive protein in schoolchildren and its relation to adiposity, physical activity, aerobic fitness and habitual diet. *Br J Sports Med* 2008; **42**: 357–360.
86. Visser M, Bouter LM, McQuillan GM *et al*. Low-grade systemic inflammation in overweight children. *Pediatrics* 2001; **107**: E13–E19.
87. Warnberg J, Nova E, Moreno LA *et al*. Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA Study. *Am J Clin Nutr* 2006; **84**: 505–512.
88. Yoshida T, Kaneshi T, Shimabukuro T *et al*. Serum C-reactive protein and its relation to cardiovascular risk factors and adipocytokines in Japanese children. *J Clin Endocrinol Metab* 2006; **91**: 2133–2137.

Appendix

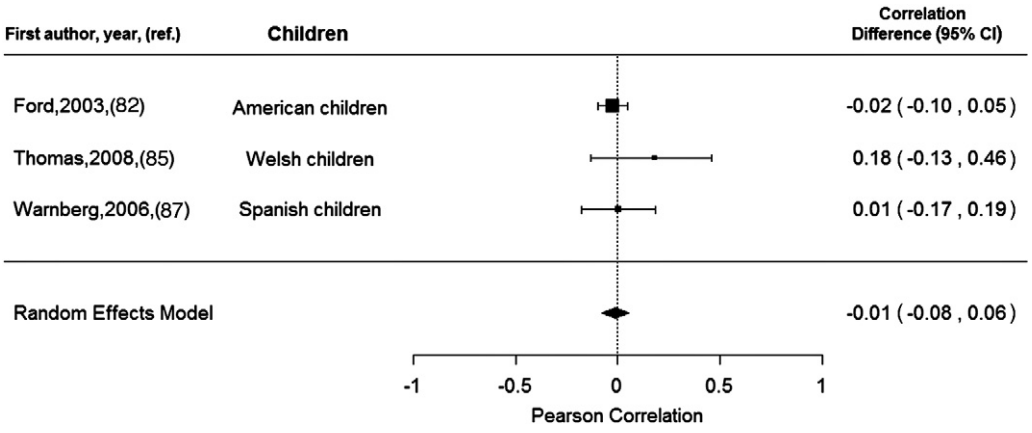

Figure A1 Sex difference in Pearson coefficient estimates from studies linking BMI and ln(CRP) in children of North American/European populations. Error bars indicate 95% CIs. Negative value indicates stronger correlation in girls.

Table A1 Search strategies

MEDLINE (until 3 October 2011)
1. C-reactive protein[MeSH]
2. CRP [Text Word]
3. C reactive protein[Text Word]
4. 1 or 2 or 3
5. Obesity[MeSH]
6. Body mass index[Text Word]
7. BMI[Text Word]
8. Waist circumference[Text Word]
9. Waist-hip ratio[Text Word]
10. Overweight[Text Word]
11. Body fat[Text Word]
12. Central fat[Text Word]
13. Adipose tissue[Text Word]
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 4 and 14
16. Limit 15 to yr="1966 to 2012"
17. Limit 16 to English
EMBASE (until 3 October 2011)
1. C-reactive protein/
2. CRP.mp
3. C reactive protein.mp
4. 1 or 2 or 3
5. Obesity/
6. Body mass index.mp
7. BMI.mp
8. Waist circumference.mp
9. Waist-hip ratio.mp
10. Overweight.mp
11. Body fat.mp
12. Adiposity.mp
13. Fat.mp
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 4 and 14
16. Limit 15 to yr="1966 to 2012"
17. Limit 16 to English
Google Scholar (until 3 October 2011)
1. C-reactive protein.ti
2. Obesity.ti
3. Abdominal adiposity.ti
4. Body mass index.ti
5. BMI.ti
6. Waist circumference.ti
7. Fat.ti
8. Limit 15 to yr="1990 to 2012"

Table A2 Characteristics of study sample

First author, year (Reference)	Population	Participants, *n*	Women, %	Mean age, year	Mean BMI, kg m^{-2}	Mean WC, cm	Mean WHR	Mean CRP (SD), mg L^{-1}
Adults								
Araujo, 2004 (47)	Brazilians	684	57	40.6	26.15/26.33	–	–	1.4 (0.1)/1.7 (0.1)
Arena, 2006 (48)	Americans	165	45	51.2/49.6	25/25.5	–	–	0.63 (0.44)/0.86 (0.67)
Aronson, 2004 (49)	Israelis	1,929	37	50	–	–	–	–
Assoumou, 2011 (50)	French elderly	921	60	65.6	25.94/24.9	–	0.93/0.84	2 (1–3.7)/2 (1–4)*
Choi, 2006 (51)	Koreans	1,224	40	18–64†	24/22.9	84.8/78.1	–	0.6 (0.3–1.3)/0.4 (0.2–0.9)*
Connelly, 2003 (52)	Canadian Aboriginal	512	56	35.9/35.9	26.7/29.1	99.1/104	0.97/0.96	4.17 (7)/5.62 (5.8)
Doumatey, 2010 (53)	West Africans	247	66	49.62/46.19	25.9/29.03	–	0.89/0.86	0.42 (0.83)/0.54 (1.31)
Doumatey, 2010 (53)	African–Americans	315	53	46.5/46.18	29.04/30.64	–	0.91/0.85	0.54 (1.28)/0.81 (1.2)
Dupuy, 2007 (54)	French elderly	1,709	62	69.3	–	–	–	1.63/1.61*
Festa, 2001 (46)	Americans	1,559	55	55.7/55.6	28.6/30.2	97.2/90.5	0.94/0.83	2.73/5.24
Frohlich, 2000 (55)	Germans	1,703	56	43.5	25	–	–	3.15 (7.4)
Garcia-Lorda, 2006 (56)	Spaniards	1,157	56	44.83	26.83/26.07	92.46/82.44	–	1.58 (3.1)/1.64 (3)
Gentile, 2010 (38)	Italian women	390	100	63.1	28	90.3	–	2.6
Hak, 1999 (57)	Dutch women	186	100	50.9	24.9	81.5	0.77	0.68 (0.33–1.44)*
Hoekstra, 2005 (58)	Dutch elderly	605	48	73.2/74.1	25.4/26.5	–	–	2.4 (1.2–4.7)/2.1 (1.0–3.8)*
Hung, 2008 (59)	Australians	4,009	56	50.2/50.2	26.5/25.6	–	0.93/0.79	1.3 (3.39)/1.6 (3.46)
Jeemon, 2011 (60)	Indians	600	49	39.8/38.5	22.5/23.6	82.5/77.9	–	1.1 (0.4–2.1)/1.2 (0.3–3.1)*
Kim, 2008 (61)	Koreans	160	76	41.3	26.14/25.12	–	0.94/0.88	0.07 (0.04–0.16)/0.05 (0.03–0.11)*
Lear, 2003 (26)	Canadians	182	54	36.7/41.3	24.4/25.2	84.5/78.5	0.87/0.78	0.48/0.44*
Lee, 2009 (62)	Koreans	4,923	54	20–75†	24.7/23.2	–	–	0.76 (2.48)/0.49 (2.6)
Lim, 2006 (63)	Koreans	9,773	53	52.2	24.2/24.9	83.7/81.8	0.9/0.87	1.88 (1.77)/1.75 (1.67)
Lin, 2010 (64)	Taiwanese	1,669	52	40–88†	–	–	–	–
Marsland, 2010 (65)	Americans	645	52	44.65	27.16	91	–	1.65 (1.79)
McDade, 2008 (66)	Filipino women	1,875	100	47.7	24.3	81.1	–	0.9 (0.3–2.8)*
McDade, 2009 (10)	Filipino	1,648	44	20.9	21.1/20.3	72.2/68	–	0.3 (0.1–0.9)/0.2 (0.1–0.9)*
Mora, 2006 (67)	American women	27,158	100	54.7	25.9	–	–	2 (0.8–4.4)
Nakamura, 2008 (12)	Japanese	628	58	40/45	22.8/21	82/76.7	–	0.4 (2.7)/0.3(2.5)
Nakanishi, 2005 (68)	Japanese	1,703	58	56.1/55.8	23.6/22	–	–	0.53 (0.28–1.03)/0.32 (0.2–0.61)*
Panagiotakos, 2005 (13)	Greek	3,042	50	46/45	27.4/25.3	98/84	–	–
Piche, 2005 (69)	American women	112	100	57	28.6	92	–	2.32 (2.27)
Rogowski, 2010 (70)	Israelis	12,072	36	44	–	–	–	–
Rohde, 1999 (71)	American men	1,172	0	40–84†	–	–	–	2
Ryu, 2005 (72)	Koreans	202	63	64.8/65	24.3/24.9	–	–	2.4 (3.9)/1.6(2.3)
Saito, 2003 (73)	Japanese	1,053	62	69/67.6	23.2/23.8	–	–	1/0.8
Saito, 2007 (74)	Japanese	12,284	58	64.9/62.9	23.5/23.1	–	–	0.6 (0.3–1.31)/0.45 (0.22–0.94)*
Snodgrass, 2007 (75)	Russian Aboriginals	141	60	31/32.3	23/24.7	82.2/78.4	–	1.72 (2.39)/1.34 (1.55)
Thompson, 2011 (76)	Mongolians	2,589	59	20+†	–	–	–	–
Visser, 1999 (77)	Americans	16,616	52	17+†	–	–	0.95/0.86	–
Yamada, 2001 (78)	Japanese	6,107	63	30+†	–	–	–	0.83 (3.6)/0.59 (2.7)
Yudkin, 1999 (79)	Americans	107	45	59	25.9	–	0.86	1.35 (0.57–2.18)*
Children								
Al-isa, 2010 (80)	Kuwaiti children	774	59	14.5	26.4/25.6	–	0.81/0.76	3.3 (4.7)/0.24 (4.9)
Caserta, 2010 (81)	Italian children	575	50	11–13†	21/21*	78/78*	–	0.54 (0.24–1.44)/0.33 (0.16–0.80)*
Ford, 2003 (82)	American children	2,846	48	10.1/10.5	–	–	–	1.4 (0.2)/1.7 (0.2)
Kong, 2008 (83)	Chinese children	2,102	54	16*	20.3/19.7	71.3/65.8	0.79/0.74	0.34 (0.17–0.77)/0.23 (0.13–0.59)*
Lambert, 2008 (84)	Canadian children	1,882	52	9–16†	20.3/20.2	–	–	0.2/0.3*
Lazarou, 2010 (8)	Cypriot children	83	49	9.2	–	–	–	1*
Thomas, 2008 (85)	Welsh children	164	54	12.9/12.9	20.8/21.1	69.8/65.2	–	1.07 (1.33)/1.24 (1.87)
Vikram, 2003 (11)	Indian children	377	12	18.2/16.9	20.1/19.9	70.6/68.2	0.82/0.77	0.5/0.4*
Visser, 2001 (86)	American children	3,512	51	12	19.7/20.1			–
Warnberg, 2006 (87)	Spanish children	472	47	15.28/15.24	20.13/20.42	72.6/68.9	0.81/0.75	–
Wu, 2003 (9)	Taiwanese children	835	51	13.3	21/20.6	68.4/63.1	0.78/0.71	0.301/0.188*
Yoshida, 2006 (88)	Japanese children	568	40	9.2	–	–	–	1.08 (1.5)/0.82 (1.28)

Studies are listed in alphabetical order. Numbers separated by a slash denotes values in males/females in total population.

*Median values (IQR) reported.

†Age range reported.

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; WC, waist circumference; WHR, waist-hip ratio.