SYSTEMATIC REVIEWS AND META-ANALYSES

Differences in the levels of inflammatory markers between metabolically healthy obese and other obesity phenotypes in adults: A systematic review and meta-analysis

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Abstract *Aims:* The aim of this study was to systematically review and analyze differences in the levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) comparing metabolically healthy but obese (MHO) with metabolically healthy non-obese (MHNO), metabolically unhealthy non-obese (MUNO), and metabolically unhealthy obese (MUO) subjects.

Data synthesis: We searched PubMed, Embase, Web of Science, and Scopus for studies that matched the relevant search terms. Differences in inflammatory marker levels between MHO and the other three phenotypes were pooled as standardized mean differences (SMD) or differences of medians (DM) using a random-effects model. We included 91 studies reporting data on 435,106 individuals. The CRP levels were higher in MHO than in MHNO subjects (SMD = 0.63, 95% CI: 0.49, 0.77; DM = 0.91 mg/L, 95% CI: 0.58, 1.24). The CRP levels were higher in MHO than in MUNO subjects (SMD = 0.17, 95% CI: 0.05, 0.28; DM = 0.44 mg/L, 95% CI: 0.10, 0.78). The CRP levels were lower in MHO than in MUO individuals (SMD = −0.43, 95% CI: −0.54, −0.31; DM = −0.83 mg/L, 95% CI: −1.18, −0.47). The IL-6 levels were lower in MHO than in MUO subjects. The TNF-α levels in MHO were higher than in MHNO individuals.

Conclusions: This review provides evidence that CRP levels in MHO are higher than in MHNO and MUNO subjects but lower than in MUO individuals. Additionally, IL-6 levels in MHO are lower than in MUO subjects, and TNF-α levels in MHO are higher than in MHNO individuals.

Systematic review registration: PROSPERO number: CRD42021234948.

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1. Introduction

The prevalence of obesity is increasing worldwide, with more than 1 billion people expected to be affected by this condition in the next 10 years [1]. Obesity is associated with several metabolic abnormalities, including insulin resistance, dyslipidemia and hypertension. Consequently, obesity is a risk factor for the development of type 2 diabetes and cardiovascular diseases [2]. However, accumulating evidence suggests that obesity does not always entail metabolic abnormalities and obesity-related cardio-metabolic complications [3]. There is an obese subgroup of individuals who retain a healthy metabolic profile, designated the metabolically healthy obese (MHO). This term describes a specific subpopulation in which several or all of the components of metabolic syndrome are absent. Most commonly, this favorable metabolic profile is characterized by a high degree of insulin sensitivity, a low prevalence of hypertension, and a favorable lipid profile in an individual with a body mass index (BMI) above a defined cut-off point based on ethnicity [4–6].

Recently, it was proposed that low-grade inflammation may be an important factor explaining metabolic differences among subgroups of obesity [7]. Subclinical, chronic inflammation is believed to originate from the adipose tissue, and it is a potential factor in the development of metabolic syndrome [8,9]. More precisely, the expansion of visceral adipose tissue is considered to have a central role in increased obesity-related inflammation [10]. During this progression, macrophage infiltration in adipose tissue induces chronic oxidative stress and an inflammatory response, which are underlying factors that lead to the development of other metabolic abnormalities, diabetes, and cardiovascular diseases via altered immune responses and endothelial dysfunction [11,12]. A meta-analysis suggested that a transition from MHO to an unhealthy state increases the risk of cardiovascular diseases [13]. While MHO may be an unstable state, it is unknown whether inflammation level is associated with the favorable cardio-metabolic profile of MHO subjects and if different combinations of the presence of obesity and metabolic health phenotypes have different levels of inflammatory markers.

Inflammatory cytokines behave dynamically in relation to the metabolic state [14]. Studies have shown that inflammatory markers are positively associated with insulin resistance and features of metabolic syndrome, independent of the degree of obesity [15,16]. Studies on the levels of inflammatory markers among obesity phenotypes have reported various findings [17–20], especially for the 'healthy obesity' subgroup [21,22]. To date, no systematic review has been performed to evaluate the available evidence on this topic. Thus, the objective of the current study was to systematically review the currently available scientific literature on the differences between MHO and other obese phenotypes in the three most commonly measured and reported inflammatory markers: C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).

2. Methods

2.1. Search strategy

Two investigators (ZS and LE) independently conducted an electronic literature search using four bibliographic databases, PubMed, Embase, Web of Science, and Scopus, for articles published in English before March 31, 2021 (search updated on January 31, 2022, and May 4, 2023), using the following keywords: ('C-Reactive Protein' OR 'Interleukin' OR 'Tumor Necrosis Factor' OR 'Inflammatory' OR 'Inflammation') AND ('Metabolically healthy obesity' OR 'Obesity phenotypes'). We found additional articles by searching the reference lists of the included studies. The full search string is reported in the Supplementary Document (Supplementary Document Table 1). The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO ID number: CRD42021234948). This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

2.2. Study selection criteria

We included studies that 1) compared data on the inflammatory marker(s) between MHO participants and metabolically healthy non-obese (MHNO), metabolically unhealthy non-obese (MUNO), or metabolically unhealthy obese (MUO) subjects; 2) reported blood levels of inflammatory cytokines; 3) defined a metabolic abnormality and the obesity cut-off point; 4) applied a definition of metabolic syndrome based on the following four components: blood pressure, high-density lipoprotein cholesterol, triglycerides, and blood glucose levels; and 5) the study type was a cross-sectional study or cross-sectional analysis of the inflammatory markers.

Studies were excluded if 1) participants were children or adolescents; 2) the study focused solely on morbidly obese participants (BMI $\geq$40 kg/m^2); 3) the definition of a metabolic abnormality included the CRP level as a parameter; and 4) they were review articles, case reports, letters to the editor, or conference abstracts without full-text availability.

2.3. Data extraction

Two authors (ZS and LE) independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by discussion with the third investigator (RM). The characteristics that were extracted from each article were as follows: first author's name, publication year, sample size, definition of metabolic abnormalities and obesity, mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) of levels of inflammatory markers for each phenotype, sex, age, and geographical location of the study participants.

Table 1 Characteristics of the included studies.

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Abolnezhadian et al., 2020 [86]	Iran	159	Men and women MHNO: n = 42, M: NR MUNO: n = 51, M: NR MUO: n = 42, M: NR MHO: n = 24, M: NR	NCEP ATP III No WC NR	CRP, IL-6	5
Acharya et al., 2019 [30]	India	303	Men and women MHNO: n = 81, M: 64.2% MHO: n = 222, M: 45.1%	NCEP ATP III Include WC >2	CRP	6
Ahl et al., 2015 [60]	United States	933	Men and women MHNO: n = 248, M: 39.4% MUNO: n = 694, M: 38.6% MUO: n = 1443, M: 21.3% MHO: n = 101, M: 26.7%	Modified NCEP ATP III No WC >0	IL-6, TNF-α	6
Bagheri et al., 2018 [61]	Iran	285	Men and women MHNO: n = 78, M: 38.0% MUO: n = 100, M: 49.0% MHO: n = 107, M: 36.0%	IDF No WC >1	CRP	6
Bañuls et al., 2017 [29]	Spain	82	Men and women MUO: n = 53, M: 41.5% MHO: n = 29, M: 13.8%	NCEP ATP III No WC >1	CRP	6
Berezin et al., 2017 [87]	Ukraine	89	Men and women MUO: n = 47, M: 53.2% MHO: n = 42, M: 52.4%	NCEP ATP III Include WC >1	CRP	6
Bhansali et al., 2017 [43]	India	60	Men and women MHNO: n = 20, M: 60.0% MUO: n = 20, M: 55.0% MHO: n = 20, M: 55.0%	NCEP ATP III Include WC >1	CRP, IL-6	4
Buscemi et al., 2017 [18]	Italy	1016	Men and women MHNO: n = 187, M: 24.6% MUNO: n = 97, M: 45.4% MUO: n = 530, M: 48.5% MHO: n = 202, M: 30.2%	Modified harmonized definition No WC >1	CRP	7
Canpolat et al., 2021 [52]	Turkey	150	Men and women MHNO: n = 50, M: 52.0% MUO: n = 50, M: 46.0% MHO: n = 50, M: 48.0%	NCEP ATP III Include WC >2	CRP	5
Carvalho et al., 2018 [19]	Brazil	61	Men and women MHNO: n = 24, M: 50.0% MUO: n = 21, M: 61.9% MHO: n = 16, M: 37.5%	Modified NCEP ATP III Include WC >2	TNF-α	7
Carvalho et al., 2018 [20]	Brazil	42	Men and women MUO: n = 23, M: 39.1% MHO: n = 19, M: 36.8%	NCEP ATP III Include WC >2	IL-6, TNF-α	8
Christou et al., 2020 [31]	Greece	83	Men and women MHNO: n = 25, M: 40.0% MUO: n = 33, M: 48.5% MHO: n = 25, M: 44.0%	American heart association Include WC >2	CRP	6
Chung et al., 2018 [96]	Korea	290	Men and women MHNO: n = 145, M: 62.8% MUNO: n = 23, M: 56.5% MUO: n = 63, M: 71.4% MHO: n = 59, M: 69.5%	NCEP ATP III NR NR	CRP	7
Cui et al., 2022 [107]	China	22,781	Men and women MHNO: n = 13,162, M: 71.2% MUNO: n = 2703, M: 81.0% MUO: n = 3346, M: 83.5% MHO: n = 3570, M: 77.6%	Harmonized definition No WC >1	CRP	7
Demirci et al., 2021 [54]	Turkey	90	Only women MUO: n = 44, M: 0% MHO: n = 46, M: 0%	NCEP ATP III Include WC >2	CRP	6
Donini et al., 2016 [62]	Italy	253	Men and women MUO: n = 151, M: NR MHO: n = 102, M: NR	NCEP ATP III Include WC >2	CRP	7

Table 1 (*continued*)

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Dwivedi et al., 2020 [44]	India	243	Men and women MHNO: n = 96, M: 54.2% MHO: n = 147, M: 50.3%	NCEP ATP III Include WC >2	CRP, IL-6, TNF-α	5
Efremov et al., 2020 [32]	Germany	1412	Men and women MHNO: n = 345, M: 46.1% MUNO: n = 638, M: 63.2% MUO: n = 369, M: 54.7% MHO: n = 60, M: 28.4%	Harmonized definition No WC >1	CRP, IL-6	7
Esser et al., 2013 [45]	Belgium	53	Men and women MHNO: n = 9, M: 55.6% MUO: n = 23, M: 30.4% MHO: n = 21, M: 14.3%	Harmonized definition Include WC >2	CRP	4
Esteghamati et al., 2014 [33]	Iran	4391	Men and women MUO: n = 2591, M: 38.7% MHO: n = 1800, M: 21.9%	IDF Include WC >2	CRP	7
Feng et al., 2019 [102]	Norway	27,123	Men and women MHNO: n = 14,327, M: 36.9% MUNO: n = 2043, M: 22.6% MUO: n = 7798, M: 48.8% MHO: n = 2955, M: 31.7%	IDF Include WC >2	CRP	8
Fu et al., 2022 [56]	China	541	Men and women MUO: n = 490, M: 17.6% MHO: n = 51, M: 83.7%	NCEP ATP III No WC >0	CRP	6
Gregorio-Arenas et al., 2016 [34]	Spain	228	Only women MHNO: n = 119, M: 0% MUNO: n = 39, M: 0% MUO: n = 40, M: 0% MHO: n = 30, M: 0%	Harmonized definition No WC >1	CRP	6
Hjelmgren et al., 2020 [88]	Sweden	326	Only women MHNO: n = 180, M: 0% MUO: n = 93, M: 0% MHO: n = 53, M: 0%	NCEP ATP III Include WC >2	CRP	6
Hosseini et al., 2020 [63]	Iran	154	Only women MHNO: n = 53, M: 0% MUO: n = 44, M: 0% MHO: n = 57, M: 0%	NCEP ATP III Include WC >2	CRP	5
Iglesias et al., 2017 [38]	Argentina	1458	Men and women MHNO: n = 937, M: 60.8% MUO: n = 318, M: 60.4% MHO: n = 203, M: 58.1%	NCEP ATP III Include WC >2	CRP	6
Iglesias et al., 2017 [72]	Argentina	340	Only women MHNO: n = 196, M: 0% MUO: n = 102, M: 0% MHO: n = 42, M: 0%	NCEP ATP III Include WC >2	CRP	7
Jae et al., 2018 [64]	Finland	2185	Only men MHNO: n = 232, M: 100% MUNO: n = 439, M: 100% MUO: n = 1321, M: 100% MHO: n = 193, M: 100%	NCEP ATP III No WC >0	CRP	7
Jamka et al., 2019 [42]	Poland	300	Only women MUO: n = 199, M: 0% MHO: n = 101, M: 0%	NCEP ATP III Include WC >2	CRP	5
Jung et al., 2015 [47]	Korea	36,135	Men and women MHNO: n = 20,491, M: 44.6% MUNO: n = 4696, M: 68.8% MUO: n = 4909, M: 84.2% MHO: n = 6039, M: 75.7%	NCEP ATP III No WC >1	CRP	6
Jung et al., 2015 [104]	Korea	41,194	Men and women MHNO: n = 20,329, M: 43.6% MUNO: n = 4835, M: 69.0% MUO: n = 7443, M: 83.8% MHO: n = 8587, M: 75.5%	NCEP ATP III No WC >1	CRP	7

Table 1 (*continued*)

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Kang et al., 2016 [89]	Korea	31,033	Men and women MHNO: n = 17,975, M: 41.9% MUNO: n = 2696, M: 65.9% MUO: n = 3569, M: 83.9% MHO: n = 6793, M: 74.7%	NCEP ATP III No WC >1	CRP	7
Kang et al., 2019 [50]	Korea	59	Only women MUO: n = 14, M: 0% MHO: n = 45, M: 0%	NCEP ATP III Include WC >2	TNF-α	6
Keirns et al., 2021 [108]	Unite State	20	Men and women MHNO: n = 10, M: NR MHO: n = 10, M: NR	IDF No WC >1	IL-6, TNF-α	5
Kim et al., 2013 [90]	Korea	492	Men and women MHNO: n = 260, M: 30.0% MUNO: n = 53, M: 37.7% MUO: n = 84, M: 48.8% MHO: n = 95, M: 43.2%	NCEP ATP III Include WC >2	CRP	6
Kim et al., 2017 [65]	Korea	117	Men and women MUO: n = 45, M: 20.0% MHO: n = 72, M: 22.2%	NCEP ATP III Include WC >2	CRP, IL-6, TNF-α	7
Koborová et al., 2017 [35]	Slovakia	114	Only women MHNO: n = 47, M: 0% MUO: n = 50, M: 0% MHO: n = 17, M: 0%	Modified Lynch Include WC NR	CRP	6
Kouvari et al., 2019 [66]	Greece	1890	Men and women MHNO: n = 686, M: 40.0% MUNO: n = 672, M: 54.0% MUO: n = 425, M: 58.0% MHO: n = 107, M: 50.0%	Harmonized definition No WC >0	CRP	7
Kouvari et al., 2022 [105]	Greece	2817	Men and women MHNO: n = 1085, M: 40.0% MUNO: n = 1069, M: 54.0% MUO: n = 517, M: 58.0% MHO: n = 146, M: 50.0%	NCEP ATP III No WC >0	CRP	7
Kucharska et al., 2019 [98]	Poland	138	Men and women MUO: n = 96, M: 49.0% MHO: n = 42, M: 52.4%	IDF Include WC >2	CRP	5
Kwon et al., 2013 [109]	Korea	856	Men and women MHNO: n = 263, M: 60.1% MUNO: n = 187, M: 43.3% MUO: n = 317, M: 50.8% MHO: n = 89, M: 57.3%	NCEP ATP III Include WC >2	CRP	7
Lai et al., 2021 [67]	Taiwan	2944	Men and women MHNO: n = 566, M: 38.3% MUNO: n = 555, M: 59.8% MUO: n = 1534, M: 78.8% MHO: n = 289, M: 70.6%	NCEP ATP III No WC >0	CRP	7
Lassale et al., 2018 [68]	10 European countries	6310	Men and women MHNO: n = 4282, M: 36.3% MUNO: n = 368, M: 35.2% MUO: n = 909, M: 43.3% MHO: n = 751, M: 38.3%	Harmonized definition Include WC >2	CRP	7
Lee et al., 2013 [103]	Korea	1662	Men and women MHNO: n = 535, M: 49.0% MUNO: n = 382, M: 32.0% MUO: n = 610, M: 35.0% MHO: n = 135, M: 84.4%	NCEP ATP III Include WC >0	CRP	8
Lee et al., 2015 [21]	Korea	456	Men and women MHNO: n = 247, M: 51.8% MUNO: n = 66, M: 74.2% MUO: n = 77, M: 24.9% MHO: n = 66, M: 83.4%	Modified Wildman No WC >1	IL-6, TNF-α	4

(*continued on next page*)

Table 1 (*continued*)

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Lee et al., 2018 [69]	Korea	659	Men and women MHNO: n = 158, M: 44.3% MUNO: n = 223, M: 48.0% MUO: n = 206, M: 55.8% MHO: n = 72, M: 62.5%	Harmonized definition No WC >1	CRP	7
Lejawa et al., 2021 [70]	Poland	98	Only men MHNO: n = 49, M: 100% MUO: n = 22, M: 100% MHO: n = 27, M: 100%	NCEP ATP III Include WC >2	CRP	4
Lejawa et al., 2021 [95]	Poland	95	Only men MHNO: n = 47, M: 100% MUO: n = 26, M: 100% MHO: n = 22, M: 100%	NCEP ATP III Include WC >2	CRP	5
Lin et al., 2017 [46]	China	2491	Men and women MHNO: n = 758, M: 40.2% MUNO: n = 485, M: 37.5% MUO: n = 807, M: 39.9% MHO: n = 441, M: 37.9%	NCEP ATP III No WC >1	CRP	6
Mangge et al., 2013 [91]	Austria	110	Men and women MUO: n = 79, M: 57.0% MHO: n = 31, M: 29.0%	IDF Include WC >2	CRP, IL-6	5
Manu et al., 2012 [24]	United State	1487	Men and women MHNO: n = 1173, M: 50.6% MHO: n = 314, M: 38.2%	American heart association Include WC >2	CRP	7
Martínez-Larrad et al., 2014 [36]	Spain	1059	Men and women MUO: n = 636, M: 38.2% MHO: n = 423, M: 38.1%	the Consensus Societies Include WC >2	CRP	7
Masi et al., 2022 [53]	Italy	2567	Men and women MUO: n = 1872, M: 25.4% MHO: n = 695, M: 17.7%	NCEP ATP III Include WC >1	CRP	5
Matta et al., 2016 [71]	Lebanon	196	Men and women MUO: n = 123, M: 66.0% MHO: n = 73, M: 40.0%	NCEP ATP III No WC >1	CRP	7
Mesgari-Abbasi et al., 2020 [99]	Iran	40	Men and women MUO: n = 20, M: 25.0% MHO: n = 20, M: 15.0%	NCEP ATP III Include WC >2	CRP	6
Mojiminiyi et al., 2010 [25]	Kuwait	396	Men and women MHNO: n = 94, M: 36.1% MUNO: n = 32, M: 37.5% MUO: n = 69, M: 36.2% MHO: n = 201, M: 35.8%	NCEP ATP III Include WC >2	CRP	6
Nguedjo et al., 2022 [58]	Cameroon	324	Men and women MUO: n = 300, M: NR MHO: n = 24, M: NR	Meigs Include WC >2	CRP, TNF-α	6
Ogorodnikova et al., 2013 [73]	United States	636	Only women MHNO: n = 251, M: 0% MUO: n = 89, M: 0% MHO: n = 296, M: 0%	NCEP ATP III No WC >1	CRP	6
Oguoma et al., 2022 [57]	Kuwait	1712	Men and women MHNO: n = 702, M: 53.0% MUNO: n = 207, M: 75.8% MUO: n = 275, M: 48.7% MHO: n = 528, M: 39.6%	Harmonized definition No WC >1	CRP	6
Oliveira et al., 2021 [74]	Brazil	303	Men and women MHNO: n = 43, M: 35.0% MUNO: n = 99, M: 56.0% MUO: n = 151, M: 50.0% MHO: n = 10, M: 20.0%	Harmonized definition No WC >0	IL-6, TNF-α	5

Table 1 (*continued*)

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Ostrovskaya et al., 2020 [75]	Russia	77	Men and women MUO: n = 33, M: NR MHO: n = 44, M: NR	Modified IDF No WC NR	CRP, IL-6, TNF-α	6
Pajunen et al., 2011 [48]	Finland	1620	Men and women MHNO: n = 712, M: 43.8% MUNO: n = 205, M: 39.0% MUO: n = 609, M: 44.2% MHO: n = 94, M: 28.7%	Harmonized definition Include WC >2	CRP	5
Park et al., 2011 [92]	Korea	1824	Men and women MHNO: n = 286, M: 45.0% MUNO: n = 467, M: 41.0% MUO: n = 1000, M: 53.0% MHO: n = 71, M: 52.0%	NCEP ATP III Include WC >0	CRP	6
Perreault et al., 2014 [39]	Canada	30	Men and women MHNO: n = 10, M: 30.0% MUO: n = 10, M: 30.0% MHO: n = 10, M: 30.0%	Karelis No WC >2	CRP, IL-6	6
Phillips et al., 2013 [41]	Ireland	2040	Men and women MHNO: n = 340, M: NR MUNO: n = 1032, M: NR MUO: n = 573, M: NR MHO: n = 95, M: NR	Meigs Include WC >2	CRP, IL-6, TNF-α	5
Poggiogalle et al., 2019 [76]	Italy	54	Only women MUO: n = 29, M: 0% MHO: n = 25, M: 0%	NCEP ATP III NR NR	CRP	6
Rasheed et al., 2020 [49]	India	240	Men and women MHNO: n = 120, M: 50.0% MHO: n = 120, M: 45.0%	NCEP ATP III Include WC >2	CRP	7
Roberson et al., 2014 [40]	Brazil	208	Men and women MHNO: n = 21, M: 38.0% MUNO: n = 43, M: 33.0% MUO: n = 116, M: 16.0% MHO: n = 28, M: 14.0%	NCEP ATP III No WC >1	CRP	5
Romagnolli et al., 2020 [77]	Brazil	10,335	Men and women MHNO: n = 1484, M: 24.6% MUNO: n = 6660, M: 49.3% MUO: n = 2067, M: 41.2% MHO: n = 124, M: 13.7%	Harmonized definition No WC >0	CRP	7
Ruiz et al., 2013 [78]	Spain	78	Only women MUO: n = 25, M: 0% MHO: n = 53, M: 0%	American heart association Include WC >1	CRP, TNF-α	7
Shaharyar et al., 2015 [22]	Brazil	5519	Men and women MHNO: n = 1864, M: 59.0% MUNO: n = 259, M: 80.0% MUO: n = 1371, M: 92.0% MHO: n = 2025, M: 85.0%	NCEP ATP III No WC >1	CRP	4
Shin et al., 2006 [51]	Korea	129	Only women MUO: n = 106, M: 0% MHO: n = 23, M: 0%	Modified NCEP ATP III No WC >1	CRP, IL-6	4
Strack et al., 2012 [79]	Germany	96	Men and women MUO: n = 41, M: 41.0% MHO: n = 55, M: 31.0%	NCEP ATP III Include WC >2	CRP, IL-6, TNF-α	5
Thomsen et al., 2014 [100]	Denmark	42,948	Men and women MHNO: n = 28,431, M: 33.0% MUNO: n = 3021, M: 38.0% MUO: n = 7080, M: 55.0% MHO: n = 4416, M: 32.0%	Modified harmonized definition Include WC >2	CRP	8
Tian et al., 2022 [106]	China	4160	Men and women MHNO: n = 2548, M: 46.6% MUNO: n = 955, M: 45.2% MUO: n = 459, M: 43.8% MHO: n = 198, M: 35.9%	NCEP ATP III No WC >1	CRP	5

Table 1 (*continued*)

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Torres-Castilloe et al., 2018 [97]	Mexico	238	Men and women MHNO: n = 93, M: 24.7% MUNO: n = 40, M: 30.0% MUO: n = 85, M: 17.6% MHO: n = 20, M: 15.0%	Modified NCEP ATP III No WC >1	CRP	7
Tsou et al., 2021 [37]	Taiwan	2846	Men and women MHNO: n = 1793, M: 68.7% MUNO: n = 423, M: 73.8% MUO: n = 403, M: 84.6% MHO: n = 227, M: 77.5%	NCEP ATP III Include WC >2	CRP	7
Vigevano et al., 2021 [55]	USA	112	Only men MUO: n = 97, M: 100% MHO: n = 15, M: 100%	NCEP ATP III No WC >0	IL-6	6
Wang et al., 2016 [80]	China	1292	Men and women MHNO: n = 415, M: 48.7% MUNO: n = 249, M: 43.8% MUO: n = 397, M: 46.9% MHO: n = 231, M: 59.3%	NCEP ATP III No WC >1	CRP	7
Wang et al., 2016 [81]	China	151	Men and women MHNO: n = 41, M: NR MUNO: n = 37, M: NR MUO: n = 43, M: NR MHO: n = 30, M: NR	NCEP ATP III No WC >1	CRP	6
Wang et al., 2022 [59]	China	88	Men and women MHNO: n = 49, M: 63.3% MHO: n = 39, M: 64.1%	NCEP ATP III No WC >1	IL-6, TNF-α	6
Xu et al., 2018 [94]	China	52,743	Men and women MHNO: n = 29,279, M: 76.1% MUNO: n = 6161, M: 76.8% MUO: n = 10,558, M: 81.3% MHO: n = 6745, M: 80.2%	IDF Include WC >2	CRP	8
Yang et al., 2021 [82]	China	12,499	Men and women MHNO: n = 9578, M: 34.1% MHO: n = 2921, M: 60.6%	Harmonized definition NR NR	CRP	7
Yoo et al., 2013 [26]	Korea	186	Only men MUO: n = 55, M: 100% MHO: n = 131, M: 100%	NCEP ATP III Include WC >2	CRP	5
Yoo et al., 2014 [101]	Korea	1012	Men and women MHNO: n = 555, M: 47.8% MUNO: n = 65, M: 47.7% MUO: n = 161, M: 73.9% MHO: n = 231, M: 69.3%	NCEP ATP III Include WC >2	CRP	7
Yoo et al., 2015 [28]	Korea	250	Men and women MHNO: n = 108, M: 42.6% MUNO: n = 30, M: 50.0% MUO: n = 53, M: 30.2% MHO: n = 59, M: 27.1%	NCEP ATP III Include WC >2	CRP	6
Yoo et al., 2016 [83]	Korea	1200	Men and women MHNO: n = 585, M: NR MUNO: n = 182, M: NR MUO: n = 235, M: NR MHO: n = 198, M: NR	NCEP ATP III Include WC >2	CRP	7
Zhang et al., 2014 [17]	China	2530	Men and women MHNO: n = 357, M: 54.3% MUNO: n = 1262, M: 51.1% MUO: n = 836, M: 21.9% MHO: n = 75, M: 10.7%	Modified NCEP ATP III No WC >0	CRP	7
Zhou et al., 2020 [85]	China	48	Men and women MUO: n = 26, M: 50.0% MHO: n = 22, M: 36.4%	NCEP ATP III No WC >2	CRP	3

Table 1 (continued)

Study, year	Country	Total sample size	Sample size for each phenotype and sex of participants	MetS definition/ n. components[a]	Inflammatory markers	Quality score
Zhao et al., 2022 [84]	China	55,584	Men and women MHNO: n = 20,083, M: 76.6% MUNO: n = 7915, M: 81.7% MUO: n = 14,080, M: 83.7% MHO: n = 135,056, M: 81.6%	Harmonized definition No WC >1	CRP	7
Zhao et al., 2023 [93]	China	31,128	Men and women MHNO: n = 15,968, M: 71.1% MUNO: n = 4983, M: 78.0% MUO: n = 5878, M: 81.0% MHO: n = 4299, M: 78.0%	Harmonized definition No WC >1	CRP	7

Abbreviations: M: men; n: number; MHO: metabolically healthy obese; MHNO: metabolically healthy non-obese; MUNO: metabolically unhealthy non-obese; MUO: metabolically unhealthy obese; MetS: metabolic syndrome; NCEP ATP III: National Cholesterol Education Programme Adult Treatment Panel III; IDF: International Diabetes Federation; CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; NR: not reported; WC: waist circumference.

[a] Number of abnormal metabolic syndrome components to define metabolic unhealthy; *: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK.

2.4. Quality assessment of studies

We developed a custom quality assessment scale, using several items from the Newcastle-Ottawa Scale, in combination with the National Heart, Lung, and Blood Institute (NHLBI) scale [23]. Study quality was evaluated with respect to participant selection, the measurement of inflammatory markers, the comparability of confounders, and the reliability of the study outcome. As a qualitative description of the studies, scores from 0 to 3, 4 to 6, and 7 to 8 points were used to divide the studies into three groups: low, moderate, and high quality. The custom scale we developed is included in the Supplementary Document (Supplementary Document Table 2).

2.5. Statistical analysis

For studies that reported the mean ± SD, we calculated standardized mean differences (SMD) and 95% confidence intervals (CI). For studies that reported the mean ± standard error (SE) or mean with 95% CI, we converted the SE or 95% CI to standard deviation. For studies that reported the median (IQR), the median of the difference of median (DM) and 95% CI were calculated. Both SMDs and DMs were analyzed separately using random-effects models. Two studies reported the mean ± SD for men and women separately [24,25], while another study stratified the data by age [26]. In this case, we pooled both means to derive a single estimate for inclusion in the meta-analysis. Heterogeneity between studies was quantified using the I^2 statistic. The presence of publication bias was investigated graphically with funnel plots and with the Begg and Egger tests. We used the trim and fill method to provide an estimate of the number of missing studies and an estimate of the pooled effect size if these studies were to be included in the analysis. As a sensitivity analysis, to determine the effect of the sample size on our estimate, we converted the median (IQR) CRP levels to means ± SD using the formula as reported by

Wan et al. [27] and pooled all available studies for a summary effect estimate. The reference group was the MHO phenotype.

Sources of heterogeneity with respect to CRP across studies were explored by performing subgroup analyses by geographical location, metabolic syndrome definition, number of abnormal metabolic syndrome definition components to define metabolic unhealthy by including or excluding waist circumference, and obesity cut-off points (either BMI ≥25 kg/m² or BMI ≥30 kg/m² based on the ethnicity of the study population). We did not perform a subgroup analysis for IL-6 and TNF-α due to the limited number of available studies. The threshold for statistical significance was set at p < 0.05. All statistical analyses were performed using either the metan package in STATA (version 15; Stata Corporation, College Station, TX, USA) or the metamedian package in R 4.1.0 (R Core Team, 2021).

3. Results

3.1. Search results

The search identified 11,591 potentially eligible articles, of which 1686 duplicates were excluded. After excluding 9605 papers through title and abstract review, we screened 400 full-text articles. In total, 91 articles were included in the systematic review and meta-analysis [17–22,24–26,28–109]. One article reported analyses of two separate populations [38], and we analyzed these two populations separately. For studies that reported data based on several different definitions of metabolic syndrome, we only selected the data from the definition that was part of the eligibility criteria. A flowchart presenting the study selection process is shown in Fig. 1.

The general characteristics of the included studies are presented in Table 1. In total, 435,106 individuals were included. According to geographic location, 44 studies were conducted in Asia, 31 in Europe, 7 in North America,

Table 2 Summary of meta-analysis and subgroup analysis for CRP.

	Studies reported data as mean ± SD			Studies reported data as median (IQR)		
	N	SMD (95% CI)	Heterogeneity (I^2 and p)	N	DM (95% CI)	Heterogeneity (I^2 and p)
Overall analyses						
MHNO	32	0.63 (0.49, 0.77)	$I^2 = 96.7\%$, p < 0.0001	27	0.91 (0.58, 1.24)	$I^2 = 99.9\%$, p < 0.0001
MUNO	20	0.17 (0.05, 0.28)	$I^2 = 91.4\%$, p < 0.0001	21	0.44 (0.10, 0.78)	$I^2 = 99.8\%$, p < 0.0001
MUO	44	−0.43 (−0.54, −0.31)	$I^2 = 95.9\%$, p < 0.0001	34	−0.83 (−1.18, −0.47)	$I^2 = 99.7\%$, p < 0.0001
Subgroup analyses by MetS definition						
MHNO	27	0.52 (0.38, 0.66)	$I^2 = 94.5\%$, p < 0.0001	24	0.80 (0.48, 1.13)	$I^2 = 99.9\%$, p < 0.0001
MUNO	16	0.08 (−0.01, 0.17)	$I^2 = 76.8\%$, p < 0.0001	19	0.33 (−0.02, 0.67)	$I^2 = 99.7\%$, p < 0.0001
MUO	37	−0.32 (−0.42, −0.23)	$I^2 = 90.1\%$, p < 0.0001	31	−0.89 (−1.30, −0.49)	$I^2 = 99.8\%$, p < 0.0001
Subgroup analyses by the number of MetS definition components to define metabolically unhealthy						
Include waist circumference						
More than 0 component						
MHNO	2	0.05 (−0.10, 0.20)	$I^2 = 0.0\%$, p = 0.98	0	NA	NA
MUNO	2	0.01 (−0.15, 0.16)	$I^2 = 0.0\%$, p = 0.89	0	NA	NA
MUO	2	0.00 (−0.15, 0.14)	$I^2 = 0.0\%$, p = 0.95	0	NA	NA
More than 1 component						
MHNO	1	NA	NA	0	NA	NA
MUNO	0	NA	NA	0	NA	NA
MUO	2	−0.67 (−1.44, 0.09)	$I^2 = 81.2\%$, p = 0.02	1	NA	NA
More than 2 components						
MHNO	15	0.70 (0.47, 0.94)	$I^2 = 96.6\%$, p < 0.0001	7	2.23 (0.64, 3.82)	$I^2 = 83.9\%$, p = 0.0003
MUNO	6	0.04 (−0.09, 0.18)	$I^2 = 70.2\%$, p = 0.01	4	−0.11 (−0.38, 0.15)	$I^2 = 0.0\%$, p = 0.88
MUO	21	−0.42 (−0.56, −0.28)	$I^2 = 93.2\%$, p < 0.0001	12	−1.18 (−1.87, −0.50)	$I^2 = 50.1\%$, p = 0.01
Not including waist circumference						
More than 0 components						
MHNO	4	0.37 (0.15, 0.59)	$I^2 = 83.8\%$, p < 0.0001	1	NA	NA
MUNO	4	0.24 (−0.04, 0.52)	$I^2 = 90.7\%$, p < 0.0001	1	NA	NA
MUO	4	−0.14 (−0.22, −0.07)	$I^2 = 0.0\%$, p = 0.63	2	−1.83 (−4.35, 0.69)	$I^2 = 96.6\%$, p < 0.0001
More than 1 components						
MHNO	4	0.28 (0.05, 0.51)	$I^2 = 77.2\%$, p = 0.004	14	0.66 (0.29, 1.03)	$I^2 = 99.9\%$, p < 0.0001
MUNO	3	−0.01 (−0.13, 0.12)	$I^2 = 0.0\%$, p = 0.86	13	0.36 (−0.02, 0.73)	$I^2 = 99.8\%$, p < 0.0001
MUO	5	−0.20 (−0.31, −0.09)	$I^2 = 0.0\%$, p = 0.72	15	−0.22 (−0.24, −0.20)	$I^2 = 27.0\%$, p = 0.002
Subgroup analyses by obesity definition						
BMI ≥25 kg/m²						
MHNO	10	0.63 (0.21, 1.04)	$I^2 = 96.0\%$, p < 0.0001	11	0.23 (0.15, 0.31)	$I^2 = 95.7\%$, p < 0.0001
MUNO	4	−0.04 (−0.16, 0.08)	$I^2 = 3.9\%$, p = 0.37	11	0.03 (−0.04, 0.10)	$I^2 = 87.7\%$, p = 0.0003
MUO	10	−0.23 (−0.38, −0.09)	$I^2 = 60.1\%$, p = 0.01	12	−0.20 (−0.22, −0.18)	$I^2 = 0.3\%$, p = 0.002
BMI ≥30 kg/m						
MHNO	13	0.56 (0.39, 0.73)	$I^2 = 85.7\%$, p < 0.0001	7	1.97 (1.60, 2.33)	$I^2 = 18.8\%$, p = 0.07
MUNO	8	0.21 (0.04, 0.39)	$I^2 = 73.6\%$, p < 0.0001	3	1.68 (1.11, 2.24)	$I^2 = 58.7\%$, p = 0.08
MUO	20	−0.46 (−0.66, −0.27)	$I^2 = 92.3\%$, p < 0.0001	12	−1.45 (−2.42, −0.47)	$I^2 = 81.6\%$, p < 0.0001
Subgroup analyses by continent						
Asia						
MHNO	16	0.49 (0.28, 0.69)	$I^2 = 95.5\%$, p < 0.0001	17	0.60 (0.29, 0.90)	$I^2 = 99.9\%$, p < 0.0001
MUNO	11	−0.03 (−0.10, 0.04)	$I^2 = 39.0\%$, p = 0.09	15	0.18 (−0.15, 0.52)	$I^2 = 99.7\%$, p < 0.0001
MUO	20	−0.29 (−0.40, −0.19)	$I^2 = 85.9\%$, p < 0.0001	17	−0.69 (−1.10, −0.27)	$I^2 = 99.8\%$, p < 0.0001
North America						
MHNO	4	0.75 (0.41, 1.09)	$I^2 = 84.1\%$, p < 0.0001	0	NA	NA
MUNO	1	NA	NA	0	NA	NA
MUO	3	−0.22 (−0.68, 0.24)	$I^2 = 62.5\%$, p = 0.07	0	NA	NA
South America						
MHNO	3	0.60 (0.46, 0.74)	$I^2 = 0.0\%$, p = 0.59	3	1.01 (0.11, 1.90)	$I^2 = 81.4\%$, p = 0.01
MUNO	0	NA	NA	3	0.74 (−0.14, 1.62)	$I^2 = 79.6\%$, p = 0.01
MUO	3	−0.18 (−0.34, −0.02)	$I^2 = 0.0\%$, p = 0.67	3	−0.31 (−0.43, −0.19)	$I^2 = 0.0\%$, p = 0.55

Table 2 (*continued*)

	Studies reported data as mean ± SD			Studies reported data as median (IQR)		
	N	SMD (95% CI)	Heterogeneity (I^2 and p)	N	DM (95% CI)	Heterogeneity (I^2 and p)
Europe						
MHNO	9	0.88 (0.43, 1.33)	I^2 = 98.2%, p < 0.0001	7	2.05 (1.16, 2.94)	I^2 = 99.3%, p < 0.0001
MUNO	8	0.36 (0.09, 0.64)	I^2 = 94.8%, p < 0.0001	3	1.29 (0.53, 2.04)	I^2 = 99.0%, p < 0.0001
MUO	17	−0.62 (−0.92, −0.32)	I^2 = 98.1%, p < 0.0001	14	−1.27 (−2.10, −0.44)	I^2 = 98.7%, p < 0.0001

Abbreviations: MHO: metabolically healthy obese; MHNO: metabolically healthy non-obese; MUNO: metabolically unhealthy non-obese; MUO: metabolically unhealthy obese; MetS: metabolic syndrome; N: number of studies; NA: not available; CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; SMD: standardized mean difference; DM: difference of median.

8 in South America, and 1 in Africa. For the definition of metabolic syndrome components, 53 studies used the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria [110], 5 used the modified NCEP ATP III criteria, 7 used the International Diabetes Federation (IDF) criteria [111], 1 used modified IDF criteria, 3 used the American Heart Association Criteria [112], 14 used the harmonized definition criteria [113], 2 used the modified harmonized definition, 2 use Meigs, and 4 used other criteria (modified Lynch, Modified Wildman, the Consensus Societies, or Karelis). After performing the quality analyses, 38 articles were classified as high quality and 53 as moderate quality.

3.2. CRP

In total, 82 studies were included in the meta-analysis for the comparison of CRP levels between MHO and the other three phenotypes. Of these, 47 articles reported their data as mean ± SD and 35 reported the median (IQR). Of the articles that reported the mean ± SD, 32 studies compared MHO with MHNO, 20 studies compared MHO with MUNO, and 44 studies compared MHO with MUO. Of the studies that reported the median (IQR), 27 studies compared MHO with MHNO, 21 compared MHO with MUNO, and 34 compared MHO with MUO.

The results of studies that reported CRP levels as mean ± SD were similar to those of studies that reported the median (IQR). The CRP levels were higher in MHO than in MHNO individuals (SMD = 0.63, 95% CI: 0.49, 0.77, I^2 = 96.7%; DM = 0.91 mg/L, 95% CI: 0.58, 1.24, I^2 = 99.9%) (Table 2, Fig. 2). Additionally, the CRP levels were higher in MHO than in MUNO individuals (SMD = 0.17, 95% CI: 0.05, 0.28, I^2 = 91.4%; DM = 0.44 mg/L, 95% CI: 0.10, 0.78, I^2 = 99.8%) (Table 2, Fig. 3). Lower concentrations of CRP were observed in MHO than in MUO subjects (SMD = −0.43, 95% CI: −0.54, −0.31, I^2 = 95.9%; DM = −0.83 mg/L, 95% CI: −1.18, −0.47, I^2 = 99.7%) (Table 2, Fig. 4). High I^2 values
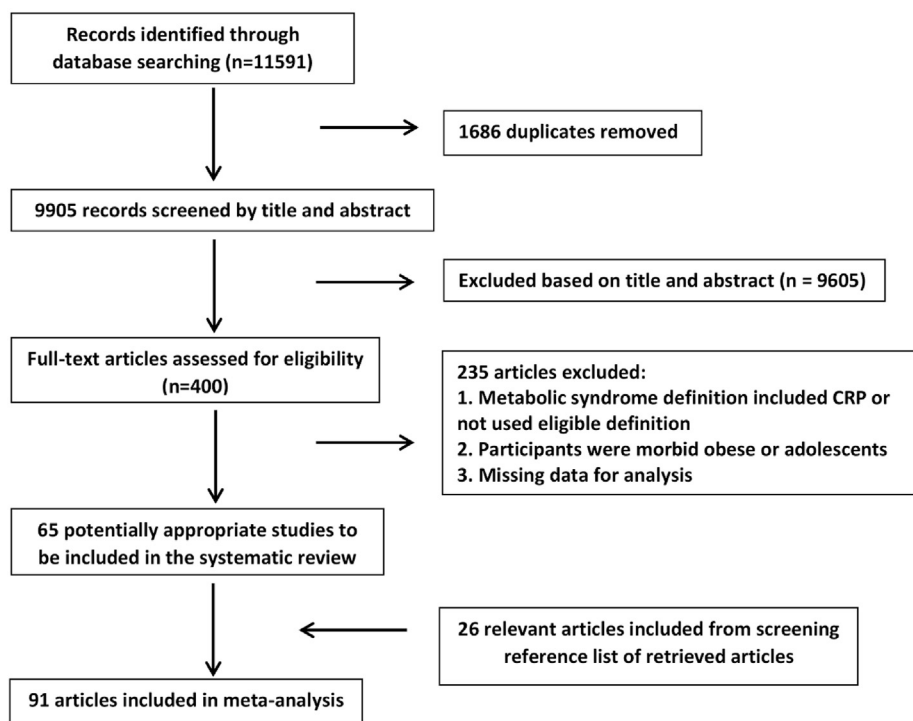
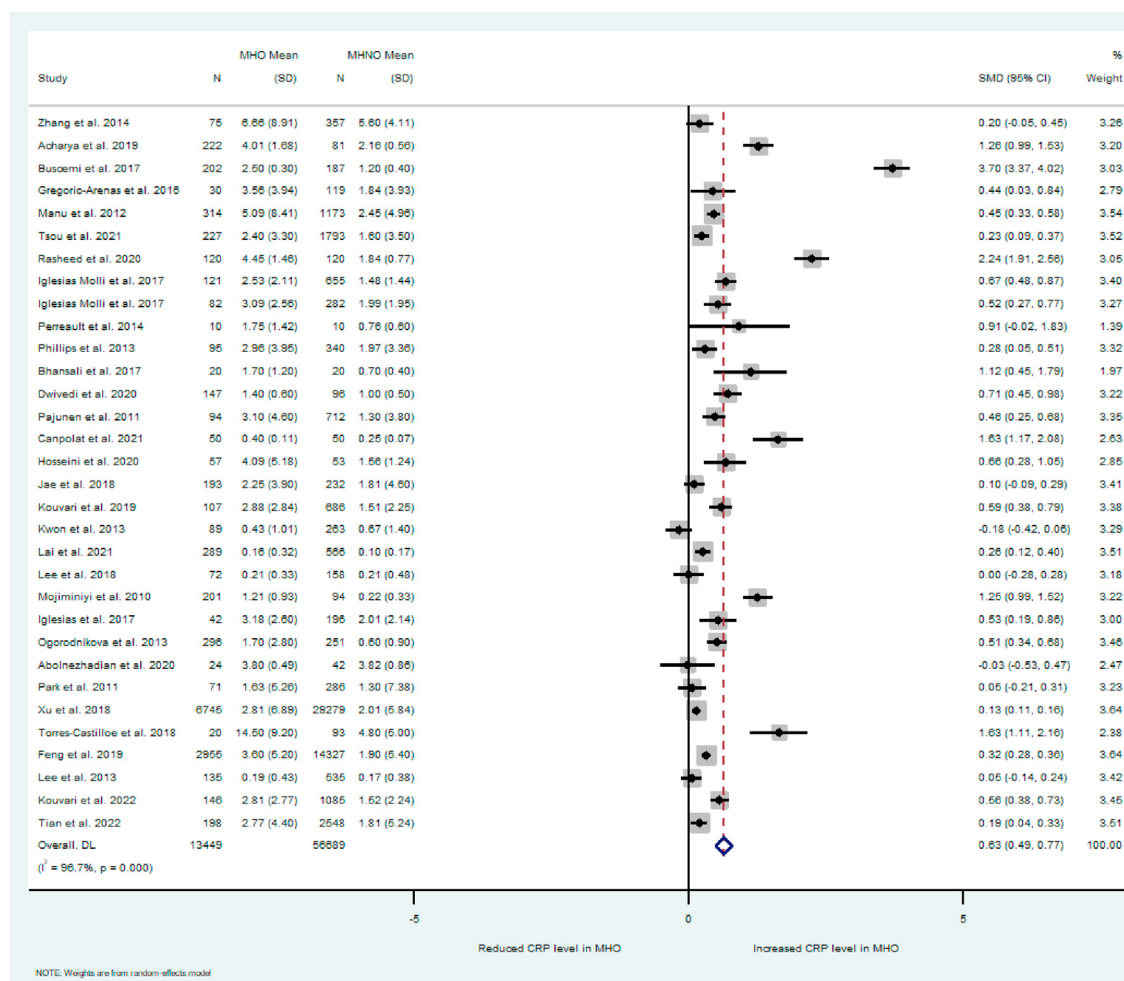**Figure 1** Flow chart of the study selection process.

Figure 2 Forest Plot of CRP for Studies that Reported Data as Mean ± SD (MHO vs MHNO). Abbreviations: N: number; SD: standard deviation; SMD: standardized mean difference; CRP: C-reactive protein; MHO: metabolically healthy obese; MHNO: metabolically healthy non-obese; N: number of participants.

indicate the presence of substantial heterogeneity between the included studies. To test the robustness of our results and the possible reason for the observed high heterogeneity, we conducted several subgroup analyses.

3.2.1. Subgroup analysis by metabolic syndrome definition and number of components

The most common metabolic syndrome definitions used were those of the NCEP ATP III, the American Heart Association, the harmonized definition, the IDF, the Consensus Societies, and Meigs et al. We performed subgroup analysis by pooling studies that applied the same or very similar definitions of metabolic syndrome. This analysis showed that there was no difference in CRP levels between MHO and MUNO individuals among studies that reported their data as mean ± SD and median (IQR). Heterogeneity slightly decreased in the MUNO and MUO groups in studies that reported their data as mean ± SD, while there were no considerable changes in the other groups (Table 2, Supplementary Document Figs. 1—3).

We did further analyses by grouping studies including or excluding waist circumference and using the same number of abnormal components to define individuals as metabolically unhealthy. The significant results were the same as the overall analysis results. Overall, heterogeneity decreased (Table 2, Supplementary Document Figs. 4—9).

3.2.2. Subgroup analysis by BMI cut-off

We conducted another analysis by BMI cut-off point for the definition of obesity (either BMI ≥25 kg/m^2 or BMI ≥30 kg/m^2) among studies included in the subgroup analysis by metabolic syndrome definition. When obesity was defined as BMI ≥25 kg/m^2, there was no difference in CRP levels between MHO and MUNO individuals among studies that reported their data as mean ± SD and median (IQR). When obesity was defined as a BMI ≥30 kg/m^2, the results were the same as the overall results. Heterogeneity decreased in all groups. (Table 2, Supplementary Document Figs. 10—12).

3.2.3. Subgroup analysis by geographical location

Subgroup analysis by geographical location in Asia showed that CRP levels in MHO were no different to MUNO subjects among studies that reported their data as mean ± SD and median (IQR). When analyzing studies from North America,
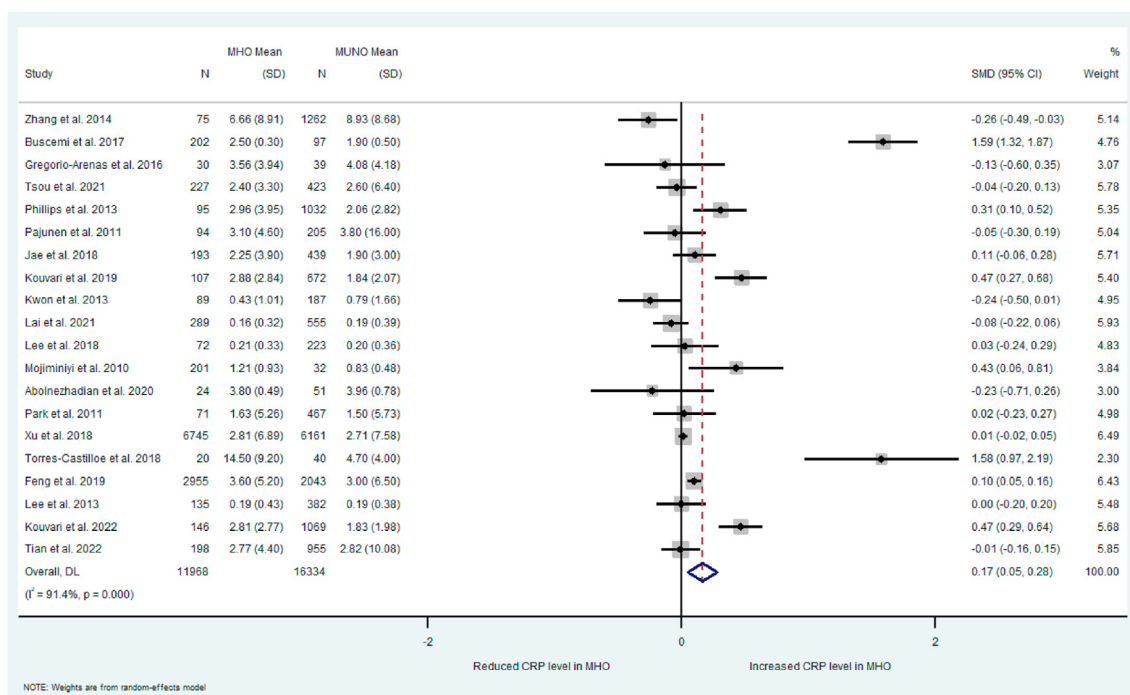
Figure 3 Forest Plot of CRP for Studies that Reported Data as Mean ± SD (MHO vs MUNO). Abbreviations: N: number; SD: standard deviation; SMD: standardized mean difference; CRP: C-reactive protein; MHO: metabolically healthy obese; MUNO: metabolically unhealthy non-obese; N: number of participants.

it was shown that CRP levels in MHO were no different from MUO individuals among studies that reported their data as mean ± SD. The analysis of studies from South America showed that CRP levels in MHO were no different to MUNO subjects among studies that reported their data as the median (IQR). Other subgroup analyses by continents were the same as the overall results. Overall, the heterogeneity decreased due to the separation of studies by location (Table 2, Supplementary Document Figs. 13−15).

3.3. IL-6

A total of 18 studies reported IL-6 levels in MHO and the other phenotypes. Of these, 11 studies compared MHO with MHNO, 6 studies compared MHO with MUNO, and 15 compared MHO with MUO. There was no difference in IL-6 levels between MHO and MHNO or MUNO subjects, while IL-6 levels were lower in the MHO than in MUO individuals (SMD = −0.32, 95% CI: −0.53, −0.12, I^2 = 71.2%) (Table 3, Supplementary Document Figs. 16−18).

3.4. TNF-α

The literature search found 15 studies reporting TNF-α levels in MHO and other phenotypes. Of these, 7 studies compared MHO with MHNO, 4 compared MHO with MUNO, and 12 compared MHO with MUO. There was no difference in TNF-α levels between MHO and MUNO or MUO individuals, while TNF-α levels were higher in MHO than in MHNO subjects (SMD = 1.26, 95% CI: 0.11, 2.40, I^2 = 98.3%) (Table 3, Supplementary Document Figs. 19−21).

3.5. Sensitivity analysis and examination of publication bias

We converted CRP median values to mean values and pooled them together with the results of studies that reported their data as mean ± SD. This analysis confirmed our findings that CRP levels in MHO subjects were higher than in MHNO and MUNO individuals but lower than those in MUO individuals. Subgroup analysis showed similar results as the primary results (Supplementary Document Table 3, Figs. 22−39).

For CRP, the funnel plots showed evidence of asymmetry, while no evident publication bias was observed by Begg's and Egger's test for MHNO and MUNO groups, but indicated publication bias for the MUO group (Begg: p = 0.005, Egger: p = 0.004). After using the trim and fill correction for potential publication bias, no potentially missing study was imputed in the funnel plot (Supplementary Document Figs. 40−43). For IL-6, the funnel plots showed evidence of asymmetry, while no evident publication bias was observed by Begg's and Egger's test for MHNO and MUNO groups, but indicated publication bias for the MUO group (Begg: p = 0.001, Egger: p = 0.003). After using the trim and fill correction for potential publication bias, no potentially missing study was imputed in the funnel plot (Supplementary Document Figs. 44−47). For TNF-α, the funnel plots showed evidence of asymmetry, while no evident publication bias was observed by Begg's and Egger's test for MHNO and MUO groups, but indicated publication bias for the MUNO group (Begg: p = 0.19, Egger: p = 0.04). The addition of one missing
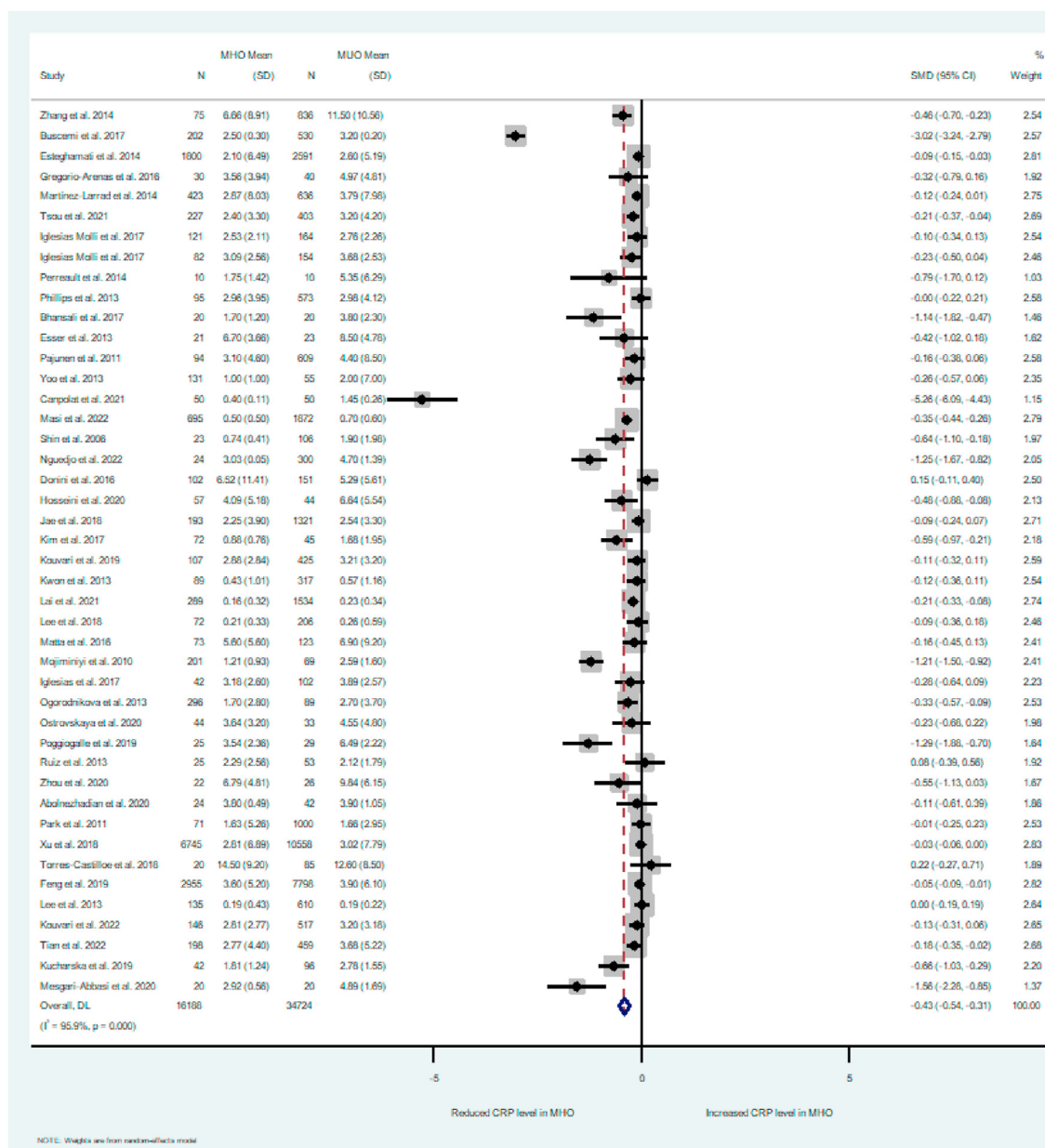
Figure 4   Forest Plot of CRP for Studies that Reported Data as Mean ± SD (MHO vs MUO). Abbreviations: N: number; SD: standard deviation; SMD: standardized mean difference; CRP: C-reactive protein; MHO: metabolically healthy obese; MUO: metabolically unhealthy obese; N: number of participants.

study imputed using the trim and fill method did not change the result, which remained non-significant (Supplementary Document Figs. 48–51).

4. Discussion

In this systematic review, we included 91 studies and 435,106 adult subjects. After summarizing the evidence, we found higher CRP levels between MHO compared to MHNO and MUNO subjects, while there was a lower level among MHO than among MUO individuals. In addition, there was no difference in IL-6 levels between MHO and MHNO or MUNO participants, while MUO individuals showed higher IL-6 levels than MHO individuals.

Moreover, we also found that TNF-α levels in MHO were higher than in MHNO but had no difference from MUNO or the MUO phenotype.

Obesity was shown to be associated with a state of chronic low-grade inflammation [114]. MHO individuals had higher CRP levels than MHNO subjects, indicating the presence of an association between inflammation and obesity status regardless of the presence of additional metabolic abnormalities. Two previous meta-analyses [115,116] showed that elevated levels of CRP, IL-6, and TNF-α were associated with a higher risk of type 2 diabetes. It has been reported that inflammation is linked to hypertension [117] and insulin resistance [118,119] and plays an important role in the development of diabetes

Table 3 Summary of pooled standardized mean differences (SMDs) for IL-6 and TNF-α.

	N	SMD (95% CI)	Heterogeneity (I^2 and p)
IL-6			
MHNO	11	0.57 (−0.02, 1.15)	$I^2 = 95.7\%$, $p < 0.0001$
MUNO	6	0.09 (−0.16, 0.34)	$I^2 = 68.5\%$, $p = 0.01$
MUO	15	−0.32 (−0.53, −0.12)	$I^2 = 71.2\%$, $p < 0.0001$
TNF-α			
MHNO	7	1.26 (0.11, 2.40)	$I^2 = 98.3\%$, $p < 0.0001$
MUNO	4	0.25 (−0.16, 0.66)	$I^2 = 81.7\%$, $p = 0.001$
MUO	12	−0.29 (−0.65, 0.07)	$I^2 = 88.6\%$, $p < 0.0001$

Abbreviations: MHO: metabolically healthy obese; MHNO: metabolically healthy non-obese; MUNO: metabolically unhealthy non-obese; MUO: metabolically unhealthy obese; N: number of studies; CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

and cardiovascular diseases [120]. The link between inflammation and metabolic abnormalities is not fully understood. Adipocytes are known to secrete several cytokines, including CRP, IL-6, and TNF-α [121]. Compared with that of lean individuals, the adipose tissue of obese subjects has been found to secrete higher amounts of such cytokines, which may be associated with insulin resistance, blood pressure, and other metabolically important traits [11]. Furthermore, macrophage infiltration into adipose tissue is a source of these inflammatory factors [122]. In addition, the pathogenicity of adipose tissue depends on the adipose tissue distribution, which can be visceral or subcutaneous [123]. Visceral fat is more strongly correlated with the metabolic syndrome than subcutaneous adipose tissue and is associated with the increased production of CRP, IL-6, and TNF-α [124,125].

Our meta-analysis showed that CRP levels in the MHO group were higher than those in MHNO but lower than those in MUO individuals; almost all of the studies were on the same side of the null effect line in the forest plots for these two comparison groups, indicating that almost all of the studies confirm this trend. CRP levels in MHO were higher than in MHNO and MUNO individuals, and the higher levels of CRP in MHO subjects may be induced by obesity. This also implies that MHO individuals may not be as healthy as MHNO and MUNO subjects. As shown by previous studies, MHO was not a stable status and may be a transient state toward MUO status [66,126]. CRP levels in MHO subjects were lower than in MUO individuals, indicating that a higher CRP level is associated with metabolic health status. The mechanism linking CRP to metabolism is still unclear. CRP has been found to be directly associated with insulin signaling, triglycerides, and HDL cholesterol levels [127]. Furthermore, CRP might participate in the development of atherosclerosis [128] and promote oxidized LDL uptake as well as cholesterol ester accumulation [129]. Moreover, CRP prevents the production of nitric oxide (NO) by endothelial cells, which may lead to vasoconstriction, leukocyte adhesion, platelet activation, oxidation, and thrombosis, resulting in the development of hypertension [130]. NF-κB is an important transcription factor with a role in the induction of proinflammatory genes [131], and CRP can stimulate NF-κB activity [132]; thus, CRP may be a key promoter of metabolic dysfunction.

Multiple definitions of metabolic syndrome have been used to define the MHO phenotype [133]. We found slightly lower heterogeneity in the CRP subgroup analysis by metabolic syndrome definition than in the overall sample. The lack of a standard definition for the MHO group makes the comparison of MHO phenotype characteristics across studies difficult and impedes evidence synthesis. In a previous study, the prevalence of the MHO phenotype was found to vary depending on the definition used [134]. A study by Phillips et al. [41] indicated that the levels of inflammatory markers were different when different metabolic abnormality criteria were used. Therefore, to enhance future research on the MHO phenotype, a consensus definition of what constitutes an unhealthy metabolic state is needed. Ethnicity is likely to affect fat distribution due to different genetic and environmental effects, resulting in disparities in the pathogenesis of metabolic abnormalities [135]. In our analysis, we found very few studies from North America, South America, and Africa; therefore, more research on the effect of ethnicity on the MHO phenotype is needed. Subgroup analysis using different cut-offs for the definition of obesity showed different results. A possible explanation for this difference is that the BMI cut-off of ≥ 25 kg/m^2 used to define obesity in studies conducted in Asia is different from the western cut-off of BMI ≥ 30 kg/m^2. Additionally, several research articles reported that Asians are more prone to visceral fat accumulation and are at a higher risk of diabetes than other ethnicities [136,137].

We did not find any significant differences in IL-6 levels between the MHO and MHNO or MUNO groups, possibly because of the small number of available studies for the meta-analysis and the low number of subjects included in the studies. Of the studies included, 7 out of 11 studies found no difference in IL-6 levels between MHO and MHNO subjects, and 3 out of 6 studies showed IL-6 levels in MHO were no different from MUNO individuals. Our findings showed that the IL-6 levels in MHO were lower than in MUO individuals, and all of the studies on the same side of the null effect line in the forest plot, which strongly confirms this trend, indicating that a higher IL-6 level is associated with metabolically unhealthy individuals. The mechanism linking the IL-6 level and metabolic abnormalities is unknown. It has been shown that an increased level of IL-6 is positively associated with insulin resistance and hypertension [138]. IL-6 may increase blood pressure by activating the central nervous system and sympathetic nervous system [139], and increasing angiotensinogen expression [140]. IL-6 can also induce insulin resistance by interfering with insulin signaling pathways [141]. On the other hand, the production of IL-6 from skeletal muscle mediates the activation of AMP-kinase, which may increase glucose uptake and fatty acid oxidation [142]. In addition, IL-6, a significant mediator of the acute phase response, affects many cell types, including hepatic cells, and increases the production of CRP [143]. All of this

suggests that IL-6 level is associated with metabolic abnormalities.

This meta-analysis found no significant difference in TNF-α levels between MHO and MUNO or MUO individuals, which may be due to the paucity of available studies and the small number of subjects included in the studies. Of the studies included, 3 out of 4 studies found TNF-α levels in MHO were no different from MUNO subjects, 8 out of 12 studies showed that TNF-α levels in MHO were no different from the results from MUO individuals. We found that TNF-α levels in MHO were higher than in MHNO subjects, and all of the studies on the same side of the null effect line in the forest plot, which strongly confirms this trend. The higher levels of TNF-α in MHO than in MHNO individuals may be because of the presence of obesity. Serum TNF-α levels were found to be positively associated with triglycerides and blood pressure and negatively associated with HDL cholesterol [144]. TNF-α can impair insulin signaling via the serine phosphorylation of IRS-1 and PP-1 and the activation of SHPTPase [145]. Furthermore, TNF-α was found to inhibit insulin-stimulated glucose uptake substantially in peripheral tissues at low concentrations [146]. Moreover, the neutralization or deletion of TNF receptors leads to lower levels of PAI-1 antigen and adipose tissue PAI-1, as well as lower plasma insulin levels [147]. In addition, with a targeted disruption of TNF-α genes, it has been proven that TNF-α modulates plasma triglyceride levels and glucose homeostasis [148]. Collectively, these lines of evidence indicate that TNF-α levels can have an influence on metabolic abnormalities. More studies are needed to confirm whether TNF-α is associated with obesity phenotypes.

4.1. Strengths and limitations

To date, this is the first meta-analysis that has attempted to summarize the differences in inflammatory marker levels between MHO and other phenotypes. The large sample size included in this meta-analysis allowed us to quantitatively evaluate the relationship between the inflammation present in the MHO subgroup and that in the other subgroups. Therefore, our findings are potentially more robust than those of any individual study. We included studies that considered the most common definitions of metabolic syndrome components to reduce the misclassification of the MHO phenotype. We excluded studies performed on children and morbidly obese individuals to reduce bias, as these subgroups of subjects may present different pathophysiological mechanisms.

The findings of our study should be interpreted within its limitations. First, visual assessment of funnel plots suggests the presence of publication bias, which may affect the results of this study. Second, noticeable heterogeneity existed in most of the analyses, and the sources of this heterogeneity could not be comprehensively explained by our subgroup analyses. Third, several subgroup analyses were performed with a very limited number of studies, making it difficult to achieve a firm conclusion about the findings. Finally, additional analysis by sex was not possible due to the fact that most studies did not report inflammatory marker levels separately for each sex. It is known that sex hormones have an influence on inflammation, and thus the inflammatory response may differ between men and women.

5. Conclusion

In summary, this systematic review indicates differences in CRP levels between MHO and MHNO, MUNO, and MUO individuals. There was no difference in IL-6 levels between MHO and MHNO or MUNO individuals, while we reported reduced levels in MHO compared to MUO subjects. There was no difference in TNF-α levels between MHO and MUNO or MUO individuals, while we found higher levels in MHO than in MHNO. These findings strengthen the evidence that the MHO phenotype is accompanied by an inflammatory response. Further research in this field could include prospective studies to appropriately determine the clinical utility of inflammatory markers in the management of MHO individuals and their possible predictive value when the transition to an unhealthier phenotype occurs.

Declaration of competing interest

There are no conflicts to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.09.002.

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