## Original Article

# Associations between Sarcopenia and Metabolic Risk Factors: A Systematic Review and Meta-Analysis

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**Background:** Metabolic risk factors can impact sarcopenia, but the direct relationship of metabolic risk factors with sarcopenia has not been examined. Our purpose was to investigate the effects of metabolic risk factors on sarcopenia in older adults.

**Methods:** Sixteen studies were found through a search of electronic databases and were subjected to a meta-analysis to investigate the differences in metabolic risk factors between patients with sarcopenia and controls. The random-effects standardized mean difference ±95% confidence interval was calculated as the effect size.

**Results:** The results showed that body mass index (BMI), fasting glucose, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), homeostasis model assessment of insulin resistance (HOMA-IR), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (d=3.252, d=2.039, d=2.956, d=2.579, d=2.123, d=1.195, d=−0.991, and d=1.007, respectively) all had relationships with sarcopenia. In addition, the effect sizes of all male groups for all variables were higher than those of the female groups. However, only the between-sex effect size of HOMA-IR ($P<0.01$) was significant, while those for BMI, fasting glucose, SBP, DBP, TG, HDL-C, low-density lipoprotein cholesterol, and total cholesterol were not. Finally, the metabolic risk factors appeared to be significantly related to loss of skeletal muscle.

**Conclusion:** Nutrition and appropriate exercise to enhance muscle strength and quality in the elderly reduce the occurrence of sarcopenia, thereby reducing the incidence of metabolic diseases.

**Key words:** Sarcopenia, Metabolic diseases, Risk factors, Meta-analysis, Aged

## INTRODUCTION

The World Health Organization has reported that the global population of people older than the age of 65 years will reach at least 2 billion by 2050.[1] The aging process can lead to sarcopenia, metabolic diseases, and other chronic diseases. According to the latest annual report on causes of death in the elderly in Korea, the number of patients with sarcopenia is rapidly increasing among those older than 65 years. Sarcopenia is considered to be a common cause of mortality in this age group.[2] In particular, sarcopenia has an increasing impact on the elderly, including incidence[3], dis-ability[4], health management costs[5], and mortality.[6] Therefore, sarcopenia is one of the major public health concerns among Korean older adults. It is suggested that the whole world should work together to cope with this health issue and prevent the occurrence of sarcopenia and sarcopenia-related complications (such as hypertension and diabetes) in old age.

Sarcopenia is a syndrome associated with impaired muscle and metabolic function characterized by an age-related decline in skeletal muscle mass and low levels of muscle function (muscle strength and physical activity).[7] A number of studies have found[8-10] that the diagnostic criteria for sarcopenia mainly consist of systolic blood

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pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and homeostasis model assessment of insulin resistance (HOMA-IR). Although sarcopenia working groups all over the world have introduced sarcopenic diagnostic criteria, sarcopenia is a relatively new concept, and assessment or diagnosis of the indicators is still controversial.

With the increase of the global elderly population, sarcopenia will be increasingly common.[11] Sarcopenia is prone to increase the mortality rate of the elderly since it can increase the risk of metabolic diseases.[12] Metabolic diseases refer to clinical syndromes in which risk factors for multiple cardiovascular diseases such as obesity, hypertension, hyperglycemia, dyslipidemia, and the like coexist in an individual. Insulin resistance is the basis of this clinical syndrome. Recent studies reported that decreased skeletal muscle mass increases insulin resistance *in vivo*, which is closely related to the occurrence of metabolic diseases.[13,14] For these reasons, increasing body mass can improve insulin sensitivity.[15] In addition, sarcopenia results in atherosclerosis and triggers high blood pressure.[16] With aging, body composition changes, loss of skeletal muscle, and/or increased fat mass may increase the risk of functional impairment and chronic metabolic disease.

Therefore, we performed a meta-analysis of the literature to determine the relationship between sarcopenia and possible metabolic risk factors. The objective of this study was to identify early-stage metabolic risk factors for sarcopenia. The results of this study should support instrumental suggestions for medical institutions and convalescent organizations to carry out corresponding preventive nutrition interventions to reduce the occurrence of metabolic diseases as early as possible.

## METHODS

Although a meta-analysis is not a primary research method, it does include steps such as formulation of a problem, collection of data (studies), coding of data, and data analysis and interpretation.[17]

### Search strategy

Two investigators (YD, JK No) independently conducted an electronic literature search of papers published from January 1, 1989 to September 1, 2017. They conducted a thorough search of the four Korean electronic databases, KMbase, KISS, NDSL, and RISS; and of three overseas databases, PubMed, ScienceDirect, and Cochrane Library. For the PubMed search, controlled vocabulary terms and the following keywords were used: ("Sarcopenia"[MeSH] OR Sarcopenia [Title/Abstract]) AND ("Metabolic Diseases"[MeSH]) OR (Metabolic Diseases [Title/Abstract]) OR (Thesaurismosis [Title/Abstract]) OR (Thesaurismoses [Title/Abstract]) OR (Diseases, Metabolic [Title/Abstract]) OR (Disease, Metabolic [Title/Abstract]) OR (Metabolic Disease [Title/Abstract]) and similar search strategy was run in other terms, which was restricted to studies published in English or Korean. In addition, the systematic identification, approval, synthesis, statistical merging, and reporting of the entire process of data extraction and selected studies were conducted based on a systematic review and meta-analysis of the National Evidence-based Healthcare Collaborating Agency.[18]

### Study selection

We included studies that (1) compared data on metabolic risk factors between participants with sarcopenia versus those without, (2) reported on metabolic risk factors such as BMI, fasting glucose, SBP, DBP, triglycerides (TG), HOMA-IR, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol, and (3) separated the data from men and women. Studies were excluded if they (1) did not measure or did not report metabolic risk factors in both sarcopenia and no sarcopenia subjects, (2) examined subjects younger than 65 years or used animal models, or (3) did not measure or report metabolic risk factors both in patients with and without sarcopenia.

### Data extraction

Two authors (YD, JK No) independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information was extracted: (1) study population characteristics (e.g., sample size, demographic), (2) survey site at which the study was performed, (3) parameters related to metabolic risk factors in individuals with sarcopenia versus no sarcopenia, and (4) compared data from men and women separately from the overall population.

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## Quality assessment

In meta-analyses, the "file drawer problem" refers to unknown, unpublished research whose results fail to confirm the pattern revealed by the published findings.[19] If no unpublished research is retrieved, a publication bias can exist in favor of significant findings, which could distort the results of the meta-analysis. Cooper[20] developed a method for determining the magnitude of the file drawer problem: calculating the minimum number of unpublished studies reporting not significant findings that would be necessary to overturn the conclusion reached in a particular meta-analysis. This number has been defined as the fail-safe number (Nfs).[20] Rosenthal and Hall[21] have proposed that a reasonable tolerance level of the file drawer problem has been achieved if the Nfs exceeds 5n+10 (n, number of studies included in the meta-analysis).

## Statistical analysis

The meta-analysis was performed using comprehensive meta-analysis V2.0 for Windows (https://www.meta-analysis.com/). Only outcomes from at least two studies can be subjected to meta-analysis, while outcomes from only one study were reported in the descriptive analyses. When combining studies, the random effects model was used to account for study heterogeneity[22] by utilizing the standardized mean difference with its 95% confidence interval (CI). Study heterogeneity was measured using the chi-square and I-square statistics, with chi-square $P \leq 0.05$ and I-square $\geq 50\%$ indicating the presence of crucial heterogeneity. Publication bias was assessed with a visual inspection of funnel plots and the Egger bias test[23] for outcomes within these metabolic risk factors. Furthermore, this study also utilized Nfs to verify the reliability of the researched nine metabolic risk factors. These factors were used for subgroup analysis based on the analysis of included studies, and the subgroup analysis compared men and women.

## RESULTS

The search identified 991 potentially eligible studies, of which 384 duplicates were excluded. After excluding 547 papers through title and abstract review, 60 full-text articles were examined. After further examination, 16 studies were included in the meta-analysis (Fig. 1).[24-39]
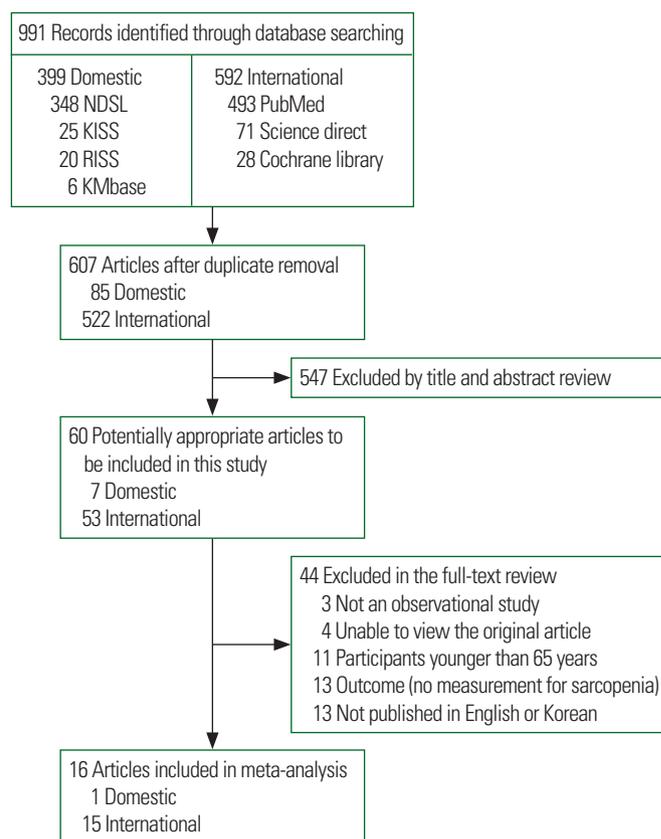


**Figure 1.** Flow of study analysis through different phases of the meta-analysis (from January 1, 1989 to September 1, 2017).

## Study and patient characteristics

Study and patient characteristics are summarized in Table 1. The 16 meta-analyzed studies included a total of 803,022 participants (62,273 with sarcopenia and 740,749 without). The majority of the studies were conducted in Asia and by social survey. All of the studies were published after the year 2000. The ages of the subjects ranged from 65 to 70 years in 11 papers (68.75%) and from 70 to 80 years in 10 papers (62.25%), and there were five papers in which the ages ranged from 65 to 80 years. There were two papers (12.5%) on studies of elderly women, four papers (25%) on elderly men, and 10 papers (62.5%) on both men and women. Among the 16 studies for the meta-analysis, the numbers of instances of the use of BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, LDL-C, and total cholesterol as adjusted variables were 27, 20, 9, 9, 14, 12, 12, 7, and 14, respectively, since there were differences between the male and female groups.

**Table 1.** Characteristics of the included studies

| Author (year), country | Sample size (with/without sarcopenia) | Sex (%) | Setting | Adjusted variable |
|---|---|---|---|---|
| Lee et al. (2013)[24], South Korea | 1,535 (510/1,025) | M: 54.30 F: 45.70 | Social | BMI, fasting glucose, HOMA-IR |
| Choi and Park (2016)[25], South Korea | 780,994 (57,246/723,748) | M: 52.85 F: 47.15 | Social | BMI, fasting glucose, SBP, DBP, TG, HDL-C, total cholesterol |
| Kang et al. (2017)[27], South Korea | 2,628 (557/2,071) | F: 100 | Social | BMI, fasting glucose, SBP, DBP, TG, HDL-C, total cholesterol |
| Chung et al. (2013)[28], South Korea | 2,943 (1,248/1,695) | M: 42.47 F: 57.53 | Social | BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, LDL-C, total cholesterol |
| Isanejad et al. (2016)[29], Finland | 496 (127/369) | F: 100 | Community | BMI |
| Kim et al. (2014)[30], South Korea | 2,264 (540/1,724) | M: 41.52 F: 58.48 | Social | BMI, TG, HOMA-IR, HDL-C, LDL-C, total cholesterol |
| Buchmann et al. (2016)[31], Germany | 1,402 (280/1,122) | M: 51.07 F: 48.93 | Community | BMI, fasting glucose, TG, HOMA-IR, HDL-C |
| Lim et al. (2010)[35], South Korea | 565 (235/330) | M: 50.80 F: 49.20 | Social | BMI, fasting glucose, TG, HOMA-IR, HDL-C, LDL-C, total cholesterol |
| Chalhoub et al. (2015)[34], United States | 3,802 (127/3,675) | M: 90.64 F: 9.36 | Community | BMI |
| Pereira et al. (2015)[33], Brazil | 173 (20/153) | M: 100 | Social | BMI |
| Ishii et al. (2014)[32], Japan | 1,971 (359/1,612) | M: 49.57 F: 50.43 | Social | BMI |
| Kim et al. (2017)[26], South Korea | 435 (138/297) | M: 100 | Social | BMI, fasting glucose, SBP, DBP, TG, HDL-C,LDL-C, total cholesterol |
| Baumgartner (2000)[36], United States | 562 (216/346) | M: 51.33 F: 48.67 | Community | BMI, fasting glucose, total cholesterol |
| Chin et al. (2013)[37], South Korea | 1,076 (176/900) | M: 100 | Social | BMI, fasting glucose, TG, HOMA-IR, HDL-C, LDL-C, total cholesterol |
| Moon et al. (2015)[38], South Korea | 674 (35/639) | M: 47.16 F: 52.84 | Social | BMI, fasting glucose, SBP, DBP, TG, HDL-C |
| Han et al. (2014)[39], South Korea | 1,502 (459/1,043) | M: 100 | Social | BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, total cholesterol |

M, male; F, female; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 2.** Summary of results, overall effect sizes, and homogeneity of d-value

| Outcome | Number* | d[†] (95% CI) Random-effect[‡] | Homogeneity of d-value Q[§] | I² (%)[∥] | P[¶] | Nfs |
|---|---|---|---|---|---|---|
| BMI | 27 | 3.252 (2.657 to 3.847) | 43,587.486 | 99.940 | 0.0000 | 5,668 |
| DBP | 9 | 2.579 (1.066 to 4.091) | 74,498.836 | 99.989 | 0.0000 | 14,903 |
| Fasting glucose | 20 | 2.039 (1.078 to 3.000) | 81,578.937 | 99.977 | 0.0000 | 740 |
| HDL-C | 16 | −0.991 (−2.081 to 0.099) | 93,333.099 | 99.984 | 0.0000 | 5,915 |
| HOMA-IR | 12 | 1.195 (0.481 to 1.910) | 2,427.413 | 99.547 | 0.0000 | 2,628 |
| LDL-C | 7 | 0.144 (−0.131 to 0.419) | 114.811 | 94.774 | 0.0000 | 21 |
| SBP | 9 | 2.956 (2.316 to 3.597) | 13,336.577 | 99.940 | 0.0000 | 608 |
| TG | 14 | 2.123 (0.542 to 3.704) | 155,743.065 | 99.992 | 0.0000 | 9,786 |
| Total cholesterol | 14 | 1.007 (−0.914 to 2.928) | 226,491.621 | 99.994 | 0.0000 | 642 |

*The number of adjusted variables; [†]Overall effect size; [‡]Indicates a significant effect ($P < 0.001$); [§]Cochran's Q indicating significance of heterogeneity; [∥]The magnitude of heterogeneity; [¶]$P$-value represents the significance of heterogeneity.
CI, confidence interval; Nfs, fail-safe number; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

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## Effect sizes

After data from the accepted 16 studies were pooled, all nine metabolic risk factors of interest were found to have a significant relationship with sarcopenia (Table 2), and the corresponding forest plots of these nine effect sizes are demonstrated in Fig. 2. Overall effect sizes under random-effects assumptions indicate that BMI (d = 3.252; 95% CI, 2.657–3.845; $P < 0.001$), fasting glucose (d = 2.039; 95% CI, 1.078–3.000; $P < 0.001$), SBP (d = 2.956; 95% CI, 2.316–3.579; $P < 0.001$), DBP (d = 2.579; 95% CI, 1.066–4.091; $P < 0.001$), TG (d = 2.123; 95% CI, 0.542–3.704; $P < 0.001$),
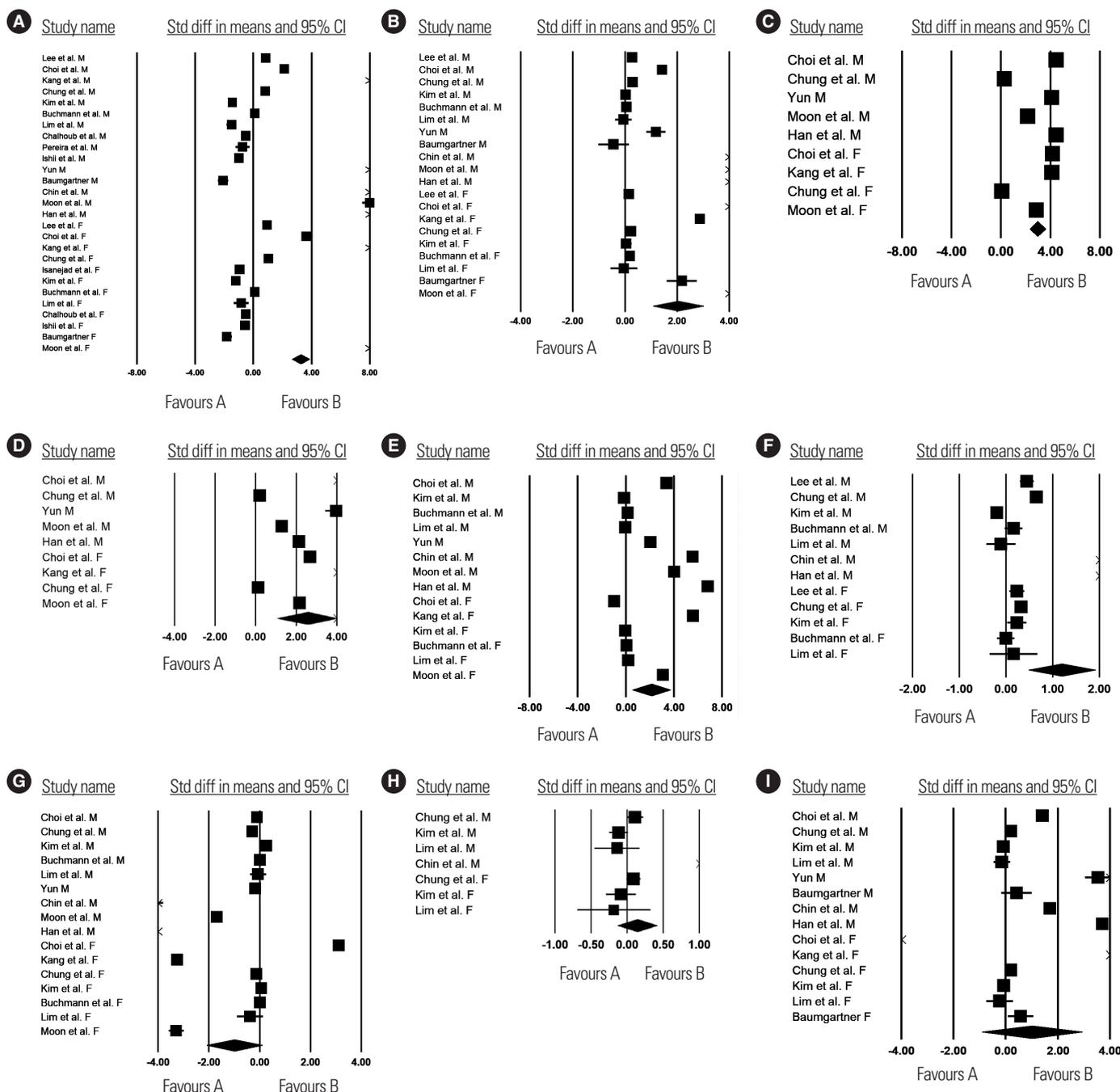


**Figure 2.** Forest plots of (A) body mass index, (B) fasting glucose, (C) systolic blood pressure, (D) diastolic blood pressure, (E) triglycerides, (F) homeostasis model assessment of insulin resistance, (G) high-density lipoprotein cholesterol, (H) low-density lipoprotein cholesterol, and (I) total cholesterol in subjects with sarcopenia vs. without sarcopenia. Std diff, standard difference; CI, confidence interval; M, male; F, female.

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**Table 3.** Effect sizes by sex

| Outcome | Subgroup | Number* | d† (95% CI) | Q‡ | I² (%)§ | P‖ |
|---|---|---|---|---|---|---|
| BMI | Male | 15 | 4.317 (3.027 to 5.608) | 13,489.344 | 99.896 | 0.071 |
|  | Female | 12 | 2.409 (0.792 to 4.025) | 16,651.096 | 99.934 |  |
| DBP | Male | 5 | 2.693 (−0.289 to 5.675) | 13,871.865 | 99.971 | 0.883 |
|  | Female | 4 | 2.437 (0.806 to 4.068) | 3,320.932 | 99.910 |  |
| Fasting glucose | Male | 11 | 2.268 (1.379 to 3.157) | 4,323.045 | 99.769 | 0.610 |
|  | Female | 9 | 1.75 (−0.031 to 3.531) | 15,143.460 | 99.947 |  |
| HDL-C | Male | 9 | −1.334 (−2.172 to −0.496) | 3,087.016 | 99.741 | 0.527 |
|  | Female | 7 | −0.546 (−2.841 to 1.749) | 16,712.701 | 99.964 |  |
| HOMA-IR | Male | 7 | 1.933 (0.665 to 3.201) | 2,270.527 | 99.736 | 0.008¶ |
|  | Female | 5 | 0.209 (0.083 to 0.335) | 9.694** | 58.739 |  |
| LDL-C | Male | 4 | 0.274 (−0.232 to 0.780) | 109.277 | 97.255 | 0.336 |
|  | Female | 3 | 0.051 (−0.035 to 0.137) | 3.096** | 35.396 |  |
| SBP | Male | 5 | 3.093 (0.973 to 5.213) | 5,610.668 | 99.929 | 0.855 |
|  | Female | 4 | 2.801 (0.504 to 5.099) | 6,791.894 | 99.956 |  |
| TG | Male | 8 | 2.723 (1.159 to 4.286) | 5,287.473 | 99.868 | 0.319 |
|  | Female | 6 | 1.322 (0.940 to 3.585) | 6,156.489 | 99.919 |  |
| Total cholesterol | Male | 8 | 1.337 (0.583 to 2.091) | 1,830.212 | 99.618 | 0.645 |
|  | Female | 6 | 0.562 (−2.648 to 3.773) | 19,166.840 | 99.974 |  |

*The number of adjusted variables; †Effect size; ‡Cochran's Q indicating significance of heterogeneity; §The magnitude of heterogeneity; ‖P-value represents the significance of heterogeneity; ¶Indicates a significant effect (P<0.01); **Indicates fixed-effects.
CI, confidence interval; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

HOMA-IR (d = 1.195; 95% CI, 0.481–1.910; $P < 0.001$), HDL-C (d = −0.991; 95% CI, −2.08 to 0.099; $P < 0.0001$), LDL-C (d = 0.144; 95% CI, −0.131 to 0.419; $P < 0.001$), and total cholesterol (d = 1.007; 95% CI, −0.914 to 2.928; $P < 0.001$) had a significant overall effect on sarcopenia. There was a large degree of heterogeneity among studies, with I² ranging from 99.547% to 99.994%.

## Subgroup analysis

The results of the random-effects categorical analysis by male and female subgroups are illustrated in Table 3. The results for the relationship of sarcopenia with metabolic risk factors in men and women were as follows: (1) the effect sizes of all of the male groups were higher than those of the female groups; (2) however, only the effect size of HOMA-IR ($P < 0.01$) was significant, while the differences of the effect sizes between men and women within each of the other eight risk factor subgroups, namely BMI, fasting glucose, SBP, DBP, TG, HDL-C, LDL-C, and total cholesterol, were not.

## Reliability test

The Nfs computed for this meta-analysis regarding the effects of

BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, LDL-C, and total cholesterol on sarcopenia were 5,668, 740, 608, 14,903, 9,786, 2,628, 5,915, 21, and 642 unpublished studies, respectively (Table 2). Only in the case of LDL-C were the Nfs not exceeded, with 45 unpublished studies; therefore, it is difficult to support the effect size.

## Publication bias

Publication bias was evaluated to examine the validity of the results of this study. The effect size of the included studies was not visually symmetrical in the funnel plot, which is illustrated in Fig. 3. An Egger linear regression test inferred the severity of the publication bias.[40] As a result, we added no new studies to convert the effect size of the included studies from asymmetry to symmetry. Therefore, the pooled effect size did not convert. To sum up, we could not ensure that the included studies had no publication bias; however, there was also no evidence to call the validity of the results into question.
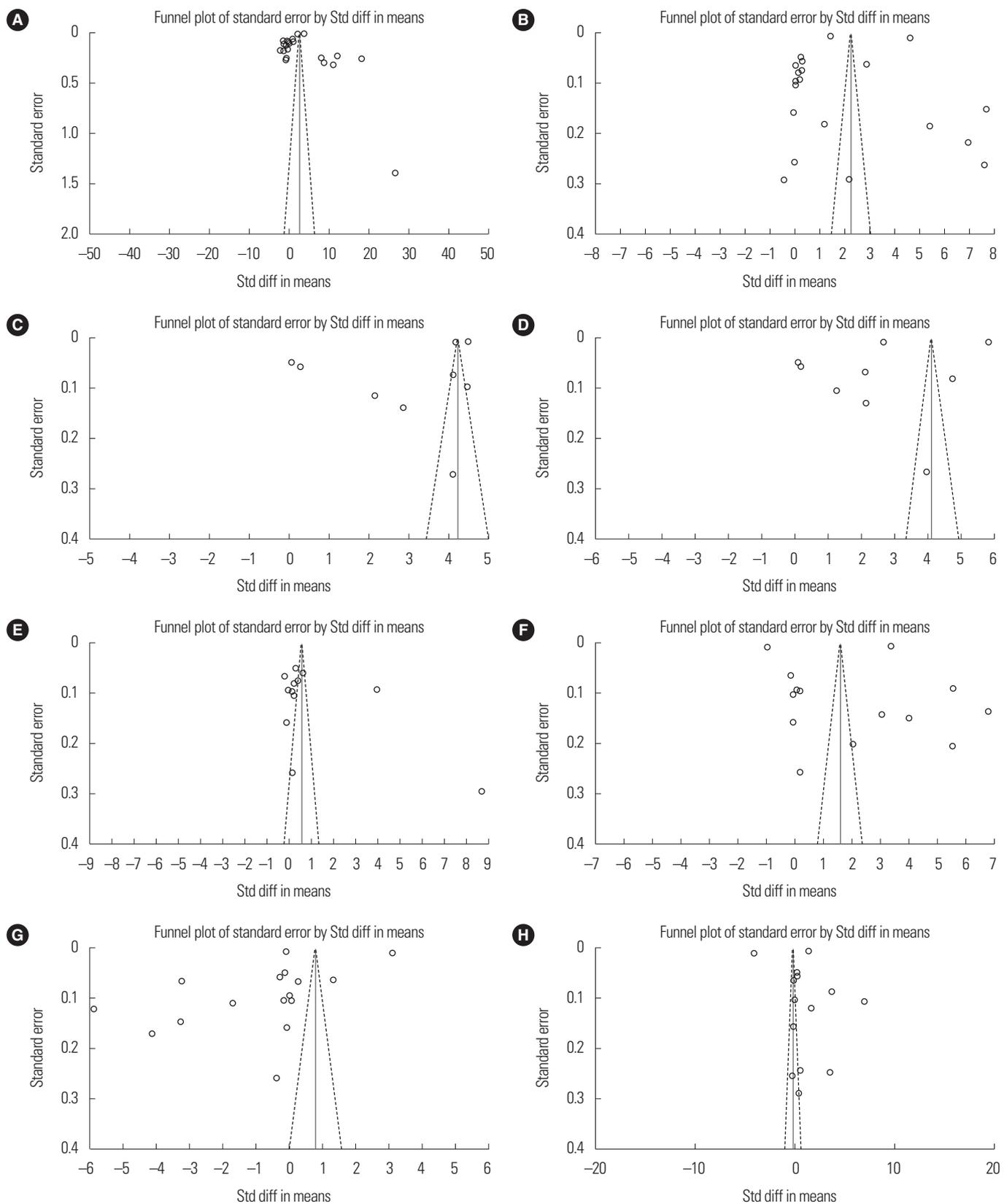
**Figure 3.** Funnel plots of (A) body mass index, (B) fasting glucose, (C) systolic blood pressure, (D) diastolic blood pressure, (E) triglycerides, (F) homeostasis model assessment of insulin resistance, (G) high-density lipoprotein cholesterol, and (H) total cholesterol. Std diff, standard difference.

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## DISCUSSION

In this meta-analysis involving 62,273 people with sarcopenia and 740,749 without, we found that the nine metabolic risk factors (BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, LDL-C, and total cholesterol) investigated are related to sarcopenia. Although LDL-C had a significant effect size, the reliability test of LDL-C showed that the results of the research did not support its effect size. Therefore, we will conduct more detailed and in-depth studies on the effects of LDL-C on sarcopenia. To some extent, other factors may be associated with sarcopenia, which we will examine in future research; for example, body fat percentage, waist circumference, and visceral fat area. To the best of our knowledge, this is the first meta-analysis to investigate the possible relationship between sarcopenia and metabolic risk factors. The findings of this study on the relationship of metabolic risk factors with sarcopenia parameters, as reported in previous papers, complement the development of this research focus and provide instrumental details and statistics for a future study.

Several recently published systematic reviews on the relationship of metabolic risk factors with sarcopenia reported similar effects with BMI[41], fasting glucose[42,43], SBP and DBP[44], TG[45], HOMA-IR[41,46], HDL-C, and total cholesterol.[45] Although the analysis investigating BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, and total cholesterol as outcomes was characterized by high heterogeneity, we explained the majority of this with our meta regression analyses. According to Lu et al.'s research[14], low muscle mass and a form of obesity called sarcopenia are associated with metabolic syndrome in the American elderly. These findings are in agreement with our previous work[41,46], in which BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, and total cholesterol were more strictly related to sarcopenia compared with LDL-C. While the exact reason for this result is not clear, systematic reviews could provide an answer. Although our findings should be clarified and further explored with future longitudinal studies, our results support the notion that BMI, fasting glucose, SBP, DBP, TG, HOMA-IR, HDL-C, and total cholesterol could be used as parameters for detecting sarcopenia.

Finally, the studies did not adjust for any confounding variables, which may have affected both the exposure and outcome.[47] Thus,

adjusting for confounders is a good way to reduce potential bias. According to previous studies, sex can affect the correlation between metabolic risk factors and elder sarcopenia.[41,46] Therefore, when we accumulate more results, we will perform a subgroup analysis. Moreover, our present subgroup analysis suggests that male sex plays an important role in explaining the association between metabolic risk factors and sarcopenia. This finding seems to be consistent with the current literature suggesting that men have higher metabolic risk factor levels compared with women. These findings suggest that, in the future, sarcopenia-preventive treatments should be sex specific. There are actually relatively few data directly addressing many of these points, all of which are important areas for future research.

This meta-analysis has several limitations. First, the number of included studies was insufficient. Second, while weight loss was not the objective in any of the included studies, we did not control for weight change among participants. Third, according to the criteria of the subgroup analysis, the study can be further refined if there are more heterogeneous samples. Last, ecological fallacy is a possibility as we did not have access to the raw data from the included studies, and we should therefore be cautious interpreting the group results as individual effects. Despite these limitations, to our knowledge, this is the first study to confirm the relationship between metabolic risk factors in sarcopenia in the elderly. We performed a comprehensive literature search using seven electronic databases. We performed moderation analysis on all variables, with sufficient data provided in the published material. Our research provides evidence for more effective and appropriate early preventive interventions and strategies to reduce the risk of metabolic diseases in the elderly. In the future, we will use a predictive model to calculate effect sizes for each significant moderator and transform that effect size into clinical units of measure for sarcopenia.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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