Associations of Dietary and Circulating Vitamin E Level With Metabolic Syndrome. A Meta-Analysis of Observational Studies

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Objective: The associations of dietary and circulating vitamin E level with metabolic syndrome (MetS) remains conflicting. This meta-analysis of observational study was therefore employed to investigate the issue above.

Methods: The PubMed, Web of Science and Embase database were searched up to April 2021. The observational studies on the associations of dietary and circulating vitamin E level with MetS were specified. The pooled relative risk (RR) of MetS for the highest vs. lowest dietary and circulating vitamin E level, and the standard mean difference (SMD) of dietary and circulating vitamin E level for MetS vs. control subjects, were calculated.

Results: A total of 25 observational studies with 51,276 participants, were included in this meta-analysis. The overall multi-variable adjusted RR demonstrated that the dietary vitamin E level was inversely associated with MetS (RR = 0.92, 95%CI: 0.85–1.00; \( P = 0.044 \)). In addition, the dietary vitamin E level in MetS was also lower than that in control subjects according to the overall combined SMD (SMD = −0.08, 95%CI: −0.14 to −0.02; \( P = 0.024 \)). On the other hand, the overall multi-variable adjusted RR showed no significant relationship between the circulating vitamin E level and MetS (RR = 1.46, 95%CI: 0.85–2.48; \( P = 0.17 \)). However, the circulating vitamin E level in MetS was lower than that in control subjects according to the overall combined SMD (SMD = −0.58, 95%CI: −1.04 to −0.13; \( P = 0.013 \)).

Conclusions: The results of this meta-analysis suggest that the dietary vitamin E level is inversely associated with MetS. On the other hand, current evidence is still insufficient to conclude a relationship between the circulating vitamin E level and MetS. More well-designed prospective cohort studies are needed to address the issues further.

Keywords: dietary vitamin E, circulating vitamin E, metabolic syndrome, meta-analysis, observational studies
INTRODUCTION

Metabolic syndrome (MetS) is a pathological state characterized by the following clinical features: elevated waist circumference, blood pressure, fasting blood glucose, triglycerides and reduced high-density lipoprotein cholesterol (1). As a common risk factor for cardiovascular disease, diabetes and death, MetS has gradually become a major global public health issue (2). With the deepening of our knowledge, nutritional factors are considered to be involved in MetS (3–7).

As a fat-soluble vitamin with antioxidant properties, vitamin E is considered to be involved in signal transduction, gene expression and immunomodulatory capabilities (8). Higher vitamin E level was reported to be inversely associated with hypertension and diabetes (9–11). Moreover, a meta-analysis of randomized controlled trials demonstrated that vitamin E supplementation was beneficial for subclinical inflammation in adults (12). Experimental evidence also indicated that vitamin E supplementation could ameliorate hypertension and diabetes (13–15), and decrease the total serum cholesterol and lipid peroxides level (16) in animal model.

A number of observational studies have examined the associations of dietary and circulating vitamin E level with MetS. However, their results are still conflicting (17–41). The present meta-analysis of observational studies was therefore employed to address the issues. It was hypothesized that both dietary and circulating vitamin E was inversely associated with MetS.

MATERIALS AND METHODS

Search Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (42). The PubMed, Web of Science and Embase electronic database were searched during April 2021 by using a combination of keywords and in-text words related to metabolic syndrome (“metabolic syndrome”) and vitamin E (“vitamin E”, “tocopherol”) (43). No language restrictions were set in the search strategy. The titles and abstracts of all articles were screened firstly, and then the full articles were read to include the eligible studies. To identify the additional studies, the reference lists for the retrieved articles were also reviewed.

Data Extraction

The data were extracted by two researchers (YZ and DZZ) independently, and disagreements were resolved by discussions. The information about first author, year of publication, location, age, gender, sample size, study design, adjustments, exposure, category of exposure, effect estimates and diagnostic criteria of MetS, was collected respectively. The corresponding effect estimates adjusted for the maximum number of confounding variables with 95% CIs for the highest vs. lowest dietary and circulating vitamin E level were extracted. Moreover, the dietary and circulating vitamin E level (mean ± SD) was also extracted to calculate the SMD (MetS vs. control).

Quality Assessment

Quality assessment was conducted according to the Newcastle-Ottawa (NOS) criteria for non-randomized studies, which was based on three broad perspectives: the selection process of study cohorts, the comparability among different cohorts and the identification of exposure or outcome of study cohorts. Disagreements with respect to the methodological quality were resolved by discussion and mutual-consultation. A study awarded seven or more stars was considered as a high-quality study (44).

Statistical Analyses

The RR for MetS and SMD for both dietary and circulating vitamin E level were the outcome measures in our study. The $I^2$ statistic, which measures the percentage of total variation across studies due to heterogeneity, was examined ($I^2 > 50\%$ was considered heterogeneity). If significant heterogeneity was observed among the studies, the random-effects model was used; otherwise, the fixed effects model was utilized. Begg’s test was employed to assess the publication bias (45). A $p$-value < 0.05 was considered as statistically significant. Moreover, subgroup analysis was employed for both dietary and circulating vitamin E level, respectively.

RESULTS

Study Identification and Selection

The detailed flow diagram of the study identification and selection was presented in Figure 1. A total of 873 potentially relevant articles (244 for PubMed, 327 for Embase and 302 for Web of Science) were retrieved during the initial literature search. After eliminating 331 duplicated articles, 542 articles were screened. 351 irrelevant studies were excluded according to the titles and abstracts. Then, 94 reviews, case reports or letters, 51 non-human studies, 27 randomized control trials studies were removed. Thereafter, 6 additional studies were acquired from the reference lists for the retrieved articles. Eventually, a total of 25 studies were selected for this meta-analysis (17–41).

Study Characteristics

Table 1 showed the main characteristics of the included studies. These studies were published between 2003 and 2021. Among which, 14 studies were performed in Asian countries [Korea (18, 19, 21, 35–39), China (29, 30, 33, 40), Iran (31, 41) and
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FIGURE 1 | The detailed flow diagram of the study identification and selection in this meta-analysis.

Saudi Arabia (28), and 4 ones were conducted in European countries [Poland (34, 38), France (20) and Finland (24)]. The other 7 studies were from US (17, 23, 25, 26, 32), Brazil (22) and Nigeria (27). Both male and female participants were considered in all included studies, except for Bruscate’s and Cho’s study (21, 22). The sample size ranged from 20 to 10,351 for a total number of 51,276. The dietary vitamin E level was assessed by food-frequency questionnaire (FFQ) in 5 studies (17, 19, 26, 33, 41), and 24 h or 3-day recall method in 18 studies (18, 20, 22, 23, 25, 27–32, 34–40), and 4-day record in 1 study (24). The circulating vitamin E level was assessed by high performance liquid chromatography (HPLC) in 11 studies (17, 18, 20, 21, 23, 25, 27, 30, 32, 38, 39), and spectrophotometric method in 1 study (34). The criteria for MetS were National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) in 16 (17–21, 23, 24, 27, 29, 30, 35–37, 39–41) and International Diabetes Federation (IDF) in 6 studies (22, 25, 28, 31, 34, 38). The others utilized American Heart Association (AHA) (26, 33) or Joint Interim Statement (JIS) (32), respectively.

RR of MetS for the Highest vs. Lowest Dietary Vitamin E Level

The overall multi-variable adjusted RR demonstrated that the dietary vitamin E level was negatively associated with MetS (RR = 0.92, 95%CI: 0.85–1.00; P = 0.044) (Figure 2). A substantial level of heterogeneity among various studies was obtained (P < 0.001, \(I^2 = 67.1\%\)). The Begg’s rank-correlation test showed no evidence of publication bias (P = 0.189). The results of subgroup analysis were presented in Table 2. The aforementioned results only existed in studies with the adjustment of BMI (RR = 0.75, 95%CI: 0.59 to 0.94; P = 0.01), physical activity (RR = 0.76, 95%CI: 0.61–0.95; P = 0.02), and energy intake (RR = 0.86, 95%CI: 0.76–0.97; P = 0.01), respectively.

SMD of Dietary Vitamin E Level for MetS vs. Control Subjects

The overall combined SMD showed that the dietary vitamin E level in MetS was lower than that in control subjects (SMD = −0.08, 95%CI: −0.14 to −0.02; P = 0.006) (Figure 3). A substantial level of heterogeneity was obtained among the various studies (P < 0.001, \(I^2 = 69.2\%\)). The Begg’s rank-correlation test showed no evidence of publication bias (P = 0.07). The results of subgroup analysis were presented in Table 3. The aforementioned results only existed in female (SMD = −0.10, 95%CI: −0.20 to 0.00; P = 0.05), NCEP ATP III (SMD = −0.11, 95%CI: −0.07 to −0.04; P = 0.002), 24 h or 3 days recall (SMD = −0.09, 95%CI: −0.16 to −0.02; P = 0.01) and high-quality (SMD = −0.07, 95%CI: −0.13 to −0.01; P = 0.02) studies, respectively.
| Reference | Location | Age years | Gender | Sample Size | Study design | Adjustments | Exposure assessment | Category of exposure | Effect Estimates (RR or SMD) | Diagnostic criteria of MetS | NOS |
|-----------|-----------|-----------|--------|-------------|--------------|-------------|---------------------|---------------------|-----------------------------|-----------------------------|-----|
| Ford (17) | US        | >20       | Both   | 8,808       | Cross-sectional | NA          | FFQ and HPLC       | Control subjects | Dietar vitamin E 9.9 (9.5, 10.3) Control subjects 9.4 (8.8, 10.0) MetS subjects 25.9 (25.5, 26.4) 30.1 (29.2, 30.9) | NCEP ATP III | 8   |
| Kim (18)  | Korea     | >60       | Both   | 404         | Cross-sectional | Age, BMI, energy intake, smoking status, alcohol, physical activity, vitamin, and mineral supplements | 24 h recall and HPLC | Male Control subjects MetS subjects Male Dietary vitamin E 8.6 (7.0, 10.2) Female Dietary vitamin E 8.6 (7.6, 9.6) Male Male Quartiles 1 Quartiles 2 Quartiles 3 Quartiles 4 Dietary vitamin E 0.71 (0.25, 2.1) 0.94 (0.33, 2.67) 0.54 (0.18, 1.62) 0.52 (0.26, 0.98) Female Female Quartiles 1 Quartiles 2 Quartiles 3 Quartiles 4 Female 8.6 (7.6, 9.6) 6.7 (5.9, 7.5) 1.0 0.71 (0.25, 2.1) 0.94 (0.33, 2.67) 0.54 (0.18, 1.62) 0.52 (0.26, 0.98) | NCEP ATP III | 7   |
| Kim (19)  | Korea     | Middle-aged | Both | 688        | Cross-sectional | NA          | FFQ                | Control subjects MetS subjects Male Dietary vitamin E 7.9 (7.5, 8.3) Male Male Quartiles 1 Quartiles 2 Quartiles 3 Quartiles 4 Dietary vitamin E 7.9 (7.5, 8.3) 7.7 (7.3, 8.2) 8.7 (8.1, 9.3) 8.1 (7.6, 8.6) | NCEP ATP III | 6   |
| Reference | Location | Age years | Gender | Sample Size | Study design | Adjustments | Exposure assessment | Category of exposure | Effect Estimates (RR or SMD) | Diagnostic criteria of MetS | NOS |
|-----------|----------|-----------|--------|-------------|--------------|-------------|---------------------|---------------------|--------------------------|----------------------------|-----|
| Czernichow (20) | France | 49 | Both | 5,520 | Cohort | Age, sex, intervention group, educational level, smoking status, physical activity and alcohol consumption | HPLC | Circulating vitamin E | Tertiles 1 | RR 1.0 | NCEP ATP III | 9 |
| | | | | | | | | Tertiles 2 | 0.94 (0.64, 1.38) |
| | | | | | | | | Tertiles 3 | 1.02 (0.70, 1.49) |
| Cho (21) | Korea | >20 | Male | 163 | Cross-sectional | NA | HPLC | Control subjects | Circulating vitamin E | 1.1533 (1.1007, 1.2060) | NCEP ATP III | 6 |
| | | | | | | | MetS subjects | 1.3157 (1.1488, 1.4825) |
| Bruscate (22) | Brazil | 69.3 | Female | 284 | Cross-sectional | Age, smoking, education, physical activity and dietary fiber | 24 h recall | Control subjects | Dietary vitamin E | 17.8 (16.7, 18.9) | IDF | 7 |
| | | | | | | | MetS subjects | 17.4 (15.7, 19.1) |
| | | | | | | | | Dietary vitamin E | Quartiles 1 | RR 1.0 |
| | | | | | | | | Quartiles 2 | 0.52 (0.25, 1.08) |
| | | | | | | | | Quartiles 3 | 0.65 (0.32, 1.33) |
| | | | | | | | | Quartiles 4 | 0.70 (0.34, 1.42) |
| Beydoun (23) | US | 20–85 | Both | 3,202 | Cross-sectional | Age, sex, race/ethnicity, marital status, educational level, PIR, smoking status, total energy intake, alcohol, caffeine, b-carotene, vitamin C, vitamin E, and dietary supplement use, serum levels of folate, thcy, vitamin B12, 25(OH)D, total cholesterol, and TG | 24 h recall and HPLC | Male | Dietary vitamin E | 8.2 (7.8, 8.6) | NCEP ATP III | 8 |
| | | | | | | | | Control subjects | 6.6 (6.4, 6.8) |
| | | | | | | | | MetS subjects | 6.1 (5.7, 6.5) |
| | | | | | | | | Female | Dietary vitamin E | 8.0 (7.6, 8.4) |
| | | | | | | | | Control subjects | 6.6 (6.4, 6.8) |
| | | | | | | | | MetS subjects | 6.1 (5.7, 6.5) |
| | | | | | | | | Male | Circulating vitamin E | 28.5 (27.5, 29.5) |
| | | | | | | | | Control subjects | 33.8 (32.0, 35.6) |
| | | | | | | | | MetS subjects | 33.8 (32.0, 35.6) |
| | | | | | | | | Female | Circulating vitamin E | 28.2 (27.2, 29.2) |
| | | | | | | | | Control subjects | 35.3 (33.5, 37.1) |
| | | | | | | | | MetS subjects | 35.3 (33.5, 37.1) |
| Reference | Location | Age years | Gender | Sample Size | Study design | Adjustments | Exposure assessment | Category of exposure | Effect Estimates (RR or SMD) | Diagnostic criteria of MetS | NOS |
|-----------|----------|-----------|--------|-------------|--------------|-------------|---------------------|----------------------|--------------------------|---------------------------|-----|
| Kouki (24) | Finland | 57–78 | Both | 1,334 | Cross-sectional | Age, alcohol consumption, smoking, education and VO\textsubscript{2} max | 4-day food record | Circulating vitamin E | Quartiles 1 | 1.0 | NCEP ATP III | 8 |
|           |          |          |       |             |              |             |         | Quartiles 2 | 0.79 (0.41, 1.52) |               |                  |    |
|           |          |          |       |             |              |             |         | Quartiles 3 | 1.54 (0.84, 2.84) |               |                  |    |
|           |          |          |       |             |              |             |         | Quartiles 4 | 1.09 (0.44, 2.67) |               |                  |    |
|           |          |          |       |             |              |             |         | Male Control subjects MetS subjects | Dietary vitamin E | 11.1 (10.6, 11.6) |               |    |
|           |          |          |       |             |              |             |         | 9.9 (9.0, 10.8) |               |                  |    |
|           |          |          |       |             |              |             |         | Female Control subjects MetS subjects | Dietary vitamin E | 9.8 (9.2, 10.4) |               |    |
|           |          |          |       |             |              |             |         | 9.5 (8.6, 10.4) |               |                  |    |
|           |          |          |       |             |              |             |         | Dietary vitamin E Male <10 mg/d | RR | 1.0 |               |    |
|           |          |          |       |             |              |             |         | 0.99 (0.96, 1.03) |               |                  |    |
|           |          |          |       |             |              |             |         | >10 mg/d RR |                  |               |                  |    |
|           |          |          |       |             |              |             |         | 1.01 (0.98, 1.05) |               |                  |    |
|           |          |          |       |             |              |             |         | Female Control subjects MetS subjects | Dietary vitamin E | 6.4 (6.2, 6.6) |               |    |
|           |          |          |       |             |              |             |         | 5.9 (4.3, 7.5) |               |                  |    |
|           |          |          |       |             |              |             |         | Control subjects MetS subjects | Circulating vitamin E | 16.6 (16.2, 19.0) |               |    |
|           |          |          |       |             |              |             |         | 20.2 (18.0, 22.4) |               |                  |    |
| Beydoun (25) | US | 12–19 | Both | 1,339 | Cross-sectional | NA | 24 h recall and HPLC | Control subjects MetS subjects | Dietary vitamin E | RR | IDF | 7 |
|           |          |          |       |             |              |             |         | 1.0 |               |                  |    |
|           |          |          |       |             |              |             |         | 1.01 (0.98, 1.05) |               |                  |    |
| de Oliveira Otto (26) | US | 45–84 | Both | 3,828 | Cohort | Energy intake, age, sex, race-ethnicity, education, study center, alcohol intake, physical activity, BMI, fiber intake, cigarette smoking, dietary supplement use, the ratio of polyunsaturated fat intake and saturated fat intake, Mg, Zn, heme iron, non-heme iron, and antioxidant intake | FFQ | Dietary vitamin E | Quintiles 1 | 1.0 | AHA | 8 |
|           |          |          |       |             |              |             |         | Quintiles 2 | 1.00 (0.79, 1.26) |               |                  |    |
|           |          |          |       |             |              |             |         | Quintiles 3 | 1.03 (0.81, 1.31) |               |                  |    |
|           |          |          |       |             |              |             |         | Quintiles 4 | 0.84 (0.65, 1.09) |               |                  |    |
|           |          |          |       |             |              |             |         | Quintiles 5 | 0.76 (0.56, 1.03) |               |                  |    |

(Continued)
| Reference | Location   | Age years | Gender | Sample Size | Study design | Adjustments | Exposure assessment | Category of exposure | Effect Estimates (RR or SMD) | Diagnostic criteria of MetS | NOS |
|-----------|------------|-----------|--------|-------------|--------------|-------------|---------------------|----------------------|--------------------------|-----------------------------|-----|
| Odum (27) | Nigeria    | 50        | Both   | 192         | Case-control | NA          | HPLC                | Control subjects     | Circulating vitamin E30.8 (29.6, 32.0)16.9 (15.9, 17.9) | NCEP ATP III           | 7   |
| Al-Daghri (28) | Saudi Arabia | 19–60   | Both   | 185         | Cross-sectional | Age, BMI and physical activity | 24 h recall | Control subjects | Dietary vitamin E2.3 (2.1, 2.5)2.0 (1.8, 2.2) | IDF                        | 7   |
| Motamed (31) | Iran     | 35–65     | Both   | 3,800       | Cross-sectional | Sex, age, physical activity level, smoking, past medical history, energy intake, and BMI | 24 h recall | Male | Dietary vitamin E14.8 (14.2, 15.4)16.6 (15.9, 17.3) | IDF                        | 7   |
| Bian (29)  | China      | 30–70     | Both   | 258         | Cross-sectional | NA          | 24 h recall | Control subjects | Dietary vitamin E29.9 (28.4, 31.4)27.5 (25.9, 29.1) | NCEP ATP III           | 8   |
| Li (30)    | China      | 18–65     | Both   | 550         | Cross-sectional | Age and sex | 3-day food record and HPLC | Control subjects | Dietary vitamin E45.7 (42.8, 48.2)45.1 (42.1, 48.1) | NCEP ATP III           | 8   |

(Continued)
TABLE 1 | Continued

| Reference | Location | Age years | Gender | Sample Size | Study design | Adjustments | Exposure assessment | Category of exposure | Effect Estimates (RR or SMD) | Diagnostic criteria of MetS | NOS |
|-----------|----------|-----------|--------|-------------|--------------|-------------|-------------------|----------------------|-----------------------------|-----------------------------|-----|
| Mah (32)  | US       | 24–40     | Both   | 20          | Case-control | NA          | HPLC              | Control subjects MetS subjects | Circulating vitamin E Quartiles 1 Quartiles 2 Quartiles 3 Quartiles 4 | RR 1.0 0.44 (0.15, 1.25) 0.88 (0.32–2.44) 1.58 (0.55–4.54) | JIS 5 |
| Wei (33)  | China    | 18–84     | Both   | 2,069       | Cross-sectional | Age, sex, cigarette smoking, alcohol, drinking, nutritional supplementary, activity level, dietary energy intake, fiber intake and protein intake | FFQ                | Control subjects MetS subjects | Dietary vitamin E 22.2 (19.5, 24.9) 23.9 (21.9, 25.9) | AHA 7 |
| Godala (34) | Poland   | 30–65     | Both   | 273         | Case-control | NA          | 3-day food record and spectrophotometric method | Control subjects MetS subjects | Dietary vitamin E 9.33 (8.27, 10.39) 8.85 (8.03, 9.67) | IDF 7 |
| Lim (36)  | Korea    | Middle-aged | Both   | 143         | Cross-sectional | Not mentioned | 3-day food record | Control subjects MetS subjects | Circulating vitamin E 25.49 (24.86, 26.12) 12.47 (12.06, 12.86) | NCEP ATP III 6 |
| Ahn (35)  | Korea    | 30–60     | Both   | 614         | Cross-sectional | Age, smoking, alcohol consumption and physical activity | 3-day food record | Male Control subjects MetS subjects Female Control subjects MetS subjects 'Dietary vitamin E Male Tertile 1 Tertile 2 Tertile 3 | Dietary vitamin E 3.5 (3.3, 3.7) 3.3 (3.2, 3.4) Diet vitamin E 3.5 (3.3, 3.7) 3.8 (3.5, 4.1) RR 1.0 1.00 (0.56, 1.76) 0.52 (0.30, 0.92) | NCEP ATP III 7 |
| Reference  | Location | Age years | Gender | Sample Size | Study design   | Adjustments                                                                 | Exposure assessment | Category of exposure | Effect Estimates (RR or SMD)                                                                 | Diagnostic criteria of MetS | NOS |
|------------|----------|-----------|--------|-------------|----------------|-----------------------------------------------------------------------------|---------------------|----------------------|---------------------------------------------------------------------------------------------|-----------------------------|-----|
| Ahn (37)   | Korea    | 19–64     | Both   | 10,351      | Cross-sectional | Age, BMI, alcohol consumption, smoking, physical activity, household income, education level and energy intake | 24 h recall         | RR                   | 1.0<br>1.16 (0.65, 2.09)<br>1.70 (0.94, 3.06)                                                | NCEP ATP III               | 8   |
| Godala (38)| Poland   | 57        | Both   | 332         | Cross-sectional | NA                                                                         | 24 h recall and HPLC| Control subjects<br>MetS subjects | Dietary vitamin E<br>9.31 (8.26, 10.35)<br>9.01 (8.37, 9.66) | IDF                         | 7   |
| Kim (39)   | Korea    | 47.1      | Both   | 5,885       | Cross-sectional | Age, sex, residence, household income, education, alcohol consumption, smoking status, physical activity, hs-CRP and BMI | HPLC                | Circulating vitamin E<br>Quartiles 1<br>Quartiles 2<br>Quartiles 3<br>Quartiles 4 | 1.0<br>1.30 (0.97, 1.74)<br>1.71 (1.30, 2.25)<br>2.56 (1.95, 3.35) | NCEP ATP III               | 9   |
| Peng (40)  | China    | >99       | Both   | 992         | Cohort         | Aex, marital status, physical activity, smoking status, alcohol intake, family history of chronic diseases and daily total energy intake | 24 h recall         | Control subjects<br>MetS subjects | Dietary vitamin E<br>17.74 (10.45, 25.03)<br>12.18 (9.00, 15.36) | NCEP ATP III               | 7   |
| Zaeemzadeh | Iran     | 30        | Both   | 42          | Case-control   | NA                                                                         | FFQ                 | Control subjects<br>MetS subjects | Dietary vitamin E<br>17.21 (14.49, 19.93)<br>6.17 (2.01, 10.33) | NCEP ATP III               | 6   |
FIGURE 2 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of MetS for the highest vs. lowest category of dietary vitamin E level.

TABLE 2 | Subgroup analysis of MetS for the highest vs. lowest dietary vitamin E level category.

| Stratification                        | Number of studies | Pooled RR | 95% CI       | P value | Heterogeneity |
|---------------------------------------|-------------------|-----------|--------------|---------|---------------|
| All studies                           | 10                | 0.92      | 0.85, 1.00   | P = 0.04| P < 0.001; I² = 67% |
| Adjustment of BMI                     |                   |           |              |         |               |
| Adjusted                              | 5                 | 0.75      | 0.59, 0.94   | P = 0.01| P = 0.02; I² = 61% |
| Unadjusted                            | 5                 | 0.99      | 0.93, 1.06   | P = 0.79| P = 0.03; I² = 58% |
| Adjustment of physical activity       |                   |           |              |         |               |
| Adjusted                              | 7                 | 0.76      | 0.61, 0.95   | P = 0.02| P = 0.004; I² = 63% |
| Unadjusted                            | 3                 | 1         | 0.98, 1.02   | P = 0.98| P = 0.18; I² = 38% |
| Adjustment of energy intake           |                   |           |              |         |               |
| Adjusted                              | 5                 | 0.86      | 0.76, 0.97   | P = 0.01| P = 0.17; I² = 34% |
| Unadjusted                            | 5                 | 0.96      | 0.88, 1.06   | P = 0.42| P < 0.001; I² = 76% |
| Adjustment for vitamin E supplement   |                   |           |              |         |               |
| Adjusted                              | 3                 | 0.8       | 0.64, 1.01   | P = 0.06| P = 0.12; I² = 48% |
| Unadjusted                            | 7                 | 0.94      | 0.87, 1.02   | P = 0.14| P < 0.001; I² = 70% |
| Study design                          |                   |           |              |         |               |
| Cross-sectional                      | 9                 | 0.93      | 0.86, 1.01   | P = 0.10| P < 0.001; I² = 67% |
| Cohort                                | 1                 | 0.76      | 0.56, 1.03   | /       | /             |

**RR of MetS for the Highest vs. Lowest Circulating Vitamin E Level**

The overall multi-variable adjusted RR showed no significant relationship between circulating vitamin E level and MetS (RR = 1.46, 95%CI: 0.85–2.48; P = 0.168) (Figure 4). A substantial level of heterogeneity was obtained among various studies (P = 0.001, I² = 75.2%). The Begg’s rank-correlation test showed no evidence of publication bias (P = 0.707). The results of subgroup analysis were presented in Table 4.

**SMD of Circulating Vitamin E Level for MetS vs. Control Subjects**

The overall combined SMD showed that the circulating vitamin E level in MetS was lower than that in control subjects (SMD = −0.58, 95%CI: −1.04 to −0.13; P = 0.013) (Figure 5). A
**FIGURE 3** | Forest plot of meta-analysis: SMD of dietary vitamin E level for MetS vs. control subjects.

**TABLE 3** | Subgroup analysis for SMD of dietary vitamin E level in MetS vs. control subjects.

| Stratification                       | Number of studies | Pooled SMD  | 95% CI         | P-value | Heterogeneity |
|--------------------------------------|-------------------|-------------|----------------|---------|---------------|
| All studies                          | 18                | −0.08       | −0.14, −0.02   | P = 0.006 | P < 0.001; I² = 69% |
| Gender                               |                   |             |                |         |               |
| Male                                 | 6                 | −0.06       | −0.22, 0.09    | P = 0.44 | P < 0.001; I² = 80% |
| Female                               | 6                 | −0.10       | −0.20, 0.00    | P = 0.05 | P = 0.02; I² = 63% |
| Diagnostic criteria of MetS          |                   |             |                |         |               |
| NCEP ATP III                         | 11                | −0.11       | −0.07, −0.04   | P = 0.002 | P < 0.001; I² = 63% |
| Other                                | 7                 | −0.04       | −0.16, 0.08    | P = 0.51 | P < 0.001; I² = 77% |
| Geographical region                  |                   |             |                |         |               |
| Asia                                 | 11                | −0.10       | −0.21, 0.00    | P = 0.05 | P < 0.001; I² = 79% |
| Non-Asia                             | 7                 | −0.06       | −0.09, −0.02   | P = 0.002 | P = 0.62; I² = 0% |
| Exposure assessment                  |                   |             |                |         |               |
| FFQ                                  | 4                 | −0.09       | −0.23, 0.06    | P = 0.24 | P = 0.001; I² = 80% |
| 24 h or 3 days recall                | 14                | −0.09       | −0.16, −0.02   | P = 0.01 | P < 0.001; I² = 66% |
| Study quality                        |                   |             |                |         |               |
| High-quality                         | 15                | −0.07       | −0.13, −0.01   | P = 0.02 | P < 0.001; I² = 67% |
| Low-quality                          | 3                 | −0.24       | −0.56, 0.08    | P = 0.14 | P = 0.001; I² = 81% |
substantial level of heterogeneity was obtained among the various studies ($P < 0.001$, $I^2 = 98.9\%$). The Begg's rank-correlation test showed no evidence of publication bias ($P = 0.246$). The results of subgroup analysis were presented in Table 5. The aforementioned results only existed in spectrophotometric method (SMD = $-4.67$, 95%CI: $-5.14$ to $-4.20$) and high-quality study (SMD = $-1.00$, 95%CI: $-1.54$ to $-0.45$; $P < 0.001$), but lost in $\alpha$-tocopherol (SMD = 0.08, 95%CI: $-0.16$ to $0.33$; $P = 0.50$) and $\gamma$-tocopherol (SMD = 0.54, 95%CI: $-1.03$ to $2.11$; $P = 0.50$), respectively.

**DISCUSSION**

In the present meta-analysis, a total of 25 observational studies were identified for examination. The pooled analysis showed that the dietary vitamin E level was inversely associated with MetS. Since both the oxidative stress and inflammation plays important role in the pathophysiology of MetS (46), the negative relationship between dietary vitamin E level and MetS may be mainly attributed to the antioxidant and anti-inflammatory property of vitamin E (12, 47, 48). Consistently, the clinical
trial evidence demonstrates that the vitamin E supplementation may ameliorate MetS via anti-inflammation and anti-oxidative stress (49, 50). Moreover, some experimental animal studies have also indicated the beneficial impact of vitamin E intake on the MetS-related context (13–16). Nevertheless, very limited prospective cohort studies are identified for meta-analysis. The dietary vitamin E level is measured after MetS event occurs in cross-sectional/case-control studies. The factors that matter the dietary vitamin E level may change after MetS, which may reverse the causality. In addition, the significant heterogeneity has also been specified ($I^2 = 67.1\%$). Therefore, these above issues should be addressed by further well-designed prospective cohort studies.

In contrast to dietary vitamin E (a general/overall estimation that calculated from the FFQ or recall method), the issue of circulating vitamin E level is rather complicated. On one hand, vitamin E is composed of 8 similar structure compounds: 4 tocopherol and 4 tocotrienol derivatives including α-, β-, γ-, δ-tocopherol and tocotrienol, respectively. All vitamin E isomers from dietary or supplementary sources are absorbed and delivered to the liver. Only α-tocopherol is preferentially recognized by the α-tocopherol transfer protein for incorporation into circulating plasma, whereas the other tocopherol and tocotrienol isomers are mostly excreted (51, 52). Indeed, the concentration of tocotrienol is significantly lower than that of α-tocopherol (52). This is the main reason...
why α-tocopherol is currently severed as the standard to estimate human vitamin E requirements (53). However, it is increasingly acknowledged that tocopherol and tocotrienol serve different biological functions (tocotrienol may result in superior therapeutic properties than tocopherol), which has greatly challenged the accuracy of α-tocopherol estimation alone (54–56). Unfortunately, only several studies reported the exposure as “tocopherol” (21, 32, 39) (most studies reported the exposure as “circulating vitamin E” directly). The combination of tocopherol/tocotrienol may probably preclude a clear clarification for this issue. On the other hand, chronic inflammation and oxidative stress caused by MetS may lower the circulating antioxidant and anti-inflammatory agent level (57). In turn, the circulating antioxidant and anti-inflammatory agent level may also increase to cope with chronic inflammation and oxidative stress caused by MetS (58). As a consequence, the level of circulating vitamin E might be dynamic in MetS condition. Taken together, the specification of tocopherol/tocotrienol and potential feedback system should be considered for circulating vitamin E in further studies.

The epidemiological data has demonstrated that BMI, physical activity and energy intake is associated with both dietary vitamin E and MetS (59–63). Indeed, our finding is lost in studies without adjustment of these factors (Table 2). The adjustment of confounding factors can exclude the effect on both exposure and outcome (leave the direct relationship between vitamin E and MetS). Therefore, BMI, physical activity and energy intake may be adjusted when further study is employed. In addition, the lower dietary vitamin E level in MetS is only obtained in females, NCEP ATP III, 24 h or 3 days recall and high-quality studies (Table 3). Although females are more precise and reliable in completing the exposure assessment, some genetic gender differences with the diet-related pathology of MetS cannot be fully excluded (64). Moreover, the diagnostic criteria of MetS and exposure assessment may also influence the results. Since a substantial improvement may exist in laboratorial techniques to assess the circulating vitamin E level, a subgroup analysis for assessment method has also been employed. Interestingly, the results only exist in spectrophotometric method, but not HPLC. Notably, the spectrophotometric method is utilized in only one study (34). Taken together, more study with appropriate confounding factors adjustment and different circulating vitamin E assessment is needed.

The strengths of the present meta-analysis are mainly reflected in the following aspects: First, this is the first meta-analysis of observational studies on the associations of dietary and circulating vitamin E level with MetS. Second, our findings for dietary vitamin E level and MetS are consistence with current corresponding experimental and clinical studies. The limitations should also be acknowledged. First, the substantial level of heterogeneity might have distorted the reliability of our results (especially for circulating vitamin E level). Second, due to the limitation in the relevant literature, very few prospective cohort studies are identified totally (precluded causal relationships). Third, the classification of exposure vary greatly among individuals. For example, “tertiles,” “quartiles” and “quintiles” are employed to classify the dietary/circulating vitamin E level. Fourth, the selection of adjusted factors and definition of MetS are not uniform. Last but not the least, very few studies have considered the isomers of tocopherol/tocotrienol. These limitations may weaken the significance of this study.

CONCLUSIONS

The results of this meta-analysis suggest that the dietary vitamin E level may be inversely associated with MetS. On the other hand, current evidence is still insufficient to conclude a relationship between the circulating vitamin E level and MetS. More well-designed prospective cohort studies with the specification of circulating tocopherol/tocotrienol are needed to address the issues further.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

YZ, DZ, and JL conceived the idea and drafted this meta-analysis. ZL and QL performed the statistical analysis. YL and JD selected and retrieved relevant papers. HG assessed each study. YZ, DZ, and JL was the guarantor of the overall content. All authors revised and approved the final manuscript.

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