Circulating vitamin E and cardiometabolic measures: a Mendelian randomization analysis

Chuanlong Fan,1 Tao Huang,2,3,4 Xuejun Kong,3 Xiaohong Zhang,1 Zuquan Zou1,* and Jing Xiao6,*

1Medical School, Ningbo University, 818 Fenhua Road, Ningbo, Zhejiang 315211, China
2Department of Epidemiology & Biostatistics and 3Department of Global Health, School of Public Health, Peking University, 5 Summer Palace Road, Haidian District, Beijing 100000, China
4Key Laboratory of Molecular Cardiovascular Sciences Ministry of Education, 5 Summer Palace Road, Haidian District, Beijing 100000, China
5Synapse program/Martinos Center, Massachusetts General Hospital, 149 13th Street, Charlestown, MA 02129, USA
6Beijing Friendship Hospital, Capital Medical University, 95 Yongan Road, Xuanwu District, Beijing 100000, China

Although a large body of literature reported that high intake of vitamin E played a possible role in reducing risk of cardiometabolic diseases, conflicting results were also found in some observational studies due to confounding factors. Hence, we used a Mendelian randomization study as an alternative way to examine the causality between circulating vitamin E and cardiometabolic diseases. Summary-level data were extracted from consortia and three single nucleotide polymorphisms were used as instrumental variables. Our study showed that a one-SD increase in circulating vitamin E levels was causally associated with an increased risk of coronary artery disease [odds ratio (OR) 3.16 (95%CI 1.74, 5.73); p = 1.91 × 10−4] at the Bonferroni-adjusted level of significance (p<0.005). Moreover, a one-SD increase in circulating vitamin E levels was associated with a 0.572-SD increase in low density lipoprotein cholesterol (mg/dl), a 0.683-SD increase in total cholesterol (mg/dl), and a 1.45-SD increase in triglyceride (mg/dl), but a 0.502-SD decrease in high density lipoprotein cholesterol (mg/dl) at the Bonferroni-adjusted level of significance (p=0.0028). Our findings indicated that genetically elevated vitamin E was associated with increased risk of coronary artery disease, suggesting an adverse causality between circulating vitamin E and coronary artery disease.

Key Words: vitamin E, cardiometabolic diseases, Mendelian randomization, coronary artery disease, low density lipoprotein cholesterol

Cardiometabolic diseases, including type 2 diabetes (T2DM), coronary artery disease (CAD), chronic kidney diseases (CKD), and stroke, are the top cause of mortality and are estimated to cause greater harm in the following decades.1,2 Therefore, effective treatment for cardiometabolic diseases still represents a major public health challenge, since drug treatments are notoriously expensive and the efficacy and safety of drugs are limited by their duration.2,3 Dietary factors are believed to play positive roles in reducing risk of cardiometabolic diseases, especially vitamin E supplementation.4,5 In agreement, several observational studies5−10 suggested that vitamin E intake had a beneficial effect on protecting against cardiometabolic diseases. However, a large body of compelling literatures suggested that increased vitamin E intake was more likely to be associated with higher risk of cardiometabolic diseases.11−14 For instance, a meta-analysis of 68 trials of lifestyle interventions with vitamin E reported that treatment with vitamin E may increase mortality in patients with CAD, implying a possible adverse effect of vitamin E in patients with cardiometabolic diseases.15,16 Therefore, the roles of vitamin E on cardiometabolic diseases are still controversial in epidemiological studies.

Correlations between vitamin E and disease risk from observational studies are unable to fully account for confounding by shared risk factors, such as socioeconomic status and unmeasured lifestyle factors. In addition, reverse causality whereby the presence of disease may influence vitamin E level. Therefore, the causality of observations remains to be determined. To more precisely examine the causality between vitamin E and cardiometabolic diseases, we used Mendelian randomization analysis as an alternative way.

Mendelian randomization (MR) analysis has been a widely-used technique, which uses genetic variants as instrumental variables (IVs) to explore causal association between risk factors and outcomes.17−19 Due to random classification of genotypes at conception, confounding and bias are limited in MR.19 In addition, socioeconomic status and unmeasured lifestyle factors confounding the associations of observations are not present in MR analysis.19,20

Therefore, in the present study, we used MR analysis to examine the hypothesis that increased circulating vitamin E levels were associated with higher risk of cardiometabolic diseases and related quantitative traits.

Methods

Study design. Our aim was to examine whether circulating vitamin E was associated with T2DM, CAD, CKD, ischaemic stroke (IS) and its subtypes, including large artery stroke (LAS), small vessel stroke (SVS), cardioembolic stroke (CE), intracerebral hemorrhage (ICH), lobar intracerebral hemorrhage (Lobar ICH), and nonlobar intracerebral hemorrhage (Nonlobar ICH). The genetic variants used in MR analysis must: 1) be associated with circulating vitamin E levels, 2) be not associated with any confounder of circulating vitamin E levels and cardiometabolic diseases, 3) be not associated with outcomes of interest through other pathways (Fig. 1).20

For primary outcomes, we examined the causal association between circulating vitamin E and T2DM, CAD, CKD, IS and its subtypes, including LAS, SVS, CE, ICH, Lobar ICH, and Nonlobar ICH. For secondary outcomes, we explored the causal effect of circulating vitamin E upon cardiometabolic traits including anthropometrics, glycemic traits, and lipids (Fig. 2).

Single nucleotide polymorphisms selection (SNPs) and validation of IV. We selected three SNPs (p<5 × 10−8) identified from genome-wide association studies (GWAS). This GWAS included three replication studies—Alpha-Tocopherol, Beta-Carotene...
Cancer Prevention (ATBC) Study cohort, replicated findings in a combined meta-analysis with the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Study and the Nurses’ Health Study (NHS).\(^{(21)}\) Data from the NHS, a cohort of US women, was also used to replicate the most significant findings (approximately 100 SNPs with \(p < 1 \times 10^{-5}\) or higher) obtained in the original GWAS.\(^{(22)}\) 7,781 participants included in this GWAS were 52% of residents of southwestern Finland and 48% of Americans. Age-adjusted SD scores were created for circulating vitamin E levels at the latest time point; the mean age was between 60.6 ± 5.4 years.

In this GWAS,\(^{(21)}\) vitamin E levels were log-transformed to normalize the distributions. A linear model adjusted for age, BMI and cancer status was used to relate the log-transformed outcomes to a SNP by assuming an additive mode of inheritance. Moreover, total cholesterol (TC) and high density lipoprotein cholesterol (HDL) were adjusted for the analysis due to the effect of circulating lipids on serum vitamin E levels. The likelihood ratio test was used to detect the association between the vitamin E levels and the SNPs as well as identify the independent effect of other SNPs in the initial GWAS sample with the most significant SNP and those covariates involved in the basic model. In addition, a fixed effects meta-analysis and a sensitivity analysis were performed on the GWAS and replication studies to adjust for the covariates. Combined, selected three SNPs explained 1.7% of the residual variance in log vitamin E levels (Fig. 1).\(^{(21)}\)

**Data Sources.** For disease outcomes, summary-level data were extracted from the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (\(n = 149,821\)) for type 2 diabetes, MAGIC (\(n = 133,010\)) for glycemic traits, CKDGen (\(n = 133,814\)) for CKD and kidney function, CARDioGRAMplusC4D (60,801 CAD case subjects and 123,504 control subjects) for CAD, SIGN (29,979 IS case subjects and 50,728 control subjects) for IS, LAS, SVS, and CE, GERFHS (3,090 case subjects and 1,481 control subjects) for ICH, Lobar ICH, and Nonlobar ICH, GLGC (\(n = 188,577\)) for lipids, and GIANT for BMI (\(n = 339,224\)), WCadjBMI and WHRadjBMI (\(n = 224,459\)), and height (\(n = 253,288\)).

---

*See online. [https://doi.org/10.3164/jcbn.19-12](https://doi.org/10.3164/jcbn.19-12)

C. Fan et al.
method, weighted median method, and simple median method were used to analyze the estimates of the causal effect of circulating vitamin E on cardiometabolic diseases and quantitative traits.

We analyzed the association between three SNPs with circulating vitamin E concentrations as per unit change (mg/L) in the natural scale. The effect size for each meta-analysis was reported in the main results as the effect of a one-SD (1 SD in circulating vitamin E concentrations corresponds to about 1.6 mg/L) change in circulating vitamin E concentrations because this metric was more interpretable than an arbitrary difference. Graphpad Prism 7 and R ver. 3.2.4 (R Project for Statistical Computing) were used to perform analysis. The threshold of statistical significance for T2DM, CAD, CKD, IS, LAS, SVS, CE, ICH, Lobar ICH, and Nonlobar ICH as primary outcomes was \( p < 0.005 \) (0.05/10 = 0.005) to account for testing ten associations. The threshold of significance for the analysis of cardiometabolic quantitative traits as secondary outcomes was \( p < 0.0028 \) (0.05/18 = 0.0028) to account for 18 tests.

**Results**

**Selected SNPs and IVs validation.** First, IVs were selected from GWAS database of vitamin E \((p < 5 \times 10^{-8})\). After preliminarily selected, three SNPs that passed quality control were shown in Table 1. All selected IVs met \( p < 5 \times 10^{-8} \), indicating that selected IVs were vitamin E-related loci. Our MR analysis had about 80% power, assuming that 1.7% of circulating vitamin E levels was explained by the three SNPs. Second, we extracted the results for vitamin E-cardiometabolic diseases associations in the database of cardiometabolic diseases (Supplemental Table 1, 2, 3, 4, 5 and 6*). These findings showed that selected IVs satisfied the basic hypothesis of MR analysis: IVs were related to vitamin E, but no associations with cardiometabolic diseases.

**Pleiotropy identification.** To satisfy assumption 3, we adopted MR-Egger regression to test the direct pleiotropy of IVs. Our findings showed that the intercept term estimated for CAD from MR-Egger regression was centered at origin with a CI including null \( [175,186,376] (95\% CI 2,780,457,943,3,130,830,694); p = 0.908 \) (Supplemental Table 7*), indicating that no pleiotropy influenced the results. Similarly, results for T2DM, CKD, IS, LAS, SVS, ICH, Lobar ICH, Nonlobar ICH and cardiometabolic traits were not influenced by pleiotropy (Supplemental Table 7*).

**Causal effect of circulating vitamin E levels on risk of T2DM, CAD, CKD, stroke and its subtypes.** In the present MR study, the IVW method was used as the primary approach to test the causal effect. We found that a one-SD increase in circulating vitamin E levels was associated with an increased risk of CAD [odds ratio (OR) 3.16 (95% CI 1.74, 5.73); \( p = 1.91 \times 10^{-11} \)] at the Bonferroni-adjusted level of significance \((p = 0.005)\). However, circulating vitamin E were not associated with T2DM [OR 1.15 (95% CI 0.89, 1.48); \( p = 0.286 \)], CKD [OR 1.38 (95% CI 0.79, 2.4); \( p = 0.266 \)], IS [OR 1.45 (95% CI 0.77, 2.72); \( p = 0.251 \)], LAS [OR 2.35 (95% CI 0.64, 8.62); \( p = 0.201 \)], SVS [OR 1.49 (0.38, 5.92); \( p = 0.580 \)], CE [OR 1.54 (0.45, 5.26); \( p = 0.503 \)], ICH [OR 1.97 (95% CI 0.31, 12.55); \( p = 0.539 \)], Lobar ICH [OR 2.05 (0.19, 22.60); \( p = 0.568 \)] and Nonlobar ICH [OR 1.45 (0.77, 2.72); \( p = 0.251 \)]. In addition, we used simple median-based

| SNP       | Chromosome | Position | Nearest gene | EA/OA | MAFF | \( \beta \) | SE       | \( p \)  |
|-----------|------------|----------|--------------|-------|------|---------|---------|-------|
| rs964184  | 11         | 116154127| BUD13/ZNF259/APOA5 | G/A  | 0.15 | 0.04    | 0.01    | \( 2.7 \times 10^{-10} \) |
| rs2108622 | 19         | 15851431 | CYMPF2       | T/C   | 0.21 | 0.04    | 0.01    | \( 1.7 \times 10^{-8} \) |
| rs11057830| 12         | 123873006| SCARB1       | A/V   | 0.15 | 0.04    | 0.01    | \( 2.0 \times 10^{-8} \) |

The data source was the EGG consortium. EA/OA, effect allele/other allele; MAFF, minor allele frequency. The effect size (\( \beta \)) was reported per unit change in mg/L in natural scale per effect allele.

Table 1. 3 SNPs associated with circulating vitamin E levels

*See online. https://doi.org/10.3164/jcbn.19-12
### Table 1: MR of circulating vitamin E levels and T2DM, CAD, and CKD

| MR methods | Case/Control | MR estimates |
|------------|--------------|--------------|
|            | n            | OR (95%CI)   | p value   |
| T2DM       | 34,840/114,981 | 1.15 (0.89, 1.48) | 0.286 |
| IVW        |              | 1.28 (0.92, 1.79) | 0.138 |
| Weighted median |          | 1.28 (0.91, 1.81) | 0.150 |
| Simple median |              |              |          |
| CAD        | 41,476/65,743 | 3.16 (1.74, 5.73) | 1.91×10⁻³ |
| IVW        |              | 3.06 (1.28, 7.32) | 1.16×10⁻³ |
| Weighted median |          | 2.99 (1.27, 7.06) | 1.16×10⁻³ |
| Simple median |              |              |          |
| CKD        | 12,385/104,780 | 1.38 (0.79, 2.40) | 0.266 |
| IVW        |              | 1.33 (0.7, 2.52) | 0.381 |
| Weighted median |          | 1.38 (0.69, 2.79) | 0.377 |
| Simple median |              |              |          |

**Fig. 3.** MR of circulating vitamin E levels and type 2 diabetes, CAD, and CKD.

## Table 2: MR of circulating vitamin E levels and IS, LAS, SVS, and CE

| MR methods | Case/Control | MR estimates |
|------------|--------------|--------------|
|            | n            | OR (95%CI)   | p value   |
| CE         | 4,816/50,728 | 1.54 (0.45, 5.26) | 0.503 |
| IVW        |              | 2.02 (0.42, 9.75) | 0.391 |
| Weighted median |          | 1.37 (0.22, 8.45) | 0.751 |
| Simple median |              |              |          |
| SVS        | 4,203/50,728 | 1.49 (0.38, 5.92) | 0.580 |
| IVW        |              | 1.60 (0.32, 8.06) | 0.580 |
| Weighted median |          | 1.85 (0.32, 10.64) | 0.497 |
| Simple median |              |              |          |
| LAS        | 3,007/50,728 | 2.35 (0.64, 8.62) | 0.201 |
| IVW        |              | 2.29 (0.47, 11.2) | 0.310 |
| Weighted median |          | 2.35 (0.46, 12.15) | 0.314 |
| Simple median |              |              |          |
| IS         | 17,953/50,728 | 1.45 (0.77, 2.72) | 0.251 |
| IVW        |              | 1.50 (0.68, 3.31) | 0.320 |
| Weighted median |          | 1.20 (0.5, 2.92) | 0.883 |
| Simple median |              |              |          |

**Fig. 4.** MR of circulating vitamin E levels and IS, LAS, SVS, and CE.
method and weighted median-based method to replicate the MR analysis and the results were consistent with IVW method (Fig. 3, 4 and 5).

Causal effect of circulating vitamin E levels on cardiometabolic quantitative traits. The IVW method showed that a one-SD increase in circulating vitamin E levels was causally associated with a 0.572-SD increase in low density lipoprotein cholesterol (LDL) \( \beta = 0.572 \) (95% CI 0.423, 0.721; \( p = 2.45 \times 10^{-9} \)), a 0.693-SD increase in TC \( \beta = 0.693 \) (95% CI 0.548, 0.838; \( p = 4.17 \times 10^{-7} \)) and a 1.145-SD increase in triglyceride (TG) \( \beta = 1.145 \) (95% CI 1.009, 1.281; \( p = 2.31 \times 10^{-7} \)), respectively, but a 0.502-SD decrease in HDL \( \beta = -0.502 \) (–0.640, –0.364; \( p = 5.2 \times 10^{-7} \)) at the Bonferroni-adjusted level of significance \( (p<0.0028) \) (Table 2). However, there was no significant causality of circulating vitamin E with other cardiometabolic traits such as height, BMI, fasting glucose, HbA1C, log-transformed HOMA-B, and log-transformed HOMA-IR (Table 2). Moreover, we found that the intercept term had no statistical significance in MR regression analysis, suggesting the robustness of our results without influence by pleiotropy (Table 2).

Sensitivity analyses of MR. Four different methods, including the IVW method, simple median-based method and weighted median-based method were used in sensitivity analyses method. The results showed that causal effects are consistent (Fig. 3–5, and Table 2), suggesting the robustness of our outcomes.

Participants. The collaboration investigating the association of vitamin E and cardiometabolic measures consists of 8 cohorts. Of the 8 cohorts, six were conducted in the USA, one in France and one in Denmark. This study comprised a meta-analysis of directly genotyped and imputed SNPs from European ancestry cohorts including 1,648,833 individuals (Table 3).

In the present study, the association of vitamin E with cardiometabolic measures among cohorts was assessed. We found that each 1.6 mg/L increase in vitamin E concentrations was associated with a higher relative risk of CAD (1.35, 1.87 to 1.96, combined \( p = 0.03 \)), LDL (1.48, 1.34 to 1.89, combined \( p = 0.05 \)), TC (1.56, 1.27 to 1.79, combined \( p = 0.04 \)), and TG (1.68, 1.42 to 1.95, combined \( p = 0.03 \)), but a lower relative risk was observed for HDL (0.58, 0.37 to 0.67, combined \( p = 0.01 \)) (Fig. 6 and 7). In addition, we found no associations between vitamin E and other cardiometabolic measures, such as BMI (0.98, 0.92 to 1.23, combined \( p = 0.45 \)) or T2DM (0.97, 0.95 to 1.13, combined \( p = 0.54 \)) (Fig. 6 and 7).

Discussion

Through MR analysis, we found that a one-SD increase in circulating vitamin E levels was associated with higher risk of CAD, as well as an increase in LDL, TC, and TG, but a decrease in HDL. These findings of our study indicated a causal effect of genetically increased circulating vitamin E levels on higher risk of CAD and related traits.

The findings of our study were consistent with results from the majority of randomized controlled trials (RCTs).\(^{14,34,35}\) These RCTs indicated that increased vitamin E intake was associated with higher risk of CAD. In agreement, a well-designed trial conducted by Marchioli et al.\(^{12}\) showed that incidence of congestive heart failure in patients treated with vitamin E for 3.5 years was increased. Moreover, a meta-analysis of 19 clinical trials reported that the relationship between vitamin E dosages and all-cause mortality of patients with CAD was statistically significant when vitamin E dosages were greater than 150 IU/day.\(^{36}\) Although the majority of published RCTs provided evidence to support the adverse effects of vitamin E on CAD,\(^{14,34,35}\) there were conflicting results reporting that vitamin E had no effects or protective effects on CAD.\(^{6,37,38}\) For example, a contrasting result was obtained by Mörike\(^{37}\) who observed that treatment of CAD with vitamin E supplementation for a median of 510 days decreased the rate of non-fatal myocardial infarction, which challenged adverse results derived from well-designed RCTs.\(^{14,34,35}\) Therefore, the discrepancy between MR results and observations existed. A possible explanation was that SNPs selected as IVs may play a potential role in CAD and further investigation with specific SNPs was required to examine the causal association between circulating vitamin E and risk of CAD. Another possible explanation was that residual confounding, such as socioeconomic status and unmeasured life-

| MR methods | Case-Control n | MR estimates | p value |
|------------|----------------|--------------|---------|
|            |                | OR (95%CI)   |         |
| ICH        | 1,545/1,481    | 1.97 (0.31, 12.55) | 0.539   |
| IVW        |                | 2.64 (0.28, 24.93) | 0.688   |
| Simple median |              | 2.42 (0.23, 25.41) | 0.471   |
| Lobar ICH  | 664/1,481      | 2.05 (0.19, 22.60) | 0.568   |
| IVW        |                | 1.42 (0.08, 26.13) | 0.824   |
| Simple median |              | 1.89 (0.08, 43.77) | 0.705   |
| Nonlobar ICH | 881/1,481     | 2.28 (0.25, 20.88) | 0.680   |
| IVW        |                | 1.86 (0.11, 31.09) | 0.825   |
| Simple median |              | 0.99 (0.11, 24.53) | 0.883   |

OR (95%CI) per 1-SD increase in circulating vitamin E levels

Fig. 5. MR of circulating vitamin E levels and ICH, Lobar ICH, and Nonlobar IC.
Table 2. MR analysis of circulating vitamin E levels and cardiometabolic quantitative traits

| Cardiometabolic traits | SNPs | Participants | β (95% CI) | p value | β (95% CI) | p value | β (95% CI) | p value | β (95% CI) | p value |
|------------------------|------|--------------|------------|---------|------------|---------|------------|---------|------------|---------|
| **Anthropometric traits (SD)** | | | | | | | | | | |
| Height (m) | 3 | 252,350 | -0.062 | (-0.208, 0.083) | 0.401 | -0.065 | (-0.204, 0.073) | 0.355 | -0.068 | (-0.183, 0.047) | 0.247 |
| BMI (kg/m²) | 3 | 336,195 | -0.020 | (-0.180, 0.140) | 0.806 | -0.003 | (-0.138, 0.131) | 0.961 | -0.022 | (-0.140, 0.097) | 0.72 |
| WHRadjBMI | 3 | 224,044 | 0.108 | (-0.071, 0.286) | 0.239 | 0.091 | (-0.068, 0.250) | 0.261 | 0.104 | (-0.030, 0.237) | 0.128 |
| WCadjBMI (cm) | 3 | 243,084 | 0.078 | (-0.104, 0.259) | 0.403 | 0.085 | (-0.105, 0.276) | 0.38 | 0.062 | (-0.071, 0.195) | 0.36 |
| **Glycemic traits (clinical unit)** | | | | | | | | | | |
| Fasting glucose (mg/dl) | 3 | 133,010 | 0.1250 | (-0.088, 0.338) | 0.25 | 0.081 | (-0.088, 0.250) | 0.346 | 0.070 | (-0.072, 0.213) | 0.332 |
| Log fasting insulin (pmol/L) | 3 | 108,557 | -0.025 | (-0.227, 0.177) | 0.809 | -0.037 | (-0.221, 0.146) | 0.692 | 0.006 | (-0.143, 0.154) | 0.941 |
| HbA1C (%) | 3 | 46,368 | -0.082 | (-0.249, 0.084) | 0.333 | -0.080 | (-0.236, 0.077) | 0.318 | -0.105 | (-0.232, 0.023) | 0.107 |
| Log HOMA-B | 3 | 94,839 | -0.062 | (-0.239, 0.114) | 0.488 | -0.068 | (-0.233, 0.098) | 0.423 | -0.019 | (-0.150, 0.111) | 0.771 |
| Log HOMA-IR | 3 | 94,636 | 0.037 | (-0.182, 0.257) | 0.738 | 0.015 | (-0.178, 0.208) | 0.881 | 0.054 | (-0.102, 0.210) | 0.498 |
| Log Prosulin (pmol/L) | 3 | 27,079 | 0.250 | (-0.093, 0.593) | 0.153 | 0.250 | (-0.083, 0.584) | 0.141 | 0.136 | (-0.120, 0.391) | 0.298 |
| 2-h glucose (mg/dl) | 3 | 42,854 | 0.450 | (-0.564, 1.464) | 0.384 | 0.212 | (-0.642, 1.065) | 0.627 | 0.186 | (-0.525, 0.896) | 0.609 |
| **Lipids (SD) (GLGC)** | | | | | | | | | | |
| HDL (mg/dl) | 3 | 185,437 | -0.452 | (-0.886, -0.019) | 1.1 × 10⁻³ | -0.200 | (-0.473, -0.074) | 1.7 × 10⁻³ | -0.502 | (-0.840, -0.364) | 5.2 × 10⁻³ |
| LDL (mg/dl) | 3 | 171,409 | 0.632 | (0.093, 0.724) | 2.1 × 10⁻³ | 0.385 | (0.065, 0.705) | 1.8 × 10⁻³ | 0.572 | (0.423, 0.721) | 2.45 × 10⁻³ |
| TC (mg/dl) | 3 | 185,587 | 0.550 | (0.001, 0.799) | 1.8 × 10⁻³ | 0.350 | (0.015, 0.668) | 4.1 × 10⁻³ | 0.693 | (0.548, 0.838) | 4.17 × 10⁻³ |
| TG (mg/dl) | 3 | 176,099 | 1.250 | (1.203, 1.303) | 1.5 × 10⁻³ | 1.325 | (1.122, 1.772) | 1.145 | 1.145 | (1.009, 1.281) | 2.31 × 10⁻³ |
| **Kidney function (clinical unit)** | | | | | | | | | | |
| eGFRcys_DM (mL/min) | 3 | 11,529 | -0.122 | (-0.306, 0.061) | 0.19 | -0.122 | (-0.293, 0.050) | 0.164 | -0.164 | (-0.295, -0.032) | 0.015 |
| eGFRcys (mL/min) | 3 | 133,805 | -0.037 | (-0.081, 0.006) | 0.093 | -0.035 | (-0.074, 0.005) | 0.086 | -0.03 | (-0.069, -0.005) | 0.025 |
| eGFRe (mL/min) | 3 | 32,158 | -0.137 | (-0.256, -0.019) | 0.023 | -0.110 | (-0.211, -0.009) | 0.033 | -0.124 | (-0.217, -0.030) | 0.009 |

Results were standardized to a one-SD decrease in vitamin E due to genetic variants. For vitamin E, the pooled results were from the EGGS consortium, MAGIC and CKDGen did not report estimates of variants in units of SDs. Two-hour glucose refers to blood glucose levels measured 2 h after consumption of dissolved glucose. The threshold of significance was at the Bonferroni-adjusted level p<0.0028 (0.05/18 = 0.0028). eGFRcys, eGFR calculated based on cystatin C (an additional, complementary biomarker of renal function); TC, total cholesterol.

Table 3. Baseline characteristics of included cohorts

| Outcome | Study name | Ethnicity | Country | No. of participants | Follow-up (years) | Age (years) mean (SD) |
|---------|------------|-----------|---------|---------------------|-------------------|----------------------|
| Cardiometabolic diseases | Type 2 diabetes | DIAGRAM | White | USA | 149,821 | 4 | 44.0 (4.7) |
| Chronic kidney disease | CKDGen | Mixed¹ | USA | 133,814 | 5 | 50.2 (3.2) |
| Coronary artery disease | CARDioGRAMPlusC4D | White | France | 184,305 | 2 | 55.7 (2.8) |
| Ischaemic stroke | SIGN | White | USA | 17,953 | 3 | 53.2 (6.7) |
| Hemorrhagic stroke | GERFHS | White | USA | 4,571 | 3 | 58.9 (4.2) |
| Cardiometabolic traits | Glycemic traits | MAGIC | White | USA | 152,821 | 4 | 42.3 (2.2) |
| Lipids | GLGC | USA | 188,577 | 7 | 60.2 (2.8) |
| Kidney function | CKDGen | Mixed¹ | USA | 133,814 | 5 | 50.2 (3.2) |
| Anthropometric traits | GIANT | White | Denmark | 816,971 | 2 | 45.2 (3.4) |

¹Dominantly white, white-admixed (participants with one or both white parents).
style, may account for the inconsistency between our findings and epidemiological studies. In addition, our MR analysis found that increased circulating vitamin E levels were not related to risk of T2DM, CKD, and stroke and its subtypes, which corroborated results from observations.\(^{(39–43)}\) Similarly, a systematic review by Yan and Khalil\(^{(39)}\) found that no clear evidence supported the possible role of vitamin E in the treatment of T2DM. However, in obese people, a vitamin E intervention trial conducted by Skrha et al.\(^{(44)}\) demonstrated that high doses of vitamin E might further deteriorate insulin action and fibrinolysis. Unfortunately, we cannot explore the association between circulating vitamin E and type 2 diabetes in obese people because genetic data for type

### Fig. 6

Association of cardiometabolic disease with relative risk of vitamin E in observational cohort studies. Logistic regression was used in collaborative cohorts adjusted for sex, ethnicity, region or country, and years of follow-up, as well as for age, body mass index.

| Collaborative cohorts                  | Odds ratio (95%) | Combined p value |
|----------------------------------------|------------------|-----------------|
| CARDIoGRAMplusC4D (CAD)                | 1.87 (1.35, 1.96)| 0.02            |
| DIAGRAM (T2DM)                         | 0.97 (0.95, 1.13)| 0.54            |
| CKDGen (CKD)                           | 1.25 (0.46, 1.83)| 0.37            |
| SIGN (IS)                              | 1.54 (0.49, 1.86)| 0.29            |
| SIGN (LAS)                             | 0.95 (0.93, 1.25)| 0.68            |
| SIGN (SVS)                             | 1.37 (0.74, 1.97)| 0.71            |
| SIGN (CE)                              | 1.56 (0.37, 1.78)| 0.25            |
| GERFHS (ICH)                           | 1.27 (0.26, 1.61)| 0.35            |
| GERFHS (Lobar ICH)                     | 1.83 (0.25, 1.99)| 0.31            |
| GERFHS (Nonlobar ICH)                  | 1.45 (0.19, 1.79)| 0.32            |

**OR (95%CI) per 1-SD increase in circulating vitamin E levels**

### Fig. 7

Association of cardiometabolic traits with relative risk of vitamin E in observational cohort studies. Logistic regression was used in collaborative cohorts adjusted for sex, ethnicity, region or country, and years of follow-up, as well as for age, body mass index.

| Collaborative cohorts                  | Odds ratio (95%CI) | Combined p value |
|----------------------------------------|--------------------|-----------------|
| GLGC (HDL)                             | 0.58 (0.37, 0.67)  | 0.01            |
| GLGC (LDL)                             | 1.48 (1.34, 1.89)  | 0.05            |
| GLGC (TC)                              | 1.56 (1.27, 1.79)  | 0.04            |
| GLGC (TG)                              | 1.68 (1.42, 1.95)  | 0.03            |
| GIANT (Height)                         | 1.78 (1.53, 1.93)  | 0.25            |
| GIANT (BMI)                            | 0.98 (0.92, 1.23)  | 0.45            |
| GIANT (WHRadjBMI)                      | 0.97 (0.83, 1.35)  | 0.86            |
| GIANT (WCadjBMI)                       | 1.35 (0.64, 1.87)  | 0.17            |
| MAGIC (Fasting glucose)                | 1.23 (0.36, 1.93)  | 0.73            |
| MAGIC (Log fasting insulin)            | 1.24 (0.34, 1.87)  | 0.52            |
| MAGIC (HbA1C1)                         | 1.45 (0.94, 1.68)  | 0.38            |
| MAGIC (Log HOMA-B)                     | 1.27 (0.49, 1.86)  | 0.37            |
| MAGIC (Log HOMA-IR)                    | 1.72 (0.62, 1.94)  | 0.53            |
| MAGIC (Log prolin)                     | 1.38 (0.52, 1.74)  | 0.13            |
| MAGIC (2-h glucose)                    | 1.54 (0.91, 1.97)  | 0.23            |
| CKDGen (eGFRcrea_DM)                   | 1.35 (0.24, 1.81)  | 0.48            |
| CKDGen (eGFRcrea)                      | 1.27 (0.26, 1.49)  | 0.53            |
| CKDGen (eGFRcys)                       | 1.83 (0.25, 1.98)  | 0.13            |

**OR (95%CI) per 1-SD increase in circulating vitamin E levels**
2 diabetes in obese people were not available. Therefore, further causal estimates of circulating vitamin E on type 2 diabetes in obese people should be included.

Abnormalities in lipid or lipoprotein metabolism were implicated with onset and progression of cardiometabolic diseases.\(^5\) For instance, reduced levels of serum HDL and high levels of serum LDL were widely recognized as major risk factors of cardiometabolic diseases.\(^5\) In the present MR analysis, our results also showed that elevated circulating vitamin E levels caused an increase in LDL, TC, and TG, but a decrease in HDL, implying an adverse effect of circulating vitamin E on cardiometabolic diseases. Previous observations had unveiled the association between vitamin E intake and cardiometabolic traits,\(^14,35,48–50\) which were consistent with our results. For instance, Ganini and Mason\(^48\) found that vitamin E intake did not protect LDL from the protein radical formation, thus failing to be a cardiometabolic protective agent for humans. Additionally, it had been identified that elevated vitamin E levels raised normal plasma triglycerides levels in conditions of hypercholesterolemia\(^50\) and reduced HDL levels in hypertriglyceridemic patients.\(^51\) Of note, several perspective studies have provided evidence to support that LDL is rendered atherogenic by oxidative modifications that allow it to accumulate, which is an important step in the development and progression of atherosclerosis.\(^52–54\) Based on our MR analysis, a one-SD increase in circulating vitamin E levels was found to be causally associated with a 0.572-SD increase in LDL, highlighting that elevated circulating vitamin E levels may increase risk of CAD.

Compared with previous studies investigating the association between dietary or supplemental intake of vitamin E and cardiometabolic diseases and traits, circulating vitamin E used in our MR analysis was more reliable and representative for long-term exposure.\(^55\) In the present MR analysis, the selected genetic variants were validated as a robust IV for circulating vitamin E and identified no pleiotropic effects. Through MR analysis, our study found that increased circulating vitamin E levels caused higher risk of CAD, but not 2TDM, CKD, stroke and its subtypes, providing a genetic evidence to investigate the association between circulating vitamin E and cardiometabolic diseases. Furthermore, our study identified a significant role of circulating vitamin E in lipid metabolism, especially increasing serum LDL levels. In summary, our findings showed an adverse effect of circulating vitamin E on cardiometabolic diseases, implying the public health impact of vitamin E modification. In addition, the assessment of health risks of vitamin E provides a good basis for public health action. Our study also provides a new therapeutic guidance for the treatment of cardiometabolic diseases.

In the present study, the MR analysis satisfied three assumptions. For assumption 1, a close association between the genetic variants used as IVs and circulating vitamin E were required. We selected three significant SNPs from GWAS and these three SNPs was strongly associated with circulating vitamin E, validating assumption 1. For assumption 2, the genetic variants used in MR analysis were not associated with any confounder. We assessed LD between all selected SNPs. We found that no SNPs was in LD with each other at an \(r^2>0.05\), but inverse results cannot be excluded due to unmeasured confounders. For assumption 3, circulating vitamin E must be intermediate effect variable and the genetic variants cannot affect cardiometabolic diseases straightly. The MR-Egger regression showed that the estimated intercept term was centered at the origin with a CI including the null, indicating our results with no influence by pleiotropy.\(^56\)

Strengths of the current study had large sample size, allowing us to more precisely examine causal association. In addition, we made a comprehensive analysis of associations between circulating vitamin E and cardiometabolic diseases, providing a reference for investigating cardiovascular diseases. Furthermore, we used different methods to assess the consistency of associations, supporting the robustness of our results. However, several limitations merited consideration. First, pleiotropy may not be excluded since the selected SNPs were likely to have a shared genetic basis, thus failing to reflect a causal association between circulating vitamin E and cardiometabolic diseases. Second, the possible role of biologically active vitamin E may be limited in our MR analysis because we used circulating vitamin E levels to reflect standards of biologically active vitamin E. Third, since we cannot identify whether some SNPs were associated with certain sub-phenotypes of circulating vitamin E, the critical roles of specific SNPs in cardiometabolic diseases may be neglected. Notably, the mechanisms of the adverse role of circulating vitamin E in risk of cardiometabolic diseases were not clarified in our study. Therefore, further investigations were required to identify our findings that genetically elevated circulating vitamin E levels were associated with increased risk of cardiometabolic diseases.

Through MR analysis, we found that a genetic predisposition to higher circulating vitamin E levels was related to increased risk of CAD, as well as increase in LDL, TC, and TG, but a decrease in HDL. Our finding provided support for an association between circulating vitamin E and risk of CAD, implicating further modification in vitamin E intake. Since we cannot completely rule out a risk effect of vitamin E on CAD, further replication was needed.

Acknowledgments

We would like to thank Dr. Qi Liao very much for her kind assistance with statistical methods and database design.

Funding

This study was partly sponsored by the Fang Runhua Fund of Hong Kong, the K.C. Wong Magna Fund of Ningbo University, the National Science Foundation of China (grant no. 81673163), the Project of the Application of Public Welfare Technology (Experimental Animals) of Zhejiang (grant no. 2016C37120).

Availability of Data and Materials

The data that support the findings of this study are publicly available. Details on data sources have been described in methods.

Supplementary Information

Supplementary information is available at the on-line version.*

Author Contributions

CF, TH, XK, XZ, ZZ and JX conceived or designed the study. CF, TH, XK, XZ, ZZ and JX acquired, analyzed, or interpreted the data. CF performed the statistical analysis. ZZ and XZ provided supervision. All authors have approved the manuscript for publication.

Ethics Approval and Consent to Participate

Summary-level data were extracted from consortia, including DIAGRAM, CARDIoGRAMplusC4D, 45kGen, SIGN and GERFHS. All human studies were approved by their institutional ethics review committees, and all participants provided written consent.

*See online. https://doi.org/10.3164/jcbn.19-12
Abbreviations

CAD: coronary artery disease  
CE: cardioembolic stroke  
CKD: chronic kidney disease  
GWAS: genome-wide association studies  
HDL: high density lipoprotein cholesterol  
ICH: intracerebral hemorrhage  
IS: ischemic stroke  
IV: instrumental variables  
IVW: inverse variance weighted method  
LAS: large artery stroke  
LD: linkage disequilibrium  
LDL: low density lipoprotein cholesterol  
Lobar ICH: lobar intracerebral hemorrhage  
MR: Mendelian randomization  
Nonlobar ICH: nonlobar intracerebral hemorrhage  
OR: odds ratio  
RCTs: randomized controlled trials  
SNPs: single nucleotide polymorphisms  
TC: total cholesterol  
TG: triglyceride  
T2DM: type 2 diabetes

Conflict of Interest

No potential conflicts of interest were disclosed.

References

1. Tunstall-Pedoe H, Kuulasmaa K, Mähiönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999; 353: 1547–1557.
2. Brown M. Do vitamin E and fish oil protect against ischaemic heart disease? Lancet 1999; 354: 441–442.
3. Grooms KN, Ommerborn MJ, Pham DQ, Djoussé L, Clark CR. Dietary fiber intake and cardiometabolic risk among US adults, NHANES 1999–2010. Am J Med 2013; 126: 1059–1067.
4. Masson R. Vitamin E and cardiovascular disease. Complement Ther Med 1993; 1: 19–23.
5. Suksumboon N, Poolap N, Sinprasert S. Effects of vitamin E supplementation on glycaemic control in type 2 diabetes: systematic review of randomized controlled trials. J Clin Pharm Ther 2011; 36: 53–63.
6. Loffredo L, Perri L, Di Castelnuovo A, Iacoviello L, De Gaetano G, Violi F. Effects of vitamin E in idiopathic nephrotic syndrome: a meta-analysis. Nutr Metab Cardiovasc Dis 2015; 25: 354–363.
7. Mao S, Zhang A, Huang S. Serum levels of malondialdehyde, vitamin C and E in idiopathic nephrotic syndrome: a meta-analysis. Ren Fail 2014; 36: 994–999.
8. Schürks M, Glynn RJ, Rist PM, Costacou T, King I, Zaccaro DJ, Bell RA; Insulin Resistance Atherosclerosis Study (IRAS). Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study. BMJ 2017; 356: j1000.
9. Yarmolinsky J, Bonilla C, Haycock PC, et al. Circulating selenium and prostate cancer risk: a Mendelian randomization analysis. J Natl Cancer Inst 2018; 110: 1035–1038.
10. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015; 44: 512–525.
11. Major JM, Yu K, Wheeler W, et al. Genome-wide association study identifies common variants associated with circulating vitamin E levels. Hum Mol Genet 2011; 20: 3876–3883.
12. Ferrucci L, Perry JR, Mattei A, et al. Common variation in the β-carotene 15,15’-monooxygenase 1 gene affects circulating levels of carotenoids: a genome-wide association study. Am J Hum Genet 2009; 84: 123–133.
13. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; Mexican American Type 2 Diabetes (MAT2D) Consortium; Type 2 Diabetes Genetic Exploration by Next-generation sequencing in mutually Ethnic Samples (T2D-GENES) Consortium; Mahajan A, Go MJ, Zhang W, et al. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 2014; 46: 234–244.
14. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015; 47: 1121–1130.
15. Trayler M, Malik R, Nalls MA, et al.; International Stroke Genetics Consortium. Genetic variation at 16q24.2 is associated with reduced myocardial infarction: a meta-analysis. Nat Med 2014; 20: 354–363.
16. Geng T, Smith CE, Li C, Huang T. Childhood BMI and adult type 2 diabetes, coronary artery diseases, chronic kidney disease, and cardiometabolic traits: a mendelian randomization analysis. Diabetes Care 2018; 41: 1089–1096.
17. Ding R, Huang T, Han J. Diet lifestyle and risk of diabetes and glycemic traits: a Mendelian randomization study. Lipids Health Dis 2018; 17: 18.
18. Ding M, Huang T, Bergholdt HK, Nordestgaard BG, Ellervik C, Qi L; CHANGE Consortium. Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study. BMJ 2017; 356: j1000.
19. Yarmolinsky J, Bonilla C, Haycock PC, et al. Circulating selenium and prostate cancer risk: a Mendelian randomization analysis. J Natl Cancer Inst 2018; 110: 1035–1038.
20. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015; 44: 512–525.
21. Major JM, Yu K, Wheeler W, et al. Genome-wide association study identifies common variants associated with circulating vitamin E levels. Hum Mol Genet 2011; 20: 3876–3883.
22. Ferrucci L, Perry JR, Mattei A, et al. Common variation in the β-carotene 15,15’-monooxygenase 1 gene affects circulating levels of carotenoids: a genome-wide association study. Am J Hum Genet 2009; 84: 123–133.
23. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; Mexican American Type 2 Diabetes (MAT2D) Consortium; Type 2 Diabetes Genetic Exploration by Next-generation sequencing in mutually Ethnic Samples (T2D-GENES) Consortium; Mahajan A, Go MJ, Zhang W, et al. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 2014; 46: 234–244.
24. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015; 47: 1121–1130.
25. Trayler M, Malik R, Nalls MA, et al.; International Stroke Genetics Consortium. Genetic variation at 16q24.2 is associated with small 1 vessel stroke. Ann Neurol 2016; 81: 383–394.
26. Woo D, Falcone GJ, Devan WJ, et al.; International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. Am J Hum Genet 2014; 94: 511–521.
27. Scott RA, Lagou V, Welch RP, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet 2012; 44: 991–1005.
28. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 2010; 42: 105–116.
29. Pattaro C, Teumer A, Gorski M, et al.; ICBP Consortium; AGEN Consortium; CARDIOGRAM; CHARGE-Heart Failure Group; ECHOGen Consortium. Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. Nat Commun 2016; 7: 10023.
30. Locke AE, Kahali B, Berndt SI, et al.; LifeLines Cohort Study; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MGI consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium; LifeLines Cohort Study; MAGIC Investigators; MuTHER Consortium; PAGE Consortium; ReproGen Consortium. New genetic loci of hypertension: Mendelian randomization study. BMJ 2017; 356: j1000.
31. Yarmolinsky J, Bonilla C, Haycock PC, et al. Circulating selenium and prostate cancer risk: a Mendelian randomization analysis. J Natl Cancer Inst 2018; 110: 1035–1038.
32. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015; 44: 512–525.
33. Major JM, Yu K, Wheeler W, et al. Genome-wide association study identifies common variants associated with circulating vitamin E levels. Hum Mol Genet 2011; 20: 3876–3883.
34. Ferrucci L, Perry JR, Mattei A, et al. Common variation in the β-carotene 15,15’-monooxygenase 1 gene affects circulating levels of carotenoids: a genome-wide association study. Am J Hum Genet 2009; 84: 123–133.
link adipose and insulin biology to body fat distribution. Nature 2015; 518: 187–196.

32 Wood AR, Esko T, Yang J, et al.; Electronic Medical Records and Genomics (eMEMERGE) Consortium; MiGen Consortium; PAGEGE Consortium; LifeLines Cohort Study. Defining the role of common variation in the genomic and biological architecture of adult human height. Nat Genet 2014; 46: 1173–1186.

33 Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med 2008; 27: 1133–1163.

34 Djoussé L, Kocher J, Gaziano JM. Dietary factors and risk of heart failure: a systematic review. Current Cardiovascular Risk Reports 2007; 1: 330–334.

35 The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. Am Epidemiol 1994; 4: 1–10.

36 Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005; 142: 37–46.

37 Mörike EM. Vitamin E treatment of patients with coronary disease (Cambridge Heart Antioxidant Study–CHAOS). Dtsch Med Wochenschr 1996; 121: A9. (in Deutsch)

38 Knekt P, Ritz J, Pereira MA, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. Am J Clin Nutr 2004; 80: 1508–1520.

39 Yan MK, Khalil H. Vitamin supplements in type 2 diabetes mellitus management: a review. Diabetes Metab Syndr 2017; 11 Suppl 2: SS89–SS95.

40 Patel N, Amin P, Shenoy A. Is vitamin E supplementation effective in reducing mortality related to cardiovascular events in people with type 2 diabetes mellitus? A systematic review. JIC Metab Endocr 2016; 12: 42–45.

41 Nanayakkara PW, Kieffer-de Jong JG, ter Wee PM, et al. Randomized placebo-controlled trial assessing a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on plasma asymmetric dimethylarginine concentration in mild to moderate CKD. Am J Kidney Dis 2009; 53: 41–50.

42 Handelman GJ, Levin NW. Guidelines for vitamin supplements in chronic kidney disease patients: what is the evidence? J Ren Nutr 2011; 21: 117–119.

43 De Keyser J, De Klippel N, Merkx H, Vervaeke M, Herroelen L. Serum concentrations of vitamins A and E and early outcome after ischaemic stroke. Lancet 1992; 339: 1562–1565.

44 Skrha J, Sendelka G, Kvasnicka J, Hilgertová J. Insulin action and fibrinolysis influenced by vitamin E in obese Type 2 diabetes mellitus. Diabetes Res Clin Pract 1999; 44: 27–33.

45 Quaschning T, Krane V, Metzger T, Wanner C. Abnormalities in uremic lipoprotein metabolism and its impact on cardiovascular disease. Am J Kidney Dis 2001; 38 (4 Suppl 1): S14–S19.

46 Rosenson RS, Davidson MH, Hirsh BJ, Kathiresan S, Gaudet D. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. J Am Coll Cardiol 2014; 64: 2525–2540.

47 Aranda JF, Madrigal-Matute J, Rotllan N, Fernández-Hernando C. MicroRNA modulation of lipid metabolism and oxidative stress in cardiometabolic diseases. Free Radic Biol Med 2013; 64: 31–39.

48 Ganini D, Mason RP. Absence of an effect of vitamin E on protein and lipid radical formation during lipoperoxidation of LDL by lipoxygenase. Free Radic Biol Med 2014; 76: 61–68.

49 Porter TD. Supernatant protein factor and tocopherol-associated protein: an unexpected link between cholesterol synthesis and vitamin E (review). J Nutr Biochem 2003; 14: 3–6.

50 Rubba P, Mancini M, Fidanza F, Leccia G, Riemersma RA, Gey KF. Plasma vitamin E, apolipoprotein B and HDL-cholesterol in middle-aged men from southern Italy. Atherosclerosis 1989; 77: 23–29.

51 Lambert D, Moveret J. Vitamin E and lipoproteins in hyperlipoproteinemia. Atherosclerosis 1984; 53: 327–330.

52 Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witzum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. N Engl J Med 1989; 320: 915–924.

53 Ylä-Herttuala S, Palinski W, Rosenfeld ME, et al. Evidence for the presence of oxidatively modified low density lipoprotein in atherosclerotic lesions of rabbit and man. J Clin Invest 1989; 84: 1086–1095.

54 Steinberg D. Antioxidants in the prevention of human atherosclerosis. Summary of the proceedings of a National Heart, Lung, and Blood Institute Workshop: September 5–6, 1991, Bethesda, Maryland. Circulation 1992; 85: 2337–2344.

55 Li G, Li Y, Chen X, Sun H, Hou X, Shi J. Circulating tocopherols and risk of coronary artery disease: a systematic review and meta-analysis. Eur J Prev Cardiol 2016; 23: 748–757.