



## Background

Vitamin C has several important functions and many health benefits; however, its protective role in multiple disease outcomes remains ambiguous. Mendelian randomization (MR) is an increasingly explored method to strengthen causal inference.

## Objectives

This systematic review aimed to summarize the causal relationship between vitamin C and disease outcomes based on current evidence in MR studies.

## Methods

We searched the Cochrane, Embase, and PubMed databases from inception to 23 September 2022. All published articles using the MR approach to explore potential causal relationships between circulating vitamin C (and its metabolites) and health outcomes were included. Two reviewers independently conducted title and abstract screening, full-text review, and data extraction. Associations with a p-value below the Bonferroni-corrected threshold were defined as significant, while associations with a p-value between the corrected threshold and 0.05 were considered suggestive evidence.

## Results

- We included 29 MR studies investigating the causal effect of vitamin C on 53 disease outcomes, including various cancers, cardiovascular diseases, and neurodegenerative diseases.
- Of these 53 outcomes, 38 showed null associations.
- Genetically predicted higher plasma vitamin C levels (and its metabolites) have shown protective effects on colon cancer, colorectal cancer, liver cancer, ovarian cancer, small intestine cancer, stomach cancer, any stroke, cardioembolic stroke, Alzheimer's disease, and intraocular pressure; but conferred an increased risk of breast cancer, endometrial cancer, pancreatic cancer, atrial fibrillation, and varicose veins.

Table 1: Mendelian randomization studies included in the review, demonstrating significant associations between genetically predicted Vitamin C (and its metabolites) and multiple health outcomes.

|                                   | Health outcome                   | Reference                        | Consortium                         | Cases/controls or sample size | SNP source (No. of SNPs) | OR/beta (95% CI/SE)  | p-value | Correct p-value              | Key Findings                  |
|-----------------------------------|----------------------------------|----------------------------------|------------------------------------|-------------------------------|--------------------------|----------------------|---------|------------------------------|-------------------------------|
| <b>Cancers</b>                    |                                  |                                  |                                    |                               |                          |                      |         |                              |                               |
| Absolute circulating ascorbate    | Breast cancer                    | Fu 2021                          | UK Biobank                         | 10,892/237,406                | Zheng 2021 (10)          | 1.34 (1.14, 1.57)    | < 0.001 | 0.01                         | Significant risk factor       |
|                                   | Colon cancer                     | Chen H. 2022                     | UK Biobank                         | n = 462,933                   | Zheng 2021 (6)           | 0.997 (0.994, 0.999) | 0.003   | 0.0045                       | Significant protective effect |
|                                   |                                  | Zhang 2022                       | UK Biobank                         | 3,759/416,772                 | Zheng 2021 (10)          | 0.774 (0.608, 0.985) | 0.037   | 0.01                         | Suggestive protective effect  |
|                                   |                                  | Meta-analysis UK Biobank FinnGen |                                    | 3,759/416,772 1,803/174,006   | Zheng 2021 (10)          | 0.764 (0.623, 0.936) | 0.010   | 0.01                         | Suggestive protective effect  |
|                                   | Colorectal cancer                | Larson 2022                      | UK Biobank                         | 7,543/359,999                 | Zheng 2021 (10)          | 0.82 (0.69, 0.97)    | 0.023   | 0.008                        | Suggestive protective effect  |
|                                   |                                  | Meta-analysis UK Biobank FinnGen |                                    | 7,543/359,999 4,957/304,197   | Zheng 2021 (10)          | 0.84 (0.73, 0.96)    | 0.013   | 0.008                        | Suggestive protective effect  |
|                                   | Endometrial cancer               | Peng 2022                        | ECAC                               | 12,906 /108,979               | Zheng 2021 (11)          | 1.374 (1.128, 1.674) | 0.0016  | 0.05                         | Significant risk factor       |
|                                   | Liver cancer                     | Larson 2022                      | FinnGen                            | 518/308,636                   | Zheng 2021 (10)          | 0.38 (0.15, 0.96)    | 0.041   | 0.008                        | Suggestive protective effect  |
|                                   |                                  | Zhang 2022                       | FinnGen                            | 304/174,006                   | Zheng 2021 (10)          | 0.344 (0.139, 0.856) | 0.022   | 0.01                         | Suggestive protective effect  |
|                                   | Ovarian cancer                   | Chen H. 2022                     | UK Biobank                         | n = 463,010                   | Zheng 2021 (5)           | 0.998 (0.996, 1.000) | 0.040   | 0.0045                       | Suggestive protective effect  |
| Small intestine cancer            | Larson 2022                      | FinnGen                          | 411/308,743                        | Zheng 2021 (10)               | 0.41 (0.17, 1.00)        | 0.049                | 0.008   | Suggestive protective effect |                               |
|                                   | Meta-analysis UK Biobank FinnGen |                                  | 515/367,027 411/308,743            | Zheng 2021 (10)               | 0.55 (0.32, 0.94)        | 0.029                | 0.008   | Suggestive protective effect |                               |
| Stomach cancer                    | Zhang 2022                       | UK Biobank                       | 764/419,767                        | Zheng 2021 (10)               | 0.572 (0.338, 0.969)     | 0.038                | 0.01    | Suggestive protective effect |                               |
| Circulating ascorbate metabolites | Pancreatic cancer                | Zhang 2022                       | UK Biobank                         | 933/419,992                   | Shin 2014 (14)           | 1.398 (1.053, 1.858) | 0.021   | 0.01                         | Suggestive risk factor        |
| <b>Cardiovascular disease</b>     |                                  |                                  |                                    |                               |                          |                      |         |                              |                               |
| Absolute circulating ascorbate    | Any stroke                       | Yuan 2022                        | UK Biobank                         | 12,036/355,525                | Zheng 2021 (10)          | 0.84 (0.73, 0.97)    | 0.02    | 0.003                        | Suggestive protective effect  |
|                                   | Atrial fibrillation              | Yuan 2022                        | Meta-analysis Nielsen 2018 FinnGen | 60,620/970,216 17,325/97,214  | Zheng 2021 (10)          | 1.09 (1.00, 1.18)    | 0.049   | 0.003                        | Suggestive risk factor        |
|                                   | Cardioembolic stroke             | Chen 2021                        | MEGASTROKE                         | 7,193/204,570                 | Zheng 2021 (11)          | 0.773 (0.622, 0.959) | 0.019   | 0.005                        | Suggestive protective effect  |
| Yuan 2022                         |                                  | MEGASTROKE                       | 7,193/406,111                      | Zheng 2021 (10)               | 0.79 (0.64, 0.99)        | 0.04                 | 0.003   | Suggestive protective effect |                               |
| <b>Neurodegenerative diseases</b> |                                  |                                  |                                    |                               |                          |                      |         |                              |                               |
| Absolute circulating ascorbate    | Alzheimer's disease              | Chen 2021                        | Jansen 2020                        | 71,880/383,378                | Zheng 2021 (10)          | 0.968 (0.946, 0.991) | 0.007   | 0.005                        | Suggestive protective effect  |
|                                   |                                  | Liu H. 2021                      | UK Biobank AD proxy                | 42,034/272,244                | Zheng 2021 (11)          | 0.93 (0.88, 0.98)    | 0.007   | 0.05                         | Significant protective effect |
|                                   |                                  |                                  | UK Biobank Maternal AD             | 27,696/260,980                | Zheng 2021 (11)          | 0.89 (0.84, 0.94)    | < 0.001 | 0.05                         | Significant protective effect |
| <b>Other health outcomes</b>      |                                  |                                  |                                    |                               |                          |                      |         |                              |                               |
| Absolute circulating ascorbate    | Varicose Veins                   | Yuan 2021                        | FinnGen                            | 13,928/153,951                | Zheng 2021 (10)          | 1.24 (1.05, 1.48)    | 0.014   | 0.002                        | Suggestive risk factor        |
| Circulating ascorbate metabolites | Intraocular pressure             | Hysi 2019                        | UK Biobank                         | n = 1,571                     | Shin 2014 (13)           | -0.696 (0.304)       | 0.022   | 0.05                         | Significant protective effect |
|                                   |                                  |                                  | EPIC Norfolk                       | n = 8,623                     | Shin 2014 (13)           | -3.219 (1.371)       | 0.019   | 0.05                         | Significant protective effect |

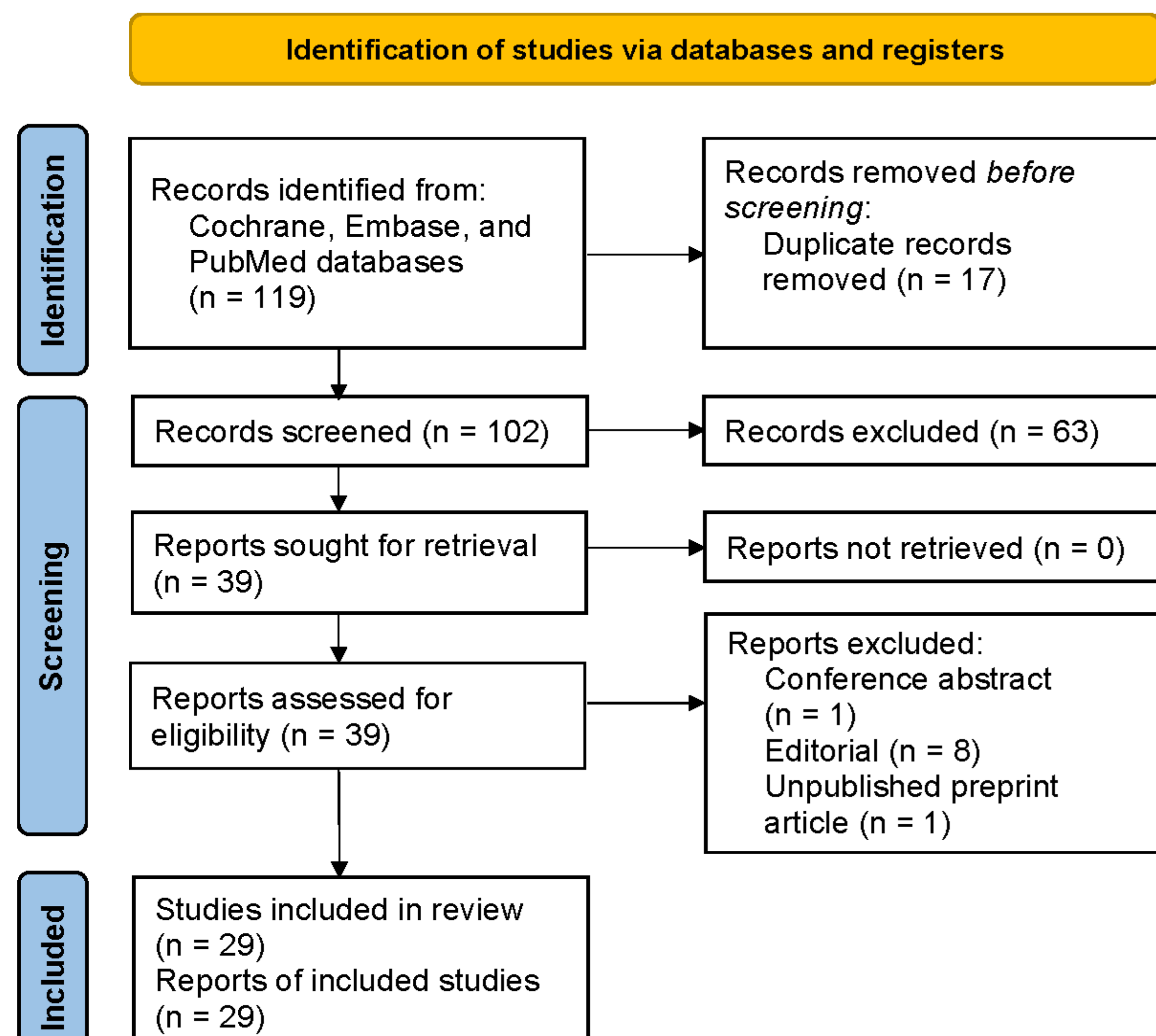


Figure 1. Flowchart of the study selection process

## Conclusion

This systematic MR review provides a comprehensive summary of the current evidence regarding the impact of vitamin C on various diseases, emphasizing its potential implications for disease prevention.

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