NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

Efficacy of Flavan-3-ols on Cardiometabolic Health: An Umbrella Review of Systematic Reviews and Meta-Analyses of Randomized Controlled Trials and Observational Studies.

Elizabeth Leon-Cuevas, Ana Rodriguez-Mateos, Charlotte Mills, Brian Óg Murphy, Catarina Rendeiro, Chris Gill, Christian Heiss, Cristiana Mignogna, David Vauzour, Dragan Milenkovic, Elena Philippou, Federico Bernuzzi, Pedro Mena, Tatjana Ruskovska, Tonny Kiyimba

Citation
Elizabeth Leon-Cuevas, Ana Rodriguez-Mateos, Charlotte Mills, Brian Óg Murphy, Catarina Rendeiro, Chris Gill, Christian Heiss, Cristiana Mignogna, David Vauzour, Dragan Milenkovic, Elena Philippou, Federico Bernuzzi, Pedro Mena, Tatjana Ruskovska, Tonny Kiyimba. Efficacy of Flavan-3-ols on Cardiometabolic Health: An Umbrella Review of Systematic Reviews and Meta-Analyses of Randomized Controlled Trials and Observational Studies.. PROSPERO 2025 CRD420251074385. Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420251074385.

REVIEW TITLE AND BASIC DETAILS

Review title
Efficacy of Flavan-3-ols on Cardiometabolic Health: An Umbrella Review of Systematic Reviews and Meta-Analyses of Randomized Controlled Trials and Observational Studies.

Condition or domain being studied
Cardiovascular disease; Metabolic Disease; Biomarker analysis; Cardiovascular Event; Cardiovascular Mortality; Metabolic Syndrome ; Type 2 Diabetes Mellitus; Obesity; Atherosclerosis

Rationale for the review
Non-communicable diseases (NCDs) remain the leading global health burden; according to the World Health Organization (WHO), seven out of the ten leading causes of death globally in 2021. Today, ischemic heart disease ranks first, and type 2 diabetes mellitus (the most common form of diabetes) is estimated to affect around 4.2 billion people worldwide. The pharmacological treatments for these chronic diseases are on the rise, often presenting clinical side effects and financial burdens on patients, highlighting the need for effective and accessible

preventive strategies. A mounting body of evidence suggests flavan-3-ols, a bioactive subclass of flavonoids within the polyphenol family, have potential in reducing the risk of type 2 diabetes, cardiovascular mortality, coronary heart disease, and stroke. Therefore, this umbrella review will systematically assess the credibility and certainty of associations between flavan-3-ols consumption and cardiometabolic health outcomes in adults by synthesizing the evidence from systematic reviews and meta-analyses of randomized controlled trials and observational studies.

Review objectives

What is the impact of flavan-3-ols consumption on cardiometabolic health in humans?

This umbrella review will systematically assess the credibility and certainty of associations between flavan-3-ols consumption and cardiometabolic health outcomes in adults, by synthesizing the evidence from systematic reviews and meta-analyses of randomised controlled trials and observational studies.

Keywords

Cardiometabolic health; Flavan-3ols; Umbrella review; Cardiovascular disease; Metabolic syndrome

Country

United Kingdom; United States of America; Cyprus; Italy; North Macedonia; Uganda

ELIGIBILITY CRITERIA

Population

Included

Adults aged 18 years or older.

Excluded

Children and adolescents (under 18 years old).

Intervention(s) or exposure(s)

Included

Flavan-3-ol-rich dietary sources, or flavan-3-ol-rich extracts, or pure flavan-3-ol compounds, flavan-3-ol supplements.

No restrictions on doses although doses and sources must be reported.

Comparator(s) or control(s)

Included

Placebo.

Lower flavan-3-ol intake.

No intake.

Study design

Both randomized and nonrandomized study types will be included.

Excluded

Supplemental primary studies (individual RCTs or observational studies) will not be included.

The following will also not be included: review papers that are not systematic; reviews of mechanistic studies; co-interventions; animal studies; in-vitro studies; in-silico studies, ecological studies, conference abstracts, protocol manuscripts.

Context
Only published peer-reviewed systematic reviews and meta-analyses, as defined in the Cochrane Handbook for Systematic Reviews of Interventions, will be included in this umbrella review.

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
14 July 2025

Review timeline
Start date: 16 June 2025. End date: 20 June 2026.

Date of registration in PROSPERO
25 July 2025

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has been written and uploaded to PROSPERO. The protocol will be made available after the review is completed.

SEARCHING AND SCREENING

Search for unpublished studies
Only published studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *CLIB - The Cochrane Library*, *Embase - Embase via Ovid* and *PubMed*.

Other important or specialist databases that will be searched
Web of Science

Search language restrictions
There are no language restrictions.

Search date restrictions
There are no search date restrictions.

Other methods of identifying studies
No other methods will be used.

Link to search strategy

A full search strategy has been uploaded to PROSPERO. The PDF may be accessed through this link https://www.crd.york.ac.uk/PROSPEROFILES/9da9e61fdc41c9c0cc87ed67ff31ce10.pdf.

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
Two researchers will independently perform abstract and full-text screening for inclusion and exclusion criteria, while blinded to each other's' decisions. Discrepancies between individual assessments will be resolved by consulting a third member of the review team.

A decision algorithm developed by Pollock et al. will be used for managing the overlapping studies across the systematic reviews.

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *AMSTAR-2*

GRADE (Grading of Recommendations Assessment, Development, and Evaluation)

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
Risk of bias due to missing results will be assessed

Certainty assessment
GRADE (Grading of Recommendations Assessment, Development and Evaluation) four-level scale to rate the certainty of evidence: high, moderate, low, and very low.

- Adequacy of sample size and representativeness.
- Appropriateness of control/comparator.
- Validity and reliability of surrogate measurement methods.
- Appropriate control for confounders.
- Completeness of outcome data and addressing of missing data.
- Consistency and reproducibility of findings across studies.

OUTCOMES TO BE ANALYSED

Main outcomes

Cardiometabolic clinical outcomes:

Cardiometabolic mortality

Acute cardiovascular or cerebrovascular events (unstable angina, myocardial infarction, stroke)

Atherosclerosis (intima media thickness, plaque)

Arteriosclerosis (media sclerosis)

Blood lipids (i.e., total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, etc.)

Blood pressure (systolic, diastolic, mean)

Vascular function (any measure)

Arterial stiffness (any measure)

Cardiac function (echo EF, diastolic function, 3D echo global longitudinal strain -GLS)

Cardiac rhythm (atrial or/and ventricular fibrillation)

Body mass index, waist circumference, waist to hip ratio, waist to height ratio

Insulin resistance, metabolic syndrome, pre-diabetes

Type 2 diabetes, and complications

Overweight, obesity

Blood glucose, HbA1c, blood insulin, insulin resistance (HOMA)

MAFLD, NAFLD

Hepatic function (any measure, FibroScan)

Systemic inflammation (i.e., CRP, IL6, TNF, etc.)

Cardiometabolic index

Physical activity (exercise capacity, walking distance)

Additional outcomes

Oxidative stress/damage markers

Antioxidant defense

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Data will be compiled in a tabular format and described by outcome. Meta-analyses will not be conducted.

Data will be organized and analyzed based to the population health status (healthy, at risk, or diseased).

Sex, age, or ethnicity will also be considered, if applicable.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

Publication of review results
Results of the review will be published.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members
Dr Elizabeth Leon-Cuevas. ORCID: 0000-0002-0709-2986. Kings College London. England.

No conflict of interest declared.

Dr Ana Rodriguez-Mateos (review guarantor and contact) King's College London, UK. England.

No conflict of interest declared.

Dr Charlotte Mills. University of Reading, UK. England.

No conflict of interest declared.

Dr Brian Óg Murphy. Ulster University, UK. England.

No conflict of interest declared.

Dr Catarina Rendeiro. University of Birmingham, UK. England.

Conflict of interest
Catarina Rendeiro has a PhD student (Case-BBSRC) that is supported by Barry Callebaut.

Dr Chris Gill. Ulster University. Northern Ireland.

No conflict of interest declared.

Dr Christian Heiss. University of Surrey. England.

Conflict of interest
Christian Heiss had unrestricted research funding from Lipton within the last 36 months.

Dr Cristiana Mignogna. University of Parma. Italy.

No conflict of interest declared.

Dr David Vauzour. University of East Anglia. England.

No conflict of interest declared.

Dr Dragan Milenkovic. North Carolina State University. United States of America.

No conflict of interest declared.

Dr Elena Philippou. University of Nicosia. Cyprus.

No conflict of interest declared.

Dr Federico Bernuzzi. CRUK Scotland Institute. Scotland.

No conflict of interest declared.

Dr Pedro Mena. University of Parma. Italy.

No conflict of interest declared.

Dr Tatjana Ruskovska. Goce Delcev University, Stip, North Macedonia. Macedonia (FYROM).

No conflict of interest declared.

Dr Tonny Kiyimba. Mountains of the Moon University, Fort Portal. Uganda.

No conflict of interest declared.

Named contact

Dr Ana Rodriguez-Mateos (ana.rodriguez-mateos@kcl.ac.uk). King's College London, UK. England.

Review affiliation

UK Nutrition Society Special Interest Group "Phytochemicals and Health".

Funding source

Review has no specific/external funding but is supported by guarantor/review team (non-commercial) institutions.

Peer review

There has been no peer review of this planned review.

ADDITIONAL INFORMATION

Review conflict of interest

Declared individual interests are recorded under team member details. Two review team members have declared a potential conflict of interest.This review also notes the following interests:

This work was undertaken under the "Phytochemicals and Health" Special Interest Group of the UK Nutrition Society.

Ana Rodriguez-Mateos, Charlotte Mills, Brian Óg Murphy, Chris Gill, Cristiana Mignogna, David Vauzour, Dragan Milenkovic, Elena Philippou, Elizabeth Leon-Cuevas, Federico Bernuzzi, Pedro Mena, Tatjana Ruskovska, Tonny Kiyimba declare no conflicts of interest.

Catarina Rendeiro has a PhD student (Case-BBSRC) that is supported by Barry Callebaut.

Christian Heiss had unrestricted research funding from Lipton within the last 36 months.

Medical Subject Headings

Cardiovascular Diseases; flavan-3-ol; Metabolic Diseases

SIMILAR REVIEWS

Check for similar records already in PROSPERO

PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 15 June 2025). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- The association between flavan-3-ol intake and cardiovascular risk factors and clinical outcomes in adults: a systematic review of randomized controlled trials and prospective studies [published 6 June 2018] [CRD42018035782]. The review was judged **not to be similar**
- The effects of flavon-3-ols treatments for cognitive function: a meta-analysis of randomized trials [published 5 July 2020] [CRD42020162390]. The review was judged **not to be similar**
- The effects of flavanols and their major dietary sources on blood pressure and endothelial function. A systematic review and meta-regression analysis to inform clinical guidance on reduction of cardiovascular disease risk [published 1 September 2023] [CRD42023454691]. The review was judged **not to be similar**

PROSPERO version history

- Version 1.0, published 25 Jul 2025

Disclaimer