BMJ Open

Effect of plant-based foods and (poly) phenol supplementation on gut-microbiota metabolism in participants with overweight or obesity and cardiometabolic risk: a study protocol for a single-blind, parallel and randomised controlled trial

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To cite: Lanuza F, Romero-López C, Nova-Luna R, *et al*. Effect of plant-based foods and (poly)phenol supplementation on gut-microbiota metabolism in participants with overweight or obesity and cardiometabolic risk: a study protocol for a single-blind, parallel and randomised controlled trial. *BMJ Open* 2025;**15**:e105461. doi:10.1136/bmjopen-2025-105461

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-105461).

Received 21 May 2025
Accepted 11 August 2025

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ABSTRACT

Introduction Dietary (poly)phenols have beneficial properties that may play a relevant role in the management of overweight/obesity and cardiometabolic risk factors, modulating physiological and molecular pathways involved in energy metabolism, adiposity and gut microbiota-derived metabolites.

Methods and analysis The Prevention/Precision Diet in Araucanía (PREDIET-ARAC) trial is a randomised, single-blind, parallel arm, placebo-controlled, clinical trial designed to assess the potential health benefits of (poly)phenol intake through either diet or supplementation. The study will evaluate the effectiveness of a healthy plant-based diet (PBD) rich in (poly)phenols compared with (poly)phenol supplementation during a caloric restriction intervention.

A total of 99 adults (aged 25–45 years) with overweight or obesity (body mass index: 25–35 kg/m²) and cardiovascular risk factors will be recruited from primary health centres in Temuco, Araucanía Region, Chile. Participants will be randomised (stratified by age: <35 vs ≥35 years, and sex) in a 1:1:1 ratio into one of three 12-week intervention groups, all undergoing a caloric deficit: (i) the PBD group follows a healthy hypocaloric PBD rich in (poly)phenols, (ii) supplementation group follows a healthy hypocaloric diet and receives polyphenol supplementation (≈26 g/day from maqui, green tea, olive oil leaf, cranberry and grape extracts, corresponding to ~800 mg/day of (poly)phenols) and (iii) control group that will receive a healthy hypocaloric diet with placebo supplementation. The primary outcome is body weight, while cardiometabolic risk factors serve as secondary outcomes.

Dietary data will be collected using dedicated software through three 24-hour dietary recalls at baseline and post-intervention. (Poly)phenol intake will be estimated using the Phenol-Explorer database. The main data collection will include general and lifestyle questionnaires, anthropometric and bioimpedance measurements, blood pressure assessments using sphygmomanometers, physical activity monitoring through accelerometers and strength evaluations via dynamometry. Blood samples will be collected at both baseline and after 12 weeks.

For the analysis of plasma metabolites, a large-scale targeted metabolomics approach will be employed, specifically utilising ultra-high performance liquid chromatography coupled to tandem mass spectrometry. The healthy PBD will be primarily supplied by the food

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this is one of the first randomised controlled trials in Latin America to evaluate the effects of increased dietary (poly)phenol intake—either through a healthy plant-based diet (PBD) or supplementation—on body weight and cardiometabolic risk in adults with overweight or obesity.
⇒ The intervention is grounded in culturally relevant foods and is delivered in a free-living context through a primary healthcare system, enhancing the external validity and real implementation.
⇒ Stratified randomisation by sex and comprehensive outcome assessments, including targeted metabolomics, will allow exploration of biological and behavioural differences between groups.
⇒ The 12-week duration may limit the ability to assess long-term adherence and sustainability of effects, and full blinding is not feasible due to the nature of the dietary interventions and study design.
⇒ Although gut microbiota composition will not be profiled at this stage, plasma metabolomics will capture key microbial-derived metabolites as a proxy of gut microbiota metabolic activity.

industry, encompassing a selection of regional and Latin American foods: blueberries, apple, nuts, olive oil and coffee. A descriptive and inferential statistical plan will be conducted, based on comparison tests, regression models and machine-learning algorithms.

Ethics and dissemination This trial adheres to the Declaration of Helsinki and the CONSORT statement. Signed informed consent will be obtained from all participants. Ethical approval has been granted by the Ethical-Scientific Committee of the Health Service of Araucanía Sur, Chile (Approval No 11250095–58) and the Biosafety Committee of the Catholic University of Temuco. Findings will be disseminated through peer-reviewed publications, conference presentations and engagement with healthcare professionals and policymakers.

Trial registration number NCT06911346.

INTRODUCTION

Non-communicable diseases (NCDs), especially those associated with metabolic dysfunction such as obesity, insulin resistance and cardiovascular diseases, continue to rise globally.[1 2] In Chile, the prevalence of overweight and obesity in adults reached 74.2% in 2017.[3] Unhealthy dietary patterns or suboptimal diets, characterised by insufficient intake of fruits, vegetables and legumes, alongside excessive consumption of processed meat products, sugar-sweetened beverages and ultra-processed foods are major contributors to this trend.[4]

Comprehensive dietary interventions have shown promise in preventing and managing obesity and its metabolic consequences.[5] Traditionally, these interventions have focused primarily on dietary modification and physical activity, rather than pharmacological treatments or bariatric surgery. A recent systematic review highlights that combining a hypocaloric diet with psychological support and structured exercise remains a widely recommended first-line treatment for obesity.[6] However, this approach presents challenges related to study design, variability in individual response, long-term adherence and the promotion of sustainable healthy lifestyles.[7]

Plant-based diets (PBDs) have recently gained attention for their beneficial effects on body weight, lipid profiles and insulin sensitivity.[8] However, despite the growing evidence supporting their health benefits, the adherence to PBDs remains low in most countries, including Chile.[9] Moreover, their effectiveness in real-world community settings has not been sufficiently evaluated through randomised clinical trials.

Beyond macronutrient composition, interest has grown in the role of functional food components such as dietary fibre and phytochemicals, including bioactive compounds like (poly)phenols (hereafter referred to as 'polyphenols'), which are considered to play a pivotal role in managing obesity-related risk factors.[10] These compounds are widely distributed in plant-based foods, with flavonoids and phenolic acids being the most abundant classes.[11] They are partially absorbed in the small intestine, metabolised by enzymes and excreted in the bile and urine.[12] The unabsorbed polyphenols that reach the colon are extensively metabolised by the gut microbiota into a variety of low-molecular-weight phenolic metabolites, which can subsequently be absorbed and contribute to systemic effects.[11] Numerous studies, including in vitro, animal models and a limited number of human clinical trials, have investigated the influence of polyphenol consumption on health parameters, including glucose-insulin homeostasis and lipid profiles, and adiposity.[13 14] Various potential mechanisms have been proposed, such as reducing energy intake while increasing energy expenditure; suppressing fat absorption from the gut (eg, via inhibition of digestive enzymes); enhancing glucose uptake by skeletal muscle; suppressing anabolic pathways; stimulating catabolic pathways in adipose tissue, liver and other organs; inhibiting angiogenesis in adipose tissue and pre-adipocyte differentiation; promoting apoptosis of mature adipocytes; improving gut microbiota dysbiosis; and reducing chronic inflammation associated with adiposity.[15]

Systematic reviews suggest that polyphenols may influence body weight and composition, although evidence from human studies remains limited compared with animal and in vitro research.[16] One review reported that 9 of 19 clinical trials showed a significant average weight loss of 1.5 kg over 12 weeks with polyphenol supplementation alone.[17] Another review found no consistent support for polyphenols as an effective adjunct to caloric restriction and physical activity, though some benefits were observed in cardiometabolic health markers.[18] While epidemiological and some clinical studies suggest a potential protective role of polyphenols in weight maintenance, the findings remain inconclusive.[16 19] Similar inconsistencies are noted regarding their impact on cardiometabolic risk factors.[20] Furthermore, the underlying biochemical mechanisms are not fully understood, and their efficacy in humans requires further confirmation, particularly through exploring the interaction between dietary components, their metabolites and host–microbiota environments.[21 22]

Current evidence on the health benefits of PBDs and dietary polyphenols is primarily derived from observational studies or randomised trials conducted in highly controlled research environments, which limit their generalisability into real-world, community-based settings.[8 16 17] Moreover, little is known about the feasibility and effectiveness of PBD rich in polyphenols interventions tailored to the local food culture within the primary healthcare system in Latin America, including Chile.[9]

In this context, it is hypothesised that increasing dietary polyphenols during caloric deficit, with healthy and regional plant-based foods or polyphenols supplementation, will modify metabolic signatures of gut microbiota and translate into protective effects on body weight and cardiometabolic risk in adults from Temuco, La Araucanía Region, Chile. The main objective of this study is to evaluate the impact of increased dietary polyphenol intake—either through a healthy PBD or supplementation—on body weight and cardiometabolic risk factors in adults with overweight or obesity. Study objectives are presented in table 1. In addition, exploratory outcomes

Table 1 Summary of study objectives, associated outcomes and inclusion and exclusion criteria

Primary objectives	Primary outcome	
To evaluate the impact of increased dietary polyphenol intake—either through a healthy plant-based diet (PBD) or supplementation—on body weight in adults with overweight or obesity	Improve weight-related parameters: change in body weight	Change in body weight from baseline to week 12, with the primary analysis comparing between-group mean differences at 12 weeks. Body weight will also be measured at week 6 for monitoring.
Secondary objectives	**Principal secondary outcomes**	
To evaluate the impact of increased dietary polyphenol intake—either through a healthy PBD or supplementation—on cardiometabolic risk factors in adults with overweight or obesity	Improve blood pressure control	Change in systolic and diastolic blood pressure (mm Hg) from baseline to week 12, comparing between-group mean differences.
	Improve glycaemic regulation	Change in fasting plasma glucose (mg/dL) from baseline to week 12, comparing between-group mean differences.
	Improve lipid profile	Change in total cholesterol, LDL-C, HDL-C and triglycerides (mg/dL) from baseline to week 12, comparing between-group mean differences.
	Improve weight-related anthropometric parameters	Change in BMI, hip circumference, waist circumference, waist-hip ratio from baseline to week 12, comparing between-group mean differences.
	Reduce insulin resistance	Change in HOMA-IR index from baseline to week 12, comparing between-group mean differences.
Inclusion criteria		**Exclusion criteria**
Age between 25 and 45 years (adult)		Presence of cardiovascular disease, diabetes or hypertension
Sexes: All		Illegal drug use, chronic alcoholism or problematic alcohol use
Overweight or obesity class I (BMI 25–35 kg/m²)		Obesity class II or III (BMI ≥35 kg/m²)
At least three of the following cardiometabolic risk factors: ► Current smoker ► Sedentary lifestyle (sitting time or classified as inactive per IPAQ) ► Elevated fasting glucose ► High systolic and diastolic blood pressure, ► High serum triglycerides, ► High HbA1c ► Increased waist circumference above normal parameters ► Elevated high-sensitivity C-reactive protein (hs-CRP) ► Family history of premature coronary heart disease		Severe medical conditions that may impair participation in a nutrition intervention study (eg, digestive disease, advanced malignancy, major neurological or psychiatric disease)
		Any medical condition limiting survival to less than 1 year
		Low predicted likelihood of changing dietary habits according to the Prochaska and DiClemente stages of change model
		Antibiotic use within the last month

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; IPAQ, International Physical Activity Questionnaire; LDL-C, low-density lipoprotein cholesterol.

such as changes in physical activity, muscle strength and metabolomic signatures will be assessed to support mechanistic insights and potential biomarker identification.

The hypothesis and objectives of this study are closely aligned with the design and execution of a clinical trial developed within the framework of the PREDIET-ARAC project: Prevention/Precision with Diet in Araucanía.

METHODS AND ANALYSIS

Study design, participants and setting

This single-blind, randomised controlled trial will be conducted as a part of the PREDIET-ARAC project and aims to enrol young adults with overweight or obesity. A total of 99 participants (aged 25–45 years) with cardiovascular risk factors will be recruited from primary healthcare centres supported by the Health Department of the Municipality in Temuco, Chile. Participants will be randomly assigned (1:1:1), using stratified randomisation by sex and age (<35 years and ≥35 years), to one of the three 12-week intervention arms: (i) a healthy PBD supplemented with polyphenol-rich foods: apples, blueberries, hazelnuts, extra-virgin olive oil and coffee provided at no cost to the participant (ii) a healthy diet plus polyphenol supplementation (≈26 g/day in a sachet) from a mix of maqui, green tea, olive leaf, cranberry and grape extracts or (iii) a control group receiving placebo and standard healthy diet recommendations. All groups will follow a caloric deficit. The participant timeline is

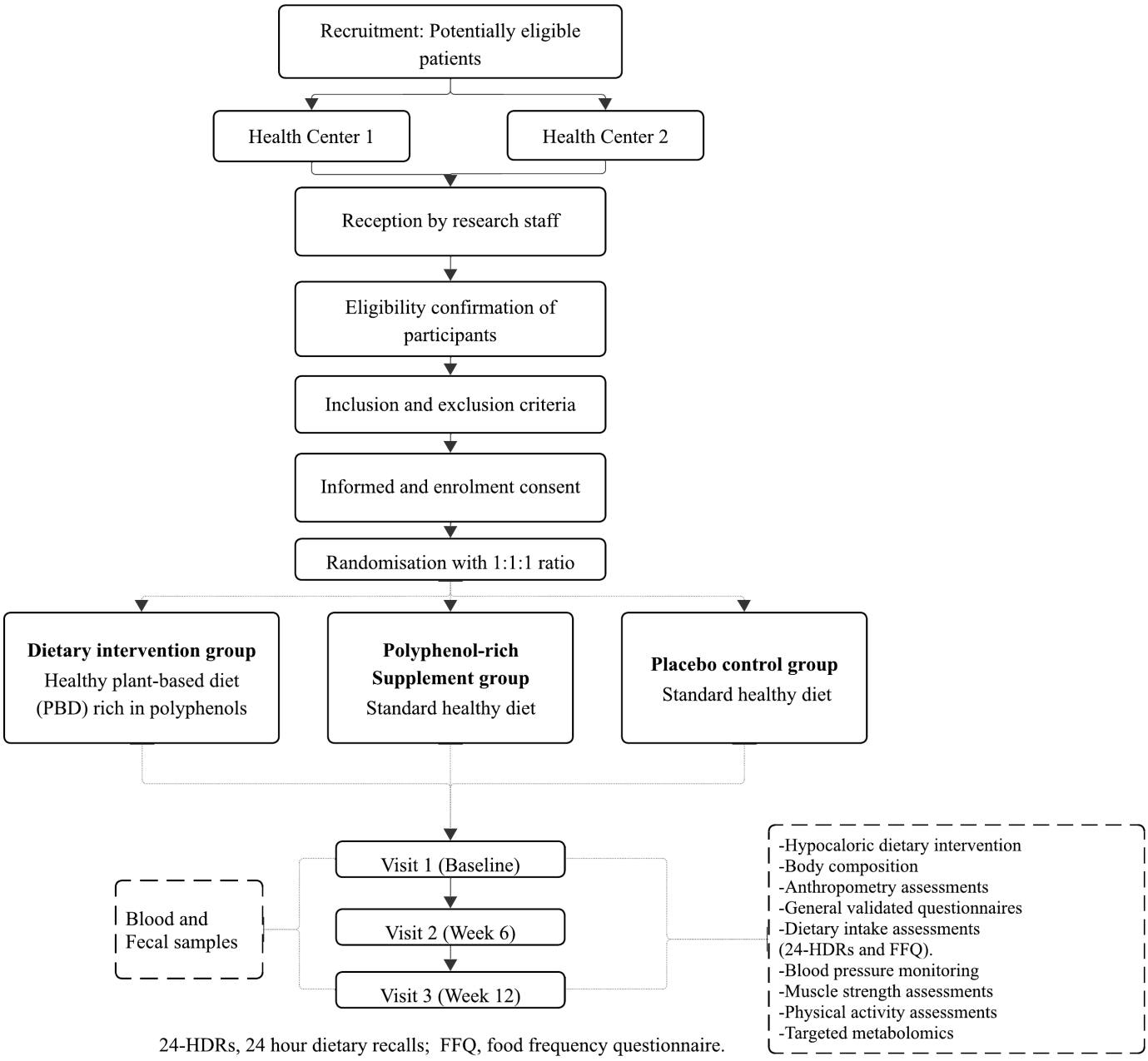

Figure 1 Study flow diagram. Overview of participant recruitment, randomisation (1:1:1 ratio), allocation to study groups (dietary intervention, polyphenol-rich supplement, placebo control) and schedule of visits (baseline, week 6, week 12) with key assessments and sample collections.

presented in the flowchart of figure 1. The study became active on 21 July 2025 with the enrolment of the first participants. Recruitment is ongoing, and final follow-up assessment is expected to be completed by 3 June 2026, as registered in ClinicalTrials.gov (NCT06911346).

Prior to recruitment, a meeting will be held with the heads of the participating health centres and healthcare staff of the Temuco Health Department to present the study objectives, methodology and technical aspects of trial implementation. Following this meeting, and on reaching management agreements between the research team and health professionals, participant assessment will begin. In the individuals' meeting, the initial eligibility criteria will be provided with an information sheet detailing the trial procedures. At the second screening, a trained recruiter will confirm the potential participant and check all inclusion and exclusion criteria (table 1).

Eligibility criteria

Eligible participants must be aged 25–45 years, have overweight or class I obesity (body mass index 25–35 kg/m²) and present with at least three cardiometabolic risk factors: (i) current smoker (more than one cigarette per day during the last month), (ii) sitting time greater than 7 hours per day or classified as inactive according to the International Physical Activity Questionnaire (IPAQ), (iii) elevated fasting glucose ≥100 mg/dL (5.6 mmol/L), (iv) high blood pressure: systolic blood

pressure >130 mm Hg and diastolic blood pressure >85 mm Hg, (v) elevated serum triglycerides (≥150 mg/dL), (vi) HbA1c ≥38 mmol/mol (>5.7%), (vii) increased waist circumference defined by Peterman *et al* for the Chilean population: 92.3 cm for men 87.6 cm for women, (viii) high high-sensitivity C-reactive protein (hs-CRP) (≥2.0 mg/L), (ix) family history of premature coronary heart disease: definite myocardial infarction or sudden death before age 55 in father or male first-degree relative, or before age 65 in mother or female first-degree relative. Eligibility will be confirmed through clinical, biochemical and anthropometric assessments at baseline. Exclusion criteria include the presence of diagnosed cardiometabolic disease, other major medical conditions, substance use disorders, morbid obesity, recent antibiotic use and low expected adherence to the clinical trial protocol.

Participants will not be permitted to take additional dietary supplements containing polyphenols or antioxidants during the study period. They will also be asked not to initiate new weight-loss medications or join other structured diet or weight-loss programmes. All participants will receive the same general lifestyle advice at baseline to ensure standardisation across groups, but no additional lifestyle interventions will be provided during the trial.

Participants who fail to attend two or more scheduled appointments prior to baseline assessments, without valid justification, will be considered non-completers and excluded prior to intervention. The development of this trial protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines, check list was used (table 2).[23]

Table 2 Participant timeline of intervention and schedule of study procedures

		Follow-up (weeks)		
Timepoints	**Enrolment**	**Visit 1 (baseline)**	**Visit 2 (week 6)**	**Visit 3 (week 12)**
RECRUITMENT AND SCREENING				
Eligibility confirmation	X			
Signed informed consent		X		
Questionnaire interview		X		
Allocation (randomisation)		X		
INTERVENTIONS				
Hypocaloric diet		X	X	X
Polyphenol-rich supplementation and placebo-control groups		X	X	X
GENERAL AND DIETARY ASSESSMENTS				
Sociodemographic lifestyle and clinical data		X	X	X
Depression, anxiety, stress (DAAS-21)		X		X
Physical self-concept (CAF questionnaire)		X		X
Dietary intake evaluation (24-HDRs and FFQ)		X		X
PHYSICAL ASSESSMENT				
Isometric quadriceps extension (hand-held dynamometer)		X		X
Handgrip (hand dynamometer)		X		X
International Physical Activity Questionnaire (IPAQ)		X		X
Physical activity (triaxial accelerometers)		X		X
BIOCHEMICAL AND CLINICAL ASSESSMENT				
Biological samples (blood and faeces)		X		X
Blood pressure (automated sphygmomanometer)		X	X	X
Glycaemic (fasting glucose, HbA1c)		X		X
Lipid profile (cholesterol, triglycerides)		X		X
Plasma metabolomics (UHPLC-MS/MS analysis)		X		X
Body weight and composition (bioelectrical impedance analysis)		X	X	X
Waist and hip circumference (manual anthropometry)		X	X	X

CAF, Cuestionario de Autoconcepto Físico (physical self-concept questionnaire); DAAS-21, Depression, Anxiety and Stress Scale–21 Items; FFQ, food frequency questionnaire; 24-HDRs, 24-hour dietary recalls; UHPLC-MS, ultra-high performance liquid chromatography-tandem mass spectrometry.

Interventions

The total duration of the intervention will be 12 weeks for each group. Each participant will attend three in-person visits: Visit 1 (baseline, week 0), Visit 2 (week 6) and Visit 3 (week 12, end of intervention). Dietary guidelines and materials will be provided during the baseline visit. Visit 2 will focus on reinforcing adherence to the assigned dietary intervention, resolving any participant concerns and performing anthropometric assessments. At this time, participants will also receive the remaining food or supplement sachets for the remainder of the intervention period.

At Visits 1 and 3, participants will complete general and lifestyle questionnaires and undergo anthropometric, physical (eg, strength tests) and clinical assessments (eg, blood pressure). Fasting blood and faecal samples will also be collected at these time points.

All study procedures, including enrolment and participant follow-up, will take place at the Universidad Católica de Temuco, San Francisco Campus. Data collection will be conducted in the facilities of the University Hospital, Clinical Laboratory and the Departamento de Procesos Terapéuticos. Trained staff will administer the questionnaires, perform anthropometric measurements and oversee the collection of fasting biological samples.

Blood and faecal samples will be stored at −80°C in ultra-low temperature freezers located in the School of Medicine at the Universidad Católica de Temuco. Participants who have consented to faecal sample donation will bring 24-hour stool samples collected the day before Visits 1 and 3. Blood tests will be analysed at the institutional laboratory of the Catholic University of Temuco and the Departamento de Procesos Diagnósticos y Evaluación. Plasma samples will be sent to a specialised research group for targeted metabolomic analysis. Faecal samples will remain stored for future microbiome analyses. No microbiota sequencing or taxonomic profiling will be performed in this phase; instead, targeted plasma metabolomics will quantify microbial-derived metabolites to infer gut microbiota metabolic activity.

Healthy plant-based food diet

Healthy PBD is supported by systematic reviews and meta-analyses demonstrating their benefits in cardiovascular disease prevention and,[24] more recently, in promoting healthy ageing.[25] These diets are typically characterised by low to minimal consumption of animal-derived foods and have been classified into the categories of healthy and less healthy plant-based foods.[21] Healthy plant food groups included whole grains, fruits, vegetables, nuts, legumes, vegetable oils and tea/coffee. Less healthy plant food groups included fruit juices, sugar-sweetened beverages, refined grains, potatoes and sweets/desserts. Animal food groups included animal fats, dairy, eggs, fish/seafood, meat and miscellaneous animal-based foods.[21] Based on this conceptual framework and calorie-restricted diet, participants will be guided to follow a structured dietary pattern that emphasises the intake of polyphenol-rich foods. This pattern is reinforced through tailored dietary guidelines and a printed food selection guide. The guide incorporates seasonal and regionally available fruits and vegetables to facilitate adherence.

The study provides participants with selected polyphenol-rich food items to support adherence to the PBD intervention. These include frozen blueberries (50 g/day), apples (1 unit/day), hazelnuts (30 g/day), extra-virgin olive oil (1 L per participant) and soluble coffee (≈3 g/day), all of which are supplied by the study throughout the 12-week period. The estimated daily intake of polyphenols in the PBD group is approximately 1200–1400 mg/day, based on the inclusion of polyphenol-rich foods such as blueberries, apples, nuts, olive oil and coffee.

Hypocaloric diet and standard dietary recommendation

Participants will be instructed to follow an individually designed hypocaloric diet consisting of a standard low-calorie plan, achieving 75% of their estimated energy requirements throughout the 12-week study period.[26] Total energy expenditure (TEE) will be estimated using the factorial method based on self-reported daily physical activity (according to Food and Agriculture Organization of the United Nations guidelines), and basal metabolic rate will be calculated using the Mifflin-St Jeor equation.[27] Caloric requirements will be determined individually according to each participant's physical activity level, which will be used to calculate both TEE and the 75% energy target.[26] Three adapted hypocaloric diets providing 1200, 1500 and 1800 kcal/day will be developed to ensure energy intake is appropriately adjusted for each participant while maintaining nutritional adequacy. Across all three intervention groups, the macronutrient distribution will be standardised at 55–60% carbohydrates, 15% protein and 25–30% fats. This consistency ensures that any observed effects can be attributed to the specific dietary patterns and polyphenol sources rather than differences in caloric intake or macronutrient balance. Table 3 summarises the hypocaloric dietary guide.

General recommendations:

1. Nutrition counselling will be based on the latest national Food-Based Dietary Guidelines.
2. Increase consumption of unprocessed or minimally processed foods, colourful natural foods, homemade meals and safe water as the main beverage.
3. Limit consumption of ultra-processed products, added sugars, saturated fats, red and processed meats, alcoholic beverages and sugar-sweetened drinks (presence of front-of-package warning labels).

Standard nutritional counselling will be provided in accordance with the updated Food-Based Dietary Guidelines (Guías Alimentarias Basadas en Alimentos, GABA) of Chile, published in 2022 by the Department of Nutrition and Food of the Ministry of Health, in collaboration with the Institute of Nutrition and Food Technology at the University of Chile.[28] The current version of the guidelines includes ten updated nutritional messages aimed

Table 3 Hypocaloric dietary guide: food groups, daily intake recommendations and standardised exchange portions

Food groups	Daily intake recommendations	Equivalent portions
Whole grains, tubers and cereal-based foods	3	► 3/4 cup cooked rice or noodles (preferably whole grain) ► 1/2 cup couscous ► 1/2 cup oatmeal ► 1 medium potato ► 1/2 unit of hallulla bread* ► 1 slice of marraqueta bread* ► 1 whole wheat pita bread ► 2 slices of sandwich bread ► 6 whole wheat crackers ► 4 commercial crackers (not sugary)
Low-fat dairy and derivatives	2.5	► 1 cup low-fat or skim milk ► 1 unit low-fat or skim yoghurt ► 1 slice of cottage cheese or 1 slice of cheese ► 2 teaspoons low-fat cream cheese
Low-fat meats, fish and eggs	1.5	► 1 palm-sized piece of lean chicken or beef ► 1 egg ► 1/3 cup tuna ► 1 portion of seabass or kingklip ► 1 slice of ham
Legumes	1	► 3/4 cup cooked legumes (eg, white and black beans, lentils, chickpeas, fava beans)
Non-starchy vegetables and root vegetables	3	► 1 medium tomato ► 3/4 cup green beans ► 1/2 cup raw carrot, cooked beet or broccoli ► 1 cup lettuce, cucumber or cabbage ► 1/4 zucchini
Fruits	3	► 1 medium apple, pear, orange or peach ► 1/2 banana ► 10 grapes ► 1 cup of berries (strawberries, raspberries, blueberries, others)
Healthy fats and lipid-rich foods	2	► 4 teaspoons of extra virgin olive oil ► 3 teaspoons of avocado ► 1 handful of peanuts, walnuts or almonds

*Hallulla and marraqueta are traditional Chilean wheat-based breads.

at the general population. These recommendations are designed to promote nutritious, safe and sustainable food choices; support sustainable food systems; prioritise fresh and minimally processed foods; consider regional diversity and seasonality in food production; value home-cooked meals; and respect local food culture.[28]

Polyphenol supplement and composition

The polyphenol-rich supplement used in this study is based on a combination of individual compounds previously tested in clinical trials, such as green tea, cranberry and grape extracts, which have demonstrated beneficial effects on obesity and cardiometabolic risk factors.[29–31]

The selection of specific polyphenol compounds was based on their prior efficacy and safety profiles. The target dosage for each component was estimated to ensure both effectiveness and tolerability, following available evidence on safe intake thresholds. Considering that the average daily intake of dietary polyphenols in Chilean and European populations is approximately 1000 mg,[32 33] the intervention sachets were designed to deliver an additional 800 mg of polyphenols per day beyond dietary intake.

The supplement comprises five different extracts: 200 mg maqui extract (25% delphinidins and 35% anthocyanins), 250 mg green tea extract (10% catechins and 75% epigallocatechin gallate), 50 mg olive leaf extract (20% hydroxytyrosol and derivatives), 4.5 g cranberry (anthocyanins and flavonols) and 7.8 g grape (8 mg of resveratrol). Participants in the intervention group will consume one 12.8 g sachet twice daily with meals (breakfast and dinner), resulting in a total daily intake of 26 g of the combined extracts, delivering approximately 800 mg of polyphenols per day. The placebo sachets contain maltodextrin and resistant starch as main bulking agents; guar gum as a stabiliser and suspending agent; ascorbic acid as an antioxidant; sucralose as a non-nutritive

sweetener; and artificial colourants such as brilliant blue (E133) and/or Allura Red (E129). The total weight of each placebo sachet is ≈3.6 g (7.2 g/day). It will be administered to the control group under the same conditions as the intervention group.

All ingredients used in the supplement are certified for quality and safety. The final formulation was developed based on stability and organoleptic testing to ensure product integrity throughout the intervention period. The blending, aliquoting and packaging of both the intervention and placebo sachets will be carried out by Laboratorio Avellina, a facility authorised by the Chilean Public Health Institute (Instituto de Salud Pública, ISP). In addition, basic quality control procedures—including internal physical and chemical stability checks—will be conducted and documented by pharmaceutical analytics researchers at the Universidad Católica de Temuco for traceability and audit purposes.

Bioavailability and safety of compounds

The bioavailability of polyphenols in humans is influenced by multiple factors, including the food matrix, food processing methods, interactions with other dietary compounds and host-related factors such as gut microbiota composition and enzymatic activity.[34] Several studies have explored the mechanistic pathways and biological properties of polyphenols, highlighting considerable variability in their absorption, metabolism and excretion depending on their structural characteristics.[11] In general, low-molecular-weight polyphenols are more absorbed in the small intestine, whereas high-molecular-weight compounds exhibit lower absorption rates and undergo extensive metabolism by the gut microbiota prior to systemic uptake.[12] The reported bioavailability of polyphenols varies widely across different subclasses, with estimates ranging from approximately 75% for compounds such as resveratrol and tyrosol, 25–40% for phenolic acids, 20–40% for flavonols, 15–40% for catechins and around 1–2% for anthocyanins.[35 36]

The occurrence of side effects associated with high doses of polyphenol extracts present in foods is very rare,[35] including more than one type of polyphenol in the supplement, which could lead to more effective functional compounds.[37] There are European Food Safety Authority Scientific Opinion reports that support the safety of green tea catechins, (poly)phenols from olives (hydroxytyrosol and derivatives) and resveratrol for human consumption.[38 39] Many animal and human studies support safe doses of Maqui extracts and its compounds[40] or cranberry extracts.[41 42]As per other compounds, for example, anthocyanins from berries or fruit flavonoids or different interventional studies in humans have reported safe doses or no adverse effects.[15 43]

All adverse events will be monitored and recorded throughout the 12-week intervention period. Any health-related occurrence reported by participants—either during scheduled visits or via email communication—will be documented and assessed by the research team. Relevant events will be reported to the principal investigator and, when appropriate, to the ethics committee. A data monitoring committee was not established for this trial, as the interventions are considered low risk, the study population is not vulnerable, and the intervention period is relatively short. This decision is consistent with international ethical guidelines for low-risk, dietary intervention trials.

Adherence monitoring

Adherence will be reinforced by structured in-person delivery of polyphenol-rich foods (for the PBD group) and sachets (for the supplement group) at weeks 0, 6 and 12. Participants will confirm receipt by signing pick-up logs and will be asked to return any unused sachets. Individual dietary counselling and printed dietary guidelines will be provided at baseline, and a group counselling session will be held between weeks 4 and 8 to reinforce motivation and clarify questions. Participants may contact the research team at any time for additional support. Dietary adherence will also be assessed at week 12 through a structured FFQ. Additionally, targeted metabolomics will allow indirect biological confirmation of adherence through the quantification of plasma metabolites (eg, hippuric acid) as objective proxies of polyphenol intake.

Data collection

General information

At the baseline visit, data on personal demographics, lifestyle habits and personal and family medical history will be collected through a structured questionnaire. In addition, participants will complete the Depression, Anxiety and Stress Scale–21 Items, a validated self-report instrument designed to assess the severity of symptoms related to depression, anxiety and stress.[44]

Anthropometric measurements

Anthropometric and body composition measurements will be conducted at all three study visits to evaluate the primary outcome: the effect of a healthy PBD rich in polyphenols or polyphenol supplementation, during a caloric restriction, on body weight and body composition.

Body weight and composition will be assessed by trained personnel using a multi-frequency segmental body composition analyser (InBody 370, InBody Co., Ltd., Seoul, Korea). Height will be measured with an integrated stadiometer (SECA Model 213, Hamburg, Germany), and waist and hip circumferences will be recorded using a flexible ergonomic measuring tape (SECA Model 201, GmbH & Co., Hamburg, Germany). Subcutaneous fat thickness will be estimated using a skinfold calliper (Lange Calliper, Beta Technology Inc., USA), following standard anatomical sites and procedures.

Dietary intake assessment

Dietary intake will be assessed using three 24-hour dietary recalls (24-HDRs), conducted by a trained dietitian. The initial recall will be performed face-to-face during the baseline visit, and the remaining two will be carried out

via telephone during the follow-up period. To ensure standardisation and accuracy in data collection, the SER-24HDR software (University of Chile), developed by CIAPEC (Center for Research in Food Environments and Prevention of Nutrition-Associated Diseases) at INTA, University of Chile, specifically adapted for the Chilean population—will be used.[45] In addition, a 26-question questionnaire will be applied to learn about the participant's eating habits. The questionnaire contains questions grouped by the frequency of consumption of specific food groups, based on the methodology applied in the third National Health Survey of Chile.[46]

Physical activity and strength

Physical activity will be objectively assessed using a triaxial accelerometer (ActivPAL), as previously validated.[47] All participants will wear an accelerometer on the thigh for 7 days. Physical activity measurements will be carried out at the beginning of the study and again at the end of the intervention, 1 week before the initial evaluation and 1 week before finishing the intervention. Maximum handgrip strength will be evaluated using a digital grip dynamometer (Jamar Plus+)[48] and the maximum isometric knee strength will be assessed with a load cell (Progressor 300, Tindeq, Norway).[49] For both maximum handgrip strength and isometric strength knee extension, three attempts will be made, and the highest value achieved for each limb will be considered, respectively. This methodology has been previously described and applied elsewhere.[47 49] Participants will also complete the IPAQ and a validated physical self-concept questionnaire.[50 51]

Blood pressure

Systolic and diastolic blood pressure will be measured at baseline and at 6 and 12 weeks by trained personnel. Measurements will be taken in a seated, resting position using a semi-automatic upper-arm blood pressure monitor (A&D UA-611, A&D Medical, Japan). This device employs the oscillometric method and features a latex-free SlimFit cuff suitable for arm circumferences of 22–32 cm. It has been clinically validated according to international standards and a WHO blood pressure classification indicator.

Blood samples

Fasting blood samples will be collected in the baseline and 12 weeks of intervention. Trained nurses will extract 20 mL from the antecubital vein of each participant following standardised procedures. Samples will be stored and analysed at the School of Medicine at the Catholic University of Temuco and affiliated institutional laboratories. Blood samples will be centrifuged at 5000*g* for 15 min, aliquoted and stored at –80°C until analysis. The following biochemical parameters will be measured: measures metabolic and function markers ((eg, complete blood count, triglycerides, total cholesterol, liver (transaminases), and renal function (eg, creatinine), glucose, insulin, uric acid, homeostatic model assessment of insulin resistance, glycosylated haemoglobin, uric acid and inflammatory biomarkers (eg, ultra-sensitive CRP)). In addition, erythrocyte membrane fatty acid composition will be analysed via gas chromatography, providing an objective biomarker of dietary fat quality over the previous weeks.[52]

Targeted metabolomics analysis and quality control assessment

Plasma samples collected at baseline and 12 weeks will be stored at –80°C for future targeted metabolomics analyses. The planned approach aims to quantify circulating polyphenols, their biotransformation products (phase I and II metabolites), gut microbiota-derived compounds and selected endogenous metabolic markers relevant to dietary interventions.

Sample processing and metabolite detection will be conducted using validated targeted metabolomics platforms based on ultra-high performance liquid chromatography coupled with tandem mass spectrometry or comparable technologies.[53] Quality control procedures will be applied to ensure data robustness, including the use of internal standards and pooled plasma samples.

Metabolomic data preprocessing will involve standard filtering and normalisation procedures, such as the exclusion of metabolites with high missingness or variability, imputation of missing values and correction of potential batch effects.[54] Autoscaling will be used for normalisation, and multivariate techniques will be applied for outlier detection. The final dataset will comprise a curated panel of metabolites suitable for downstream statistical and exploratory analyses.

Faeces samples

Participants who voluntarily consent to provide faecal samples will be asked to bring a sample at Visit 1 (baseline) and Visit 3 (week 12). These samples will be stored at –80°C in ultra-low temperature freezers located at the School of Medicine, Universidad Católica de Temuco. The samples will be preserved for future microbiota analyses.

Sample size, randomisation and statistics

The study sample and design were informed by prior literature and sample size estimations.[55 56] Previous dietary intervention trials targeting polyphenol intake for weight loss and cardiometabolic outcomes typically include 30 to 40 participants per group and span 8 to 12 weeks of intervention.[39 55] The sample size for the present study was calculated using G*Power version 3.1.9.4, based on repeated-measures Analysis of Variance (ANOVA) (between-group factor), with an alpha level of 0.05, a statistical power of 80%, and three study arms. The calculation determined a required sample size of 90 participants. Anticipating a dropout rate of approximately 10%, we aimed to recruit 99 participants (33 per group).

The sample size calculation was primarily powered to detect changes in body weight, the study's primary outcome. Based on previous polyphenol-based dietary interventions,[6 16] estimated weight reductions range between 2.5 and 4.0 kg in intervention groups and between 0.5 and 2.0 kg in control

groups, with an assumed pooled SD of 3.0 kg. Based on these estimates, a median effect size close to a moderate Cohen's d (approximately 0.5) was considered for sample size estimation. For secondary outcomes—such as clinical and biochemical parameters—relative improvements of 5–10% are expected, with SD typically ranging from 10% to 20%, depending on the specific variable.

Allocation, randomisation and blinding

Participants will be randomly allocated to one of the three 12-week intervention groups using a computer-generated random number sequence, in a 1:1:1 ratio. Randomisation will be stratified by age (<35 vs ≥35 years) and sex using a computer random number generator, to ensure balanced distribution across groups.

Due to the nature of the dietary intervention, full participant blinding is not feasible, as participants in the food-based diet group may recognise the specific dietary components they receive. Nevertheless, blinding will be maintained between the two sachet-based groups (polyphenol supplementation vs placebo), as both groups will receive identical sachets and will not be informed of their group allocation. Outcome assessors and data analysts will remain blinded to group allocation to minimise bias. Only the principal investigator will have access to the allocation list. All other members of the research team will identify participants solely by their unique study ID and will not be involved in group assignment.

Compliance will be monitored primarily through scheduled food deliveries tailored to each intervention group. For the food-based intervention group, perishable foods (eg, apples and blueberries) will be delivered every 2 weeks throughout the 12-week intervention period. For both the supplement and placebo groups, sachets will be provided in two instalments: 50% at baseline and the remaining 50% at week 6. Non-perishable food items will also be distributed at the same time points.

Intention-to-treat and per-protocol population

The primary analysis will be conducted according to the intention-to-treat (ITT) principle. Under the ITT approach, all randomised participants will be analysed in the groups to which they were originally assigned, regardless of the adherence to the intervention. Participants with major protocol violations concerning eligibility (eg, not meeting inclusion/exclusion criteria) or who formally withdrew consent before receiving any component of the intervention will be excluded from the ITT analysis. Participants with no outcome data at any follow-up visit (eg, no data at Visit 2 or Visit 3) will also be excluded. Baseline characteristics of participants lost to follow-up will be compared with those included in the final analysis to assess potential attrition bias.

A per-protocol (PP) analysis will also be conducted, including only those participants who completed the study without major protocol deviations, attended the required follow-up assessments and demonstrated sufficient compliance with the intervention (eg, sachet return, sessions attended). Participants who returned less than 75% of the expected sachets or dietary supplements will be excluded from the PP analysis due to inadequate adherence.

Superiority trial

This trial is designed to evaluate whether two polyphenol-based strategies—a healthy PBD rich in polyphenols or polyphenol supplementation combined with a healthy diet—are superior to conventional dietary advice in improving weight-related and cardiometabolic outcomes in adults with overweight or obesity, under a hypocaloric diet.

Missing data

Different methodologies will be assessed to deal with missing data. The definitive decision will be made depending on the type of missing data and the robustness of results. For longitudinal outcomes with repeated measures, generalised linear mixed-effects models will be used, which account for missing data under the missing at random assumption. Overall, it is not expected that the number of missing exceeds 10%. Sensitivity analyses will assess the robustness of the findings under different assumptions.

Baseline characteristics

Baseline characteristics will be reported by a randomised group. The following characteristics will be presented: age, sex, sociodemographic data, lifestyle factors, anthropometric measurements, energy and food group intake and biochemical and inflammatory biomarkers, among others.

Continuous variables will be presented as mean±SD or median with IQR, depending on the distribution assessed by visual inspection and Kolmogorov–Smirnov tests. Categorical variables will be expressed as counts and percentages.

Categorical variables will be expressed as number and percentage of participants for each category. Continuous variables will be presented as mean±SD in case of normal distribution, and as median and IQR in case of non-normal distribution. Normality will be assessed by plotting distributions and by the Kolmogorov-Smirnov test. Differences between baseline characteristics of both groups will be assessed by the chi-square test or t-test for independent samples.

Outcome assessments

The primary outcome is the change in body weight from baseline to week 12. The primary analysis will compare the mean difference in weight change at week 12 between each intervention group and the control group, using linear mixed-effects models adjusted for baseline weight and relevant covariates.

For anthropometric outcomes measured at three time points (baseline, week 6 and week 12), changes over time and between groups will be analysed using linear mixed-effects models with fixed effects for time, group and their interaction and random intercepts for participants.

For biochemical and cardiometabolic outcomes measured at baseline and week 12, the primary analysis will compare between-group differences at follow-up using Analysis of Covariance (ANCOVA), adjusting for baseline values. As an alternative analytical strategy, we will also compute the change (Δ = week 12 − baseline) for each participant and compare mean differences in change across groups using one-way ANOVA or the Kruskal–Wallis test, depending on distribution. Within-group pre-post comparisons will be conducted using paired t-tests or Wilcoxon signed-rank tests. All models will be adjusted for relevant covariates (eg, age, sex, lifestyle factors) as needed. Statistical significance will be set at $p<0.05$.

Although secondary outcomes will be analysed in an exploratory framework, a Benjamini-Hochberg false discovery rate adjustment will be applied where appropriate, especially for analyses involving metabolomic profiles or clusters of related cardiometabolic biomarkers.

Patient and public involvement

No patients or public were involved in the design, conduct, reporting or dissemination of this research study.

Ethics and dissemination

This trial adheres to the principles outlined in the Declaration of Helsinki and complies with the CONSORT guidelines. Written informed consent will be obtained from all participants prior to enrolment. Participants will be informed that their biological samples (blood and faeces) may be stored and used in future ancillary studies related to nutrition and health. Participant data will be stored securely at the University Campus (Department of Diagnostic Processes and Evaluation, Faculty of Health Sciences) and protected by password-access systems, with access restricted to authorised personnel designated by the principal investigator. Anonymised data will be used for all statistical analyses to ensure participant confidentiality. The principal investigator, co-investigators, clinical research coordinator, research assistants and the study statistician will have access to the final dataset. As the study involves non-invasive dietary and lifestyle interventions, no ancillary or post-trial care is anticipated according to the study design.

The study was approved by the Ethical-Scientific Committee of the Health Service of Araucanía Sur, Chile (Approval No 11250095–58) and by the Biosafety Committee of the Universidad Católica de Temuco. The trial was registered in ClinicalTrials.gov (Identifier: NCT06911346). Any significant modifications to the study protocol (eg, changes in eligibility criteria, outcomes or procedures) will be submitted for approval to the relevant ethics committees and updated in the ClinicalTrials.gov registry. Study findings will be disseminated through presentations at scientific conferences and publications in peer-reviewed international journals.

Data availability statement

No individual participant data will be shared due to confidentiality agreements and the scope of informed consent approved by the Ethics Committee. Aggregate results and summary tables will be included in peer-reviewed publications and may be made available from the corresponding author on reasonable request, subject to additional ethical and institutional approval.

DISCUSSION

Polyphenols, naturally occurring compounds found in plant foods, have been associated with a broad spectrum of biological activities relevant to the prevention and management of cardiometabolic diseases. Human trials and epidemiological studies suggest that diets rich in polyphenols may contribute to reductions in body weight, improved lipid and glycaemic management and attenuation of systemic inflammation.[11] However, many of these findings stem from studies focusing on isolated compounds or specific subclasses, conducted under tightly controlled conditions that limit generalisability to broader populations and free-living dietary conditions. In Latin America, evidence from randomised trials evaluating the effectiveness of polyphenol-rich diets or supplements remains particularly scarce.[16]

The present study protocol addresses these gaps by testing two complementary polyphenol-based strategies within a hypocaloric dietary framework: a healthy PBD rich in polyphenol foods and a targeted supplementation with a combination of polyphenol-rich extracts. This formulation includes maqui (anthocyanins), green tea (catechins), olive leaf (hydroxytyrosol), cranberry (flavonols) and grape (resveratrol), all of which have individually demonstrated beneficial metabolic effects in previous trials.[40 42 57] The intervention is innovative in its attempt to harness potential synergistic effects of multiple bioactives, while the dietary approach reinforces adherence by incorporating culturally relevant and locally accessible foods, and strategically selected for their polyphenol content such as apples, blueberries, hazelnuts, olive oil and coffee, commonly consumed in the Chilean context.[18 43 58]

A distinctive strength of this trial lies in its combination of controlled supplementation with free-living dietary intake, implemented through the primary healthcare system. In addition, the study targets a general adult population without chronic conditions or advanced cardiovascular risk[19] and stratifies randomisation by sex to account for known gender-related differences in weight-related behaviours and stigma.[16]

The use of a placebo group, matched in format and appearance to the intervention sachets, allows for a rigorous comparison while preserving participant blinding to the extent feasible. Although complete blinding is inherently challenging in dietary interventions, the inclusion of inert bulking agents and sensory-matched colouring and sweetening agents aims to minimise perception bias. This approach is consistent

with established practices in nutritional randomised controlled trials, enhancing internal validity without compromising external applicability or exerting physiologically relevant effects.[59] Importantly, the active supplement contains approximately 3 g of fibre, including both intrinsic and fermentable components derived from grape and cranberry extracts; thus, the excipient composition in the placebo group was designed to match, as closely as feasible, the bulk and texture of the intervention, without introducing a differential prebiotic load.

To explore mechanistic underpinnings, the study will incorporate targeted metabolomics to assess circulating polyphenol-derived metabolites, endogenous metabolic markers and gut microbiota-associated compounds. While the systemic bioavailability of many polyphenols remains low due to structural complexity and host metabolic variation, recent work has highlighted the importance of microbial metabolism in mediating physiological effects.[60 61] By collecting plasma samples at baseline and post-intervention, this study will enable exploratory analyses of these metabolomic signatures, contributing to the growing body of literature that links dietary polyphenols to personalised metabolic responses. A key limitation is that direct gut microbiota composition profiling will not be performed at this stage. Instead, microbial-derived metabolites in plasma will serve as proxies of gut microbiota metabolic activity. Stool samples will be biobanked for future analyses, pending additional funding and resources.

Finally, by recruiting through municipal health centres and applying interventions that align with national dietary guidelines, this trial enhances external validity and may inform scalable strategies for obesity management. The 12-week duration limits the ability to evaluate long-term effects, and although no advanced formulation technologies (such as nanoencapsulation) were applied to improve polyphenol bioavailability, the intervention supplement will be consumed dissolved in water, for easy administration and rapid onset of action, potentially improving the solubility and immediate bioaccessibility of polyphenols.

Despite inherent challenges, the study is strengthened by its dietary-focused design, stratified randomisation, use of standardised protocols, outcome assessor blinding and the combined assessment of behavioural and biological endpoints. Together, these elements contribute to the study's methodological rigour and relevance. Findings from this research may support the development of culturally tailored, evidence-based strategies for improving metabolic health in Chile and across Latin American populations.

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Acknowledgements We would like to acknowledge the support of all participating institutions, healthcare centres, research teams and the individuals who will take part in this study.

Contributors FL conceived the original idea for the trial, developed the study design, obtained funding and ethical approval and drafted the initial manuscript. FL serves as the guarantor of the study. CR-L and RN-L contributed to protocol development and manuscript drafting. They will be responsible for participant recruitment. FL, IC-V, MS-V, MM-H, RZ-R and CA-L will supervise study implementation and contribute to data interpretation and statistical analysis. NG and LD-V will support specific trial work packages. All authors critically reviewed and approved the final version of the manuscript. Declaration of AI use: During the preparation of this manuscript, ChatGPT (OpenAI) was used to assist with language editing and improving the clarity of the text. All content generated by the AI tool was critically reviewed and edited by the authors to ensure accuracy and appropriateness.

Funding This work was supported by the Chilean Government through the Agencia Nacional de Investigación y Desarrollo (ANID) grant number [FONDECYT Iniciación 11250095].

Disclaimer Apple (CHISA S.A. Company), blueberries (via the Chilean Blueberry Committee), hazelnuts (Grupo Hijuelas), extra-virgin olive oil (Olive Capital) and coffee (Nestlé) were provided as non-financial support for the dietary intervention. Polyphenol extracts used in the supplementation group—including maqui (MNL Group), cranberry (Bayas del Sur), and grape extracts (Nscipharma Group)—were also donated for use in the study.

Competing interests FL reports receiving non-financial support for this study in the form of food and ingredient donations from CHISA S.A. (apple), the Chilean Blueberry Committee (blueberries), Grupo Hijuelas (hazelnuts), Olivo Capital (extra-virgin olive oil), Nestlé (coffee), MNL Group (maqui), Bayas del Sur (cranberry) and Nscipharma Group (grape extracts). These contributions were used exclusively for the implementation of the dietary and supplementation interventions in this clinical trial. No other conflicts of interest were declared. Related to the use of the SER-24HDR software, the information, analysis and opinions presented in this document are the sole responsibility of the authors and do not represent, nor are they in any way linked to, the CIAPEC of the INTA, University of Chile.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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