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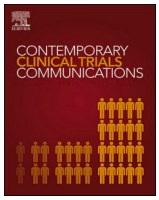

Mediterranean diet and psychological well-being intervention to reverse metabolic syndrome in Chile (CHILEMED trial)

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A R T I C L E I N F O

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A B S T R A C T

Psychosocial status and lifestyle are key risk factors of non-communicable diseases (NCDs), which, in turn, are main drivers of healthcare costs and morbimortality worldwide, including Chile. Mediterranean diet (MedDiet) is one of the healthiest dietary patterns under study. However, its impact on high-risk conditions, such as metabolic syndrome (MetS), and NCDs outside the Mediterranean Basin remains mostly unexplored. Even though Central Chile has an environment, food production, and culinary traditions comparable to those present in Mediterranean countries, few studies -some with significant methodological limitations- have evaluated the effect of MedDiet on health and/or disease in Chilean subjects. Importantly, a Mediterranean lifestyle is a *modus vivendi* that integrates physical health with mental and social well-being. Psychological well-being (PWB) is associated with healthy behaviors, positive health outcomes, and longevity, thereby emerging as a novel healthcare goal. We report here an ongoing randomized controlled clinical trial in Chilean patients with MetS seeking to test whether (1) a PWB theory-based intervention facilitates induction to and increases long-term adherence to a locally adapted MedDiet, and (2) a MedDiet intervention -implemented alone or combined with well-being promotion- is more effective at reversing MetS compared to individuals following a low-fat diet without psychological support. The CHILEan MEDiterranean (CHILEMED) diet intervention study is a 1-year trial including patients with MetS living in Chile. Participants will be assigned randomly by a computer-generated random number sequence to one of the three intervention arms: a) low-fat diet as control group, b) MedDiet alone, and c) MedDiet plus well-being support. Patients will be followed-up by individual and/or group online nutritional sessions or phone cal as well as 6- and 12-month in-person re-assessment of medical history, medication use, food intake, PWB, anthropometrics/physical exam, and blood collection for laboratory analysis. The primary outcome

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of the trial will be the effect of the MedDiet -with or without PWB intervention- on overall reversal of MetS compared to low-fat diet alone. Based on a statistical superiority trial, expected impact, and patient loss, the estimated study sample is 339 subjects (113 individuals per arm in 3 equal-sized groups). Currently, we have enrolled 179 patients, predominantly women, evenly distributed by age (group means ranging from 45.7 to 48,9 years-old), 3/4 are obese with almost all of them showing abdominal obesity, 70% are hypertensive, whereas <10% exhibit diabetes. If findings turn out as expected (e.g., MedDiet -with or without PWB intervention- is better than the low-fat diet for reversion of MetS at 1-year follow-up), CHILEMED will provide further beneficial evidence of the MedDiet on NCD risk conditions beyond the Mediterranean region.

1. Introduction

Non-communicable diseases (NCDs) are major causes of healthcare costs and morbimortality worldwide [1], including Chile, where the 2016–2017 National Health Survey showed elevated prevalence of obesity (31%), cardiovascular disease (CVD) risk (26%), and diabetes (12,3%) [2]. Metabolic syndrome (MetS) -a well-known clustering of risk factors leading to NCDs [3,4]- increased from 21% in 2003 to 40% in 2016–2017 [2,5]. Furthermore, more than 50% of deaths occurred in Chile during 2019 were attributed to CVD and cancer [6].

Predisposing distal risk factors, such as unhealthy diet and psychosocial dysfunction, are driving this global increase in NCDs. The last Chilean food intake survey performed in 2010 revealed a low overall diet quality [7]. In addition, the prevalence of MetS correlates inversely with adherence to a healthy dietary score in this population [8]. On the other hand, depression was detected in 15% and stress in 30% of Chileans >15 years-old in 2016–2017 [2], indicating a high prevalence of psychological conditions that negatively influence lifestyle [9].

The Mediterranean diet (MedDiet) is currently considered one of the healthiest dietary patterns [10–13]. Cross-sectional and prospective studies in addition to randomized clinical trials (RCT) in Europe, US, and Australia have associated higher adherence to Mediterranean-style food patterns with lower prevalence/incidence of NCDs including MetS, diabetes, CVD, cancer, neurodegenerative diseases, and overall mortality as well as better quality of life and longevity [10–15]. Nonetheless, few RCTs (most of them carried out in European countries) have evaluated the effect of MedDiet on MetS [13,16,17]. The beneficial impact of MedDiet on MetS and other risk factors and NCDs in populations living outside the Mediterranean Sea remains mostly unexplored and uncertain. Indeed, the effect of MedDiet can differ in non-Mediterranean countries due to food availability/access, genetic and metabolic variations, culinary traditions, as well as other cultural and environmental differences [18–21]. Understanding these factors is crucial for tailoring MedDiet recommendations/interventions to specific populations beyond the Mediterranean region.

There are four additional world regions -including Central Chile- characterized by Mediterranean ecosystems [22,23], displaying plant and animal production along with food availability comparable to those found in countries located around the Mediterranean Sea [19,20, 24–28]. Moreover, traditional Chilean cuisine uses food ingredients and cooking techniques that are like those utilized in Southern Europe [19, 20,24–28]. Thus, promotion of MedDiet adherence offers a notable potential for management of the ongoing epidemiological transition to NCDs in Chile.

Regardless of this geographical and alimentary context, very few and preliminary studies -with various methodological limitations- have evaluated the impact of MedDiet interventions in Chilean subjects. One small size study examined a 3-month MedDiet intervention, which showed increased antioxidant capacity and less oxidative damage in plasma [29], improved blood fatty acid profile [30], better hemostasis [31], and endothelial function [32] compared with those eating a Western-type diet. An uncontrolled calorie restricted MedDiet intervention decreased end glycation products in premenopausal women with excess weight [33]. In a 12-month workplace intervention, without control group, higher MedDiet adherence was associated with significant reduction in abdominal obesity and blood pressure together with improvement in HDL cholesterol levels [34]. Finally, a Chilean RCT is registered to evaluate the effect of avocado supplemented MedDiet on blood lipids in patients with high risk of recurrent ischemic stroke [35]. Thus, additional intervention studies -using a locally adapted and feasible MedDiet intervention- are required to further support and promote the benefits of this eating pattern as a public health policy in Chile.

In the same way as the original Greek term δίαιτα means way of life, a Mediterranean lifestyle embraces beyond mere dietary practice: it is rather a comprehensive *modus vivendi* seeking to promote overall physical health as well as mental and social well-being [36–39]. Considering this broader context in which MedDiet evolved, it is relevant to explore whether adherence to this food intake pattern aligns with science-based models of well-being/mental health [40]. Well-being encompasses three -distinctive but interrelated- positively defined core components: emotional/subjective well-being [41] together with effective functioning of the individual (psychological wellbeing, PWB) [42] within a positive community (social well-being) [43]. This conceptualization fits meaningfully with the full-blown concept of a Mediterranean lifestyle.

Furthermore, several features of PWB are linked to positive biological, behavioral, and health parameters/outcomes [44–47]. In fact, PWB indicators are associated with more salutogenic behaviors (e.g., healthy diet, exercise, good sleep, weight control) and better physiological regulation (e.g., decreased stress hormone levels, downregulated proinflammatory gene expression, reduced inflammatory and CVD risk factors).

Thus, promotion of well-being is an emerging goal in mental healthcare, shifting the focus from merely treating or preventing psychopathology to enhancing positive aspects of mental health [49]. Moreover, positive psychological interventions, such as acceptance and commitment therapy, life review therapy, and well-being therapy, have increased subjective well-being and enhanced positive psychological functioning in clinical and non-clinical populations [48–56]. Positive psychological and mood-related interventions also improved health actions (e.g., medication, diet, physical activity, and exercise adherence) [57,58]. To the extent that well-being interventions are effective in boosting adherence to key health behaviors, they constitute novel tools to improve biomarkers as well as clinical outcomes related to NCDs.

Based on well-being models that are consistent with a positive Mediterranean lifestyle, intervention programs promoting positive psychosocial resources, rather than prioritizing management of stress and depression, may increase adherence to a MedDiet intervention and enhance its impact on NCD risk. Although well-being-based interventions have been designed and evaluated [48–56], none has been specifically tested in terms of cause-effect benefits on MedDiet compliance and subsequent relevant clinical outcomes.

Overall, the main working hypothesis of the CHILEMED trial postulates that a MedDiet intervention -with or without well-being support- is more effective than a low-fat diet for reversion of MetS (primary outcome) and improving additional secondary outcomes at 1-year follow-up. To address this proposition, we describe here an integrative randomized clinical trial aimed to test in Chileans with MetS the effect of PWB theory-based support on adoption and maintenance of long-term adherence to a locally adapted MedDiet pattern as well as the impact

of this MedDiet intervention -implemented alone or combined with PWB promotion- in reversing MetS versus a low-fat diet.

2. Methodology

Overall study design. The CHILEan MEDiterranean (CHILEMED) diet intervention study is an on-going 1-year parallel group RCT including 339 individuals with MetS living in Chile (see estimated sample size in Statistics section). MetS is diagnosed following guidelines from *Ministerio de Salud* (MINSAL) of Chile [3] based on US National Cholesterol Education Program (NCEP) [59] and exclusion criteria are applied (Supplemental Content, Box 1). Participants are assigned randomly to one of the three intervention arms: a) low-fat diet as control group, b) MedDiet alone, and c) MedDiet plus well-being support (Fig. 1). This trial is being currently performed at the Clinical.

Research Center of *Universidad Católica*-Christus Health System in Santiago, Chile and is registered (NCT05454904) at ClinicalTrials.gov website of the US National Institutes of Health and US National Library of Medicine [60].

Recruitment. Our *Aliméntate Sano* initiative [61,62] includes subjects with self-reported MetS who are invited to participate in this trial. In addition, we advertised the study to individuals who attend the *Universidad Católica*-Christus Health System in addition to employees from collaborating institutions. Patient identification and referral are also supported by physicians of the Department of Nutrition, Diabetes and Metabolism from our School of Medicine.

Potential participants are contacted by phone and informed about the study. After ruling out any previous exclusion criteria, those interested who meet at least three diagnostic criteria for MetS are scheduled for the initial screening visit (Supplemental Content, Box 1). Rather than focusing on middle aged adults only, we use a broader age range as inclusion criterion because MetS is being observed in very young adults as well as older patients in our country as consequence of a high and increasing overall prevalence of overweight and obesity at all age ranges [2,4,5]. As suggested based on ethnic specific differences, we apply lower cut-offs for waist circumference as compared to Europids, including the US population. With regard to exclusion criteria, we do not recruit patients with morbid obesity because they require concomitant pharmacologic therapy and/or bariatric surgery, which will significantly confound the impact of the nutritional interventions applied in our trial. Also, we exclude patients with food allergy/intolerance, eating behavior disorders, psychiatric conditions, and restricted access to smartphones and/or online service that may impair adoption/compliance/attendance to the CHILEMED interventions.

Progress in the recruitment process in CHILEMED from August 2021 to September 2022 is shown in Fig. 2.

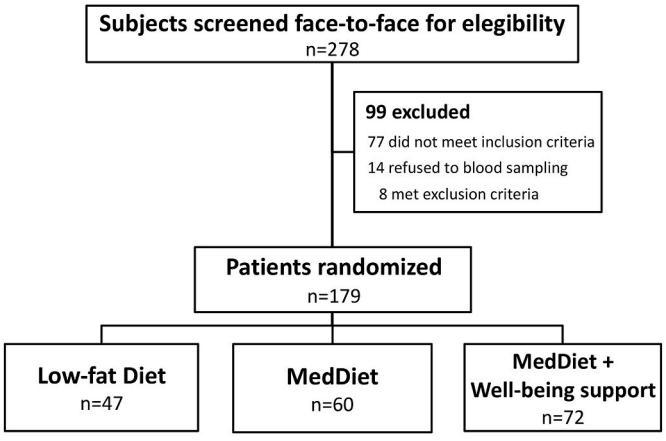

Fig. 1. Flow chart of screening and randomization of CHILEMED participants from August 2021 to September 2022.

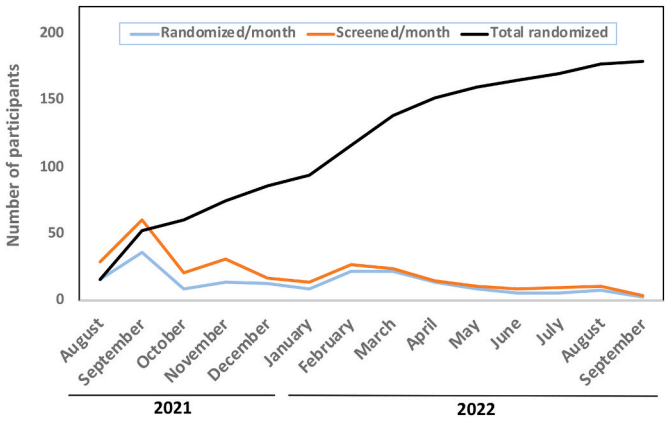

Fig. 2. Progress in recruitment process of participants in the CHILEMED trial from August 2021 to September 2022.

Screening. Baseline evaluation takes 2–3 weeks, including an initial face-to-face screening visit with a physician and a dietitian. Firstly, individuals sign an informed consent, then are asked to provide sociodemographic and medical history/medication use information, and are subjected to physical examination and anthropometric measurements (Table 1).

Under fasting, blood samples are taken for baseline standard and non-routine laboratory testing (see below). Inclusion and exclusion criteria are reviewed and assessed (Supplemental Content, Box 1). If selected to participate, patients are asked to answer a series of online questionnaires to assess food intake (24-h food recalls [63], MedDiet [61] and low-fat diet [64–66] indexes), smoking behavior [61,62], physical activity (Global Physical Activity Questionnaire (GPAQ) short version in Spanish [67]), sleep quality [68], affect (positive and negative affect [69,70]), well-being [71–74], optimism [75], subjective vitality [76], depression/anxiety/stress (DASS inventory [77]), and quality of life [78,79]. With exception of the 24-h food recalls, all questionnaires filled out by the patients are self-administered at baseline as well as during follow-up.

Randomization. Patients are randomly assigned to an intervention group by a computer-generated random number sequence. Allocation concealment is based on obtaining this random number from an independent team investigator for each patient assignment at the time that the participant was evaluated for inclusion in the study. Recruitment aims for equal-sized groups of men and women expecting a balanced distribution by sex and age in each intervention arm.

Nutritional interventions. Regarding nutritional interventions (MedDiet versus low-fat diet), we are mimicking the PREDIMED trial [61–63], a pioneer primary prevention study that demonstrated benefits of the MedDiet on various clinical outcomes [10–13], including MetS [13,16,17]. We use a low-fat diet as a comparator for several reasons. First, we thought that ethically the control group needed an active intervention due to the high risk associated to MetS for NCD development during the one-year follow-up. Second, low-fat diet counseling is still frequently used for CVD prevention in Chile. Third, this pattern was also applied as a control intervention in the well-known PREDIMED trial [64–66]. Thus, similar control and Mediterranean diet interventions in our study versus the Spanish trial will allow somewhat better comparisons of findings on MetS reversal and additional secondary outcomes in CHILEMED versus PREDIMED. In the arms involving only dietary interventions (low-fat diet and MedDiet alone), no psychological counseling is included to isolate and assess the specific effects of each nutritional approach. The third arm applies the same MedDiet intervention combined with PWB support. Nutritional interventions are scheduled and implemented as shown in Table 1.

MedDiet groups are counseled on a dietary pattern including characteristic Mediterranean ingredients locally adapted to Chilean food

Table 1
Evaluation, intervention, and follow-up of patients with metabolic syndrome participating in the CHILEMED trial.

Actions and Assessments	Screening (Week -2/-3)	Time 0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Informed consent	X													
Medical history and medications	X							X						X
Anthropometrics	X							X						X
Physical exam	X							X						X
Fasting blood sample collection	X							X						X
Randomized allocation		XX												
Inclusion/exclusion criteria review	X	X												
Final confirmation for study admission		X												
MedDiet and low-fat diet questionnaire		X			X			X			X			X
24-h food recalls		X						X						X
Physical activity questionnaire		X						X						X
Sleep questionnaire		X						X						X
Smoking questionnaire		X						X						X
Depression/anxiety/stress assessment		X						X						X
Psychological well-being scales		X		X	(X)(X)			X						X
Quality of life questionnaire		X		X				X						X
Online individual nutritional counseling		X	X		X	X			X	X		X		X
Online group nutritional counseling#				X			X			X				
Recipe and cooking videos#		X	X		X	X			X	X		X		X
Individual telephone call					X						X			
Patient recipe contest													X	
Face-to-face nutritional counseling								X						
Online well-being intervention*			X	X	(X)									
Well-being intervention follow-up						X	(X)							

Time 0: randomization and beginning of dietary intervention; M1 to M12: Month 1 to Month 12 of interventions.
#: Additional thematic videos are delivered on food preparations for Independence and Christmas holidays.
*: Online well-being workshop starts within 1–2 months of the nutritional intervention, and it is held weekly for 2 months.

availability and culture. These recommendations are guided by food intake based in the Chilean Mediterranean dietary index (MDI-Chile) [61] (Supplemental Content, Box 2). The low-fat diet group is counseled with a fat-restricted dietary pattern simulating that recommended in the control arm of the PREDIMED trial [64–66] (Supplemental Content, Box 3).

Due to the pandemic situation, nutritional counseling was designed to be performed through an online platform (Zoom) (1st, 3rd, 5th, 8th, and 10th month) with exception of 2nd, 7th, and 11th month cooking video delivery, 4th and 9th month phone calls and baseline, 6th, and 12th final face-to-face visits (Fig. 3). Dietitians oversee the dietary interventions. In the first session, subjects have individual interviews and nutritional advice followed by individual or group (<20 subjects/session) food instruction. Group sessions are organized separately for each intervention arm. Participants also receive information on batch-cooking, seasonal foods, weekly meal plans, and cooking recipes and videos. These latter were selected and/or designed by the research team. Free foods (olive oil at baseline visit and poultry at the 6- and 12-month visits in the MedDiet arms versus to fat-free milk at baseline visit and low-fat pork at the 6- and 12-month visits in the low-fat diet arm) are provided to each participant. Food is delivered at no costs by national food industry. None of the researchers has any financial link/conflict of interest with these food companies.

PWB intervention. In the MedDiet plus psychological support arm, PWB support is being tested as a facilitator to start and maintain a Mediterranean dietary pattern and further improve health-related outcomes compared with the MedDiet arm only. PWB intervention is performed in groups sessions and begins during the first two months of the MedDiet intervention as shown in Table 1.

The well-being intervention is based on the latest empirical findings

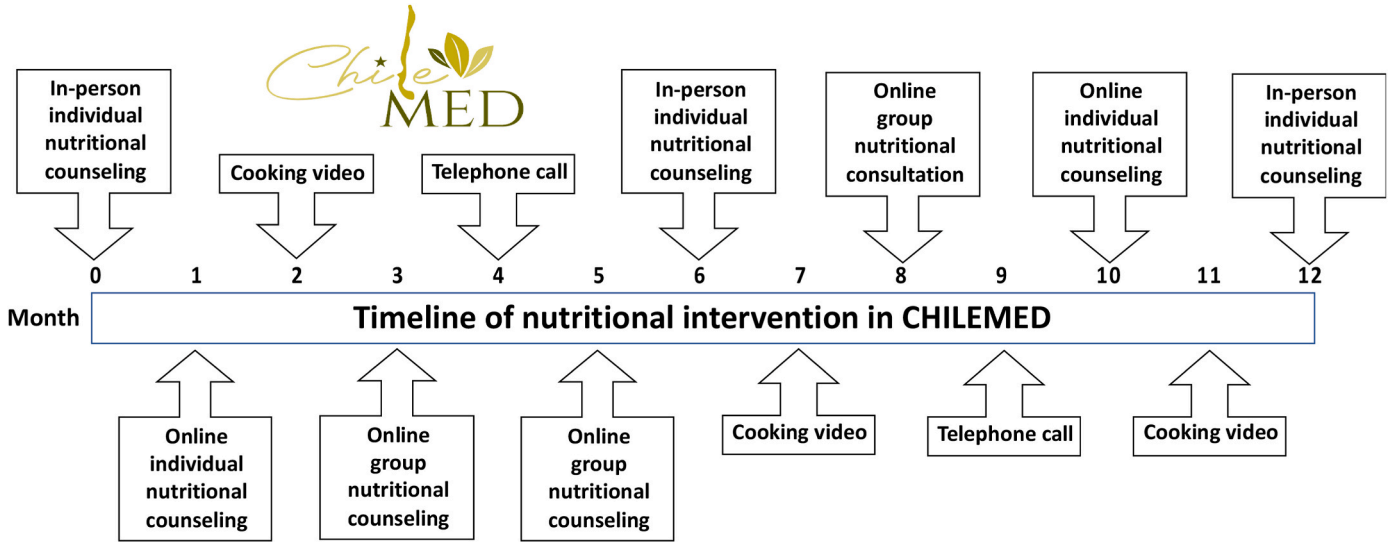

Fig. 3. Timeline and modality of nutritional counseling in the CHILEMED trial. With exception of the specific dietary pattern (MedDiet versus low-fat diet), the schedule and mode of advice are the same in the 3 interventions arms.

from PWB research [48–58], including previous experience obtained from *Lighten Up*!, a community-based well-being program [80,81]. It considers a variety of topics including concepts and activities on well-being, recognition and regulation of emotions, cognitive distortions and reframing, positive relationships through active and constructive communication, personal strengths and purpose identification in order to set goals and define a well-being action plan (Supplemental Content, Table 1).

Group sessions are guided by one coach -previously trainined in well-being and mindfulness interventions-with support from members of the research team. The coach is supervised by a psychologist with expertise in positive psychology and they meet weekly with the research team during the sessions with patients.

The PWB intervention is delivered online (8 weekly sessions, 1.5 h each) to groups of participants ($\leq$20 subjects/session) following a pre-defined sequence available in a printed workbook, where contents and activities for each session are described. Follow-up sessions are held 2 months after the intervention. Well-being group sessions and follow-up are convened separately from the MedDiet intervention in this arm. An online platform with additional well-being information, providing readings and videos, is also available during the 8-week intervention. No extra compensation/gifts are delivered for participation in the PWB intervention.

Follow-up. As shown in Table 1, nutritional follow-up of participants consists of monthly individual and/or group online sessions or phone calls, including dietary information with adjustments of shopping lists and recipes according to seasons of the year.

Food pattern adherence -using MedDiet or low-fat diet indexes depending on the intervention arms- are applied online at 3 and 9 months of the initial dietary advice and psychological assessments are repeated immediately after finishing the well-being intervention.

At 6 and 12 months, face-to-face evaluation re-assessess medical history, medication use, anthropometrics, and physical exam, and blood is collected for laboratory analysis. In addition, assessments of food intake is obtained, along with information on physical activity, smoking, sleep quality, depression, stress, psychological well-being, and quality of life as detailed above. Also, brief nutritional counseling is carried out at the 6th month visit to reinforce the low-fat or Mediterranean dietary pattern and to sustain adherence.

All participants are receiving usual healthcare from their own physicians and the research team is not providing routine medical or psychological care.

We expect a follow-up loss of $\leq$15% in each group assuming that high motivation will be obtained in subjects due to individual/group sessions and free provision of educational material and food items in all groups.

Laboratory assessments. At baseline, 6 and 12 months, serum/plasma samples are processed for blood cell counting as well as standard biochemical, lipid, thyroid hormones, liver, and glucose homeostasis (fasting glycemia, HOMA, HbA1c, and glucose tolerance if required) analyses at the Central Laboratory of *Universidad Católica*-Christus Health System (Santiago, Chile), which is certified by the US Centers for Diseases Control and Prevention.

In addition, several non-traditional/novel biomarkers will be assessed. Blood antioxidants, antioxidant capacity, and oxidative lipid and protein damage will be evaluated [29–32]. Blood oleic and linolenic fatty acid will be assessed by gas chromatography [30]. Commercial kits will be used to measure additional pro- and anti-inflammatory biomarkers. Due to budget limitations, these non-traditional/novel disease biomarkers will be analyzed as exploratory outcomes in a randomly selected subsample of participants at baseline and at the end of the trial.

Study outcomes. *Metabolic syndrome as primary outcome*. The primary outcome of the CHILEMED trial will be the effect of MedDiet with well-being intervention on overall reversal of MetS in comparison with the MedtDiet and low-fat control diet alone. MetS will be assessed at baseline and 6- and 12-months follow-up as indicated above. This study is statistically powered (see below) to demonstrate a significantly higher reduction in MetS in association with adherence to MedDiet -with or without well-being counseling- versus low fat diet intake.

This primary outcome will be assessed categorically (reversal (i.e., $\leq$2 diagnostic criteria of metabolic syndrome) versus non reversal (persistence of $\geq$3 criteria) and expressed as reversal percentage at 12 months after interventions compared to baseline for each patient) applying the current definition of this clinical condition in our country [3]. This assessment will be performed by two independent CHILEMED investigators who are not involved in patient evaluation, nutritional advice, medical counseling, or follow-up.

We will also evaluate a series of secondary outcome as follows.

Dietary adherence. Dietary adherence change will be evaluated using MDI-Chile [61], a low fat-diet score [64–66], and 24-h food recalls analyzed with ESHA Food Processor® Nutrition Analysis software (https://esha.com/products/food-processor/). Adherence to MedDiet will also be tested by measuring blood levels of oleic and linolenic acid [27].

Psychological outcomes. PWB, including a variety of positive psychological features/states/resources, and depression/anxiety/stress will be assessed through different instruments (see above). Psychological outcomes are particularly relevant. Favorable psychological findings after the 8-week well-being intervention will suggest its potential relevance for other outcomes in the MedDiet plus well-being support arm. Thus, well-being indicators -presumably improving over time- will be tested as factors underlying the link between the MedDiet intervention and the primary and secondary outcomes within this arm of the trial.

Anthropometric outcomes. Changes in body weight and other anthropometrics (e.g., waist and hip perimeters) will be evaluated and nutritional status, using BMI, and abdominal obesity, using waist circumference, will be categorized as previously [8,29–34,61,62].

Biomarker outcomes. We will also analyze changes in blood lipids, glucose metabolism-related markers as well as inflammatory, antioxidants and oxidative stress indicators [8,29–32,34,61,62]. In particular, non-traditional/novel disease biomarkers will include cytokines (e.g., high-sensitive CRP, MCP-1, IL-6, TNF-α); oxidative stress indicators (e.g., 1,1-diphenyl-2-picrylhydrazyl (DPPH), carbonyl compounds); and lipoperoxidative damage (e.g., malondialdehyde (MDA), oxidized LDL, peroxidized HDL).

Additional clinical outcomes. Clinical outcomes and event assessments will be based in study follow-up evaluation, self-reporting at study visits, and information collected from participants' physicians in charge of their routine medical care. Blood pressure control will be evaluated by systolic/diastolic measurements as recommended by the American Heart Association scientific statement from the Council on High Blood Pressure Research Professional and Public Education [82]. Type 2 diabetes mellitus will be assessed at baseline and follow-up based on American Diabetes Association definitions [83]. CVD will be registered as composite of major cardiovascular events including definite non-fatal myocardial infarction, coronary/carotid/peripheral revascularization procedures, ischemic stroke, or cardiovascular death.

Statistics. *Sample size estimation*. CHILEMED trial has a statistical superiority design in which the combined MedDiet plus well-being intervention is expected to be more effective than MedDiet alone and both will be better than the low-fat diet for reversion of MetS at 1-year follow-up. Based in previous single reports and metanalyses [13–17],34,84–87], we assumed 28% and 10% MetS reduction in the MedDiet and low-fat intervention groups, respectively. Regarding the additional impact of the PWB intervention, we are not aware of any trial evaluating this approach by itself or associated with any specific dietary pattern on MetS as clinically relevant outcome. Based on associations of baseline well-being status with incidence of MetS, well-being components (i.e., life satisfaction, positive affect, personal growth, and self-acceptance) were significant predictors of lower risk (OR 0.81–0.87) for MetS, even after adjustments by demographics and health covariates [88]. Thus, we estimated a 12% additional reversal rate in MetS due to the well-being intervention, namely overall 40% MetS reduction in the

MedDiet + PWB intervention. Under these assumptions plus 80% power (1-β = 0.8) and 1-α(0.05)/3 comparisons = 0.993 and 15% patient loss in all arms during follow-up [89–92], the total sample size estimation yielded 339 subjects: 3 equal-sized groups of 113 individuals per intervention arm.

Outcome analyses. As measure of efficacy, the primary outcome analysis will be based on intention-to-treat and will compare reversal rates of MetS between the different intervention groups. As estimated above, this trial will be powered to find a statistically significant difference when comparing this outcome between the three planned interventions. Cox regression models will be applied to determine hazard ratio (HR) and 95% confidence intervals for reversion of MetS by MedDiet interventions versus the low-fat diet at 1-year follow-up. HR of MetS reversal will be adjusted by potential confounders, including at least sex, age, energy intake, body mass index, physical activity, smoking as well as use of lipid-reducing, blood pressure-lowering, and antidiabetic medications. Bonferroni method will be used to perform multiple comparisons when exploring a differential effect of each intervention on different components of MetS at the end of follow-up. All p values will be predefined <0.05. Even though the study is not necessarily powered to assess additional outcomes, secondary analyses will also be conducted for body weight, body mass index, abdominal obesity, blood pressure, diabetes mellitus, CVD, depression, and well-being indicators. We will also analyze changes in blood lipids, glycemic indexes, inflammation markers, antioxidants, and oxidative stress indicators. When using a subsample of 51 participants from each intervention group and based in our previous experience in measuring these parameters, we will have at least 80% statistical power to detect significant differences in TNF-α, high-sensitive CRP, MDA, and carbonyl compounds between MedDiet versus low-fat interventions.

Descriptive statistics of central tendencies, dispersions of continuous and categorical variables, regressions, and statistical significance tests will be applied using appropriate software, including SPSS, Stata, SAS, and R as required.

Ethics. The Ethics Committee on Human Research of our institution reviewed and approved protocols, informed consent documents, and subjects' personal data handling of the study before starting this trial.

3. Results

Current recruitment progress, overall demographic, anthropometric, biochemical, and clinical characteristics of participants by allocated groups are displayed in Fig. 1 and Table 2. At this stage of the trial, a total number of 179 patients have been enrolled (Fig. 1), which represent 53% of the estimated total sample size (n = 339, 113 subjects in each intervention arm). Most of the subjects excluded were due to not meeting inclusion criteria for MetS (78%) (Fig. 1).

The randomization procedure is occurring properly, with patients evenly distributed by age (midlife range) and sex, even though slightly more men are included in the MedDiet arm (p = ns) (Table 1). Most anthropometric, biochemical, and clinical covariates are well balanced between groups. Approximately 3/4 of the participants are obese, almost all of them exhibit abdominal obesity, 70% are hypertensive (blood pressure ≥130/85 mmHg), whereas ≤10% exhibits diabetes. After multiple comparisons, the only statistically significant difference found at baseline pertained to total cholesterol values with lower levels detected in the MedDiet group versus MedDiet plus well-being arm (Table 2). This difference is driven by a non-statistically significant trend to reduced LDL cholesterol levels in the MedDiet participants.

Using the Chilean Mediterranean dietary index (MDI-Chile, 0–14 points scoring) [61] and a low-fat diet score (0–9 points) [64–66] to evaluate the overall eating pattern, individuals displayed basal low-to-moderate MedDiet adherence (5,5 points) without differences between intervention arms as well as similar compliance to low-fat diet.

In addition, regardless on the intervention group assignment, patients exhibited similar levels of psychological well-being as measured by the positive mental health scale [70,71].

If patient accessibility and the recruiting process remain as expected, we will reach the estimated total sample size (339 patients) by end of 2023/early 2024.

Table 2
Baseline demographics, anthropometrics, clinical, and biochemical features of patients with metabolic syndrome participating in the CHILEMED trial by group allocation.

	Low-fat diet	MedDiet	MedDiet + Well-Being support	P
Sample size (n)	47	60	72	
Age, years (mean ± SD)	48,9 ± 8,7	47,6 ± 9,9	45,7 ± 10,8	ns
Sex				
Women, n (%)	32 (68)	30 (50)	45 (63)	
Men, n (%)	15 (32)	30 (50)	27 (37)	ns
Waist circumference, cm (mean ± SD)	106,3 ± 8,2	105,0 ± 10,9	105,9 ± 9,0	ns
Body mass index, kg/m^2, (mean ± SD)	32,9 ± 3,2	31,8 ± 4,1	31,7 ± 3,6	ns
Abdominal obesity, n (%)	47 (100)	58 (97)	72 (100)	ns
Obesity, n (%)	37 (79)	43 (72)	53 (74)	ns
Systolic blood pressure, mm Hg (mean ± SD)	128,6 ± 13,8	126,4 ± 13,3	124,5 ± 12,7	ns
Diastolic blood pressure, mm Hg (mean ± SD)	82,2 ± 8,0	82,1 ± 8,9	80,3 ± 8,1	ns
Blood hypertension, n (%)	34 (72)	44 (73)	47 (65)	ns
Total cholesterol, mg/dl, (mean ± SD)	185,5 ± 32,1	178,2 ± 36,4	198,0 ± 38,9	ANOVA: p = 0,008; post-hoc Tukey: p = 0,006 for Med Diet vs. MedDiet + well-being
LDL cholesterol, mg/dl, (mean ± SD)	105,7 ± 26,4	99,6 ± 29,9	113,3 ± 35,4	ns
HDL cholesterol, mg/dl (mean ± SD	42,2 ± 10,0	41,8 ± 8,2	43,0 ± 11,5	ns
Triglycerides, mg/dl (mean ± SD)	184,6 ± 70,8	181,4 ± 78,5	195,9 ± 87,2	ns
Glucose, mg/dl (mean ± SD)	95,0 ± 10,9	96,1 ± 12,7	94,2 ± 10,5	ns
Insulin, uU/ml (mean ± SD)	22,5 ± 8,9	18,6 ± 9,2	19,6 ± 10,5	ns
HbA1c, % (mean ± SD)	5,7 ± 0,4	5,7 ± 0,5	5,5 ± 0,4	ns
Diabetes mellitus, n (%)	4 (5,8)	6 (10)	2 (2,8)	ns
MedDiet adherence, points (mean ± SD)	5,5 ± 1,8	5,5 ± 2,0	5,5 ± 2,0	ns
Low-fat diet adherence, points (mean ± SD)	6,6 ± 1,3	6,7 ± 1,6	6,7 ± 1,4	ns
Positive mental health, points (mean ± SD)	58,8 ± 14,8	62,1 ± 14,1	60,4 ± 13,2	ns

SD, standard deviation; ns, not significant. Abdominal obesity and blood hypertension were defined based on the diagnostic cut-off valuess values used for metabolic syndrome diagnosis.

4. Discussion

This research addresses a potential link between a healthy Mediterranean food intake and PWB in treating MetS, a well-known NCD risk condition, given emphasis to an overarching positive effect of this dietary pattern on physical and mental health. As main findings, we expect

that the theory-guided PWB intervention will facilitate MedDiet initiation and adherence, which in turn will be more effective -compared with a low-fat diet- at reversing MetS. In fact, this expected outcome will highlight the additional value of the PWB intervention in changing food intake through MedDiet counseling when dealing with NCDs.

Some RCTs performed in Europe have evaluated the impact of MedDiet on various individual components of MetS indicating that this dietary pattern has beneficial effects in improving most of MetS features [93]. However, significant diverseness in methodologies and findings was detected [93]. Remarkably, very few RCTs -all again carried out in European countries- have evaluated the effect of MedDiet on overall MetS. A study conducted in Italy with 180 patients diagnosed with MetS revealed that a MedDiet was better at decreasing the prevalence of MetS and related CVD risk factors compared with a low-fat diet [94]. In addition, results from the PREDIMED study with ≈5-year follow-up showed that MedDiet -versus a low-fat diet- caused reversion of MetS, but it did not prevent incident cases [95]. The ongoing PREDIMED-Plus trial (http://www.predimedplus.com) is evaluating MedDiet with caloric restriction and weight loss and has reported some preliminary findings on body weight, waist circumference, and metabolic markers after 12 months of follow-up [96]. Similarly, the CORDIOPREV trial more recently showed that adherence to a MedDiet intervention attenuated the risk of MetS development and increased the chance of reversing preexisting MetS [97].

If findings turn out as expected, CHILEMED will provide additional evidence on the beneficial effect of the MedDiet -facilitated by a PWB intervention- on MetS beyond the Mediterranean Basin, including our own country whose central region exhibits various Mediterranean-like food production features that are not currently well-known, promoted nor fulfilled at large scale.

About designing and implementing the PWB intervention of this trial, we have previous experience in well-being evaluation in Chilean subjects, its relationship with lifestyle behavior, and its application in locally developed pilot interventions in different study samples and contexts with positive findings [72,98–105]. Furthermore, two members of the research team have developed and successfully applied a well-being program at community level [80,81]. This combination of local expertise with support from external collaborators provides high chance of success in accomplishing the well-being-related aims of CHILEMED.

Regarding the nutritional counseling, strengths are due to the controlled and randomized design in a real-life scenario, previous experience in pilot MedDiet interventions [26–34], locally adapted and tailored MedDiet, use of a validated Chilean MedDiet index [61,62], and close participant monitoring. Also, aiming to a PREDIMED-like overall intervention [64–66], we will be able to make more reasonable comparisons between studies and to eventually reproduce previous findings of MedDiet on MetS [17]. Finally, secondary outcome comparisons, particularly assessing intermediate biomarkers, will identify possible mechanisms underlying MedDiet and PWB-dependent reversal of MetS.

Due to the pandemic situation at the beginning of the trial, CHILEMED developed a remote electronic counseling approach, which may reduce barriers and constraints related to time restrictions, commute burden, patient detachment, socioeconomic conditions, and low interest for in-person contact. However, modern technology may be challenging to establish and maintain patient's attention and empathetic relationships. Thus, vigilance is required, and face-to-face interpersonal interactions are planned at baseline and 6 months as critical in-person visits for more effective nutritional counseling.

Weaknesses include participants' resistance to changes in long-established dietary habits, risk of incomplete data due to losses at follow-up, or differential drop out between groups. To facilitate compliance, we will promote personal interaction and motivation in each participant through individual and group sessions, give individual feedback of progress at 6 months, and provide free foods as a thank you and encouragement for participation in the study. Uniformity in lifestyle and psychological interventions will be challenging, but detailed intervention protocols have been designed, and will be implemented and assessed during the trial, including careful beforehand research staff training. In addition, various lifestyle questionnaires applied throughout the study will allow us to visualize and adjust our analyses for diet adherence and possible changes in other health behaviors. Additional weaknesses are the use of online self-administered and -reported questionnaires. Also, all participants will maintain routine healthcare from their own physicians, which will not allow full control on management of their clinical conditions during the study.

When studying the effect of the PWB intervention and its potential synergistic influence with MedDiet, the current design of CHILEMED shows limitations as an approach to assess their interaction. A factorial design would be the best methodology. However, we could not develop such a study due to limited resources to implement a much larger trial.

Based on this locally generated evidence, MedDiet with PWB intervention might be more compellingly applied -at individual and population levels- to promote physical and mental health, more specifically to prevent and treat MetS, a highly prevalent and significant risk condition for NCDs in Chile.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101167.

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