Clinical and cost-effectiveness of remote-delivered, online lifestyle therapy versus psychotherapy for reducing depression: results from the CALM non-inferiority, randomised trial

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Summary

Background We conducted the first non-inferiority, randomised controlled trial to determine whether lifestyle therapy is non-inferior to psychotherapy with respect to mental health outcomes and costs when delivered via online videoconferencing.

Methods An individually randomised, group treatment design with computer-generated block randomisation was used. Between May 2021–April 2022, 182 adults with a Distress Questionnaire-5 score = ≥8 (indicative depression) were recruited from a tertiary mental health service in regional Victoria, Australia and surrounds. Participants were assigned to six 90-min sessions over 8-weeks using group-based, online videoconferencing comprising: (1) lifestyle therapy (targeting nutrition, physical activity) with a dietitian and exercise physiologist (n = 91) or (2) psychotherapy (Cognitive Behavioural Therapy) with psychologists (n = 91). The primary outcome was Patient Health Questionnaire-9 (PHQ-9) depression at 8-weeks (non-inferiority margin ≤2) using Generalised Estimating Equations (GEE). Cost-minimisation analysis estimated the mean difference in total costs from health sector and societal perspectives. Outcomes were assessed by blinded research assistants using Computer Assisted Telephone Interviews. Results are presented per-protocol (PP) and Intention to Treat (ITT) using beta coefficients with 95% Confidence Intervals (CIs).

Abbreviations: NICE, National Institute for Health and Care Excellence; CALM, Curbing Anxiety and depression using Lifestyle Medicine; HREC, Human Research Ethics Committees; DSMB, Data Safety Monitoring Board; CONSORT, Consolidated Standards of Reporting Trials; DQ5, Distress Questionnaire-5; CBT, Cognitive Behavioural Therapy; PHQ-9, Patient Health Questionnaire-9; DSM, Diagnostic & Statistical Manual of Mental Disorders; US, United States; MINI, Mini-International Neuropsychiatric Interview; AQoL 4D, Assessment of Quality of Life; IBS, Irritable Bowel Syndrome; QALYs, Quality-adjusted life years; K-10, Kessler-10; GEE, Generalised Estimating Equations; ANCOVA, Analysis of Covariance; CIs, Confidence Intervals; PP, Per- Protocol; ITT, Intention to Treat; meGLM, Multilevel Mixed-effects Generalised Linear Model; AUD, Australian Dollars; SD, Standard Deviation; MEDAS, Mediterranean Diet Adherence Score; NHMRC, National Health and Medical Research Council

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Findings The sample was 80% women (mean: 45-years [SD:13.4], mean PHQ-9:10.5 [SD:5.7]. An average 4.2 of 6 sessions were completed, with complete data for n = 132. Over 8-weeks, depression reduced in both arms (PP: Lifestyle (n = 70) mean difference:−3.97, 95% CIs:−5.10, −2.84; and Psychotherapy (n = 62): mean difference:−3.74, 95% CIs:−5.12, −2.37; ITT: Lifestyle (n = 91) mean difference:−4.42, 95% CIs: −4.59, −4.25; Psychotherapy (n = 91) mean difference:−3.82, 95% CIs:−4.05, −3.69) with evidence of non-inferiority (PP GEE β:−0.59; 95% CIs:−1.87, 0.70, n = 132; ITT GEE β:−0.49, 95% CIs:−1.73, 0.75, n = 182). Three serious adverse events were recorded. While lifestyle therapy was delivered at lower cost, there were no differences in total costs (health sector adjusted mean difference: PP AUD$156 [95% CIs −$182, $611, ITT AUD$190 [95% CIs −$155, $651]]; societal adjusted mean difference: PP AUD$350 [95% CIs:−$222, $1152] ITT AUD$ 408 [95% CIs −$139, $1157].

Interpretation Remote-delivered lifestyle therapy was non-inferior to psychotherapy with respect to clinical and cost outcomes. If replicated in a fully powered RCT, this approach could increase access to allied health professionals who, with adequate training and guidelines, can deliver mental healthcare at comparable cost to psychologists.

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Keywords: Lifestyle psychiatry; Digital health; Psychotherapy; Mental health; Non-inferiority

Research in context

Evidence before this study

Members of our team conducted a systematic search of the literature as part of a 2020 meta-review of lifestyle therapies for mental disorders (including exercise and nutritional interventions). On Feb 2, 2020 the Allied and Complementary Medicine (AMED), PsycINFO, Ovid MEDLINE, Health Management Information Consortium, EMBASE and the NHS Economic Evaluation and Health Technology Assessment databases were searched. The most recent and largest of the identified meta-analyses examining 35 superiority RCTs using waitlist, treatment as usual, patient education and/or placebo controls, found moderately large benefits of exercise for adults with depressive disorders (SMD = −0.66, 95% CI: −0.86 to −0.46, I^2 = 81%) but identified no randomised clinical trials comparing exercise interventions to other empirically supported treatments using a non-inferiority design. A 2019 meta-analysis by members of our team testing the efficacy of dietary interventions for (most commonly) sub-threshold depression found that dietary interventions improved depressive symptoms (g = 0.162, 95% CI = 0.055–0.269, p = 0.003) but also found no trials directly comparing this approach to psychological therapies.

Added value of this study

The Covid-19 setting, characterised by high levels of community distress and remote-delivered mental health services, introduced a key opportunity to address this critical clinical and knowledge gap. Here, we show for the first time using a non-inferiority trial that remotely-delivered, online lifestyle therapy (exercise and nutritional counselling with a dietitian and exercise physiologist) is as clinically and cost-effective as psychological treatment (psychotherapy with psychologists) of similar intensity and frequency for reducing depressive symptoms. The cost of delivering lifestyle therapy was AUD$21 per participant less than that of delivering psychotherapy largely due to clinician hourly rate.

Implications of all the available evidence

Accredited practicing dietitians and exercise physiologists have potential to provide mental health care with no lesser effects than CBT with psychologists and that this can be done remotely, via online videoconferencing. Given that the total University course and clinical training costs of dietitians (AUD$153,039) is cheaper and of shorter duration than psychologists (AUD$189,063) in Australia, there may be opportunity for allied health professionals, with appropriate support, to relieve some of the service provision burden on the mental health care system.

Introduction

Depression is one of the most common mental disorders worldwide, ranking among the top 25 causes of global disease burden.[1] This is true for both sexes, at all ages of the lifecourse, and across most regions.[1] Despite efforts to increase treatment access,[2] there has not been a notable reduction in the rates of depression since 1990.[1] Since the onset of the Covid-19 pandemic alone, over which time generalised distress in the community was substantially elevated, 50-million new cases of depression were recorded worldwide.[3] Unprecedented demand for mental healthcare has stretched existing

services and workforces,[4] and accentuated the urgent need for new, scalable care options especially for those living in regional communities or resource poor settings.

Psychological distress is commonly used in clinical practice as an indicator of depression 'cases' in accordance with the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) and the International Classification of Diseases–10th Edition (ICD-10).[5] Where depression is detected, promisingly, lifestyle therapies which target physical activity and dietary intake have surfaced as a new treatment option for a range of mental health presentations-from subthreshold to major depression.[6] Such treatments are clinically efficacious and cost-effectiveness when delivered in individual or group settings relative to sham, inactive, or comparator conditions like social support controls.[6] The Royal Australian & New Zealand College of Psychiatrists' guidelines for the management of mood disorders now endorse lifestyle therapies (including physical activity and nutritional counselling) being administered "alongside or before prescribing any form of treatment".[7] The National Institute for Health and Care Excellence (NICE) guidelines[8] also recommend exercise as an adjunctive treatment for depression.

This approach has not, however, been firmly integrated into routine mental healthcare. Barriers include accessibility to allied health professionals especially in rural and remote locations, and a critical absence of data showing it is as effective as the current standard in mental health care–psychotherapy delivered by psychologists.

Cognitive behavioural therapy (CBT) is widely recognised as a gold-standard, psychotherapeutic approach for a range of mental health presentations and is superior to pharmacotherapies over the longer term.[9] Its effectiveness has been extensively tested and professional practice standards and outcomes are comparable for face-to-face and on-line videoconferencing.[10] For individuals with depression, referral to a psychologist for CBT forms a key part of guideline-based best practice.[8] A range of non-inferiority trials have been conducted directly comparing CBT as the referent to other psychological treatments (e.g., experiential therapy[11]) but not against emerging treatments like lifestyle therapy. A non-inferiority trial, unlike a superiority trial, is a specific study design intended to demonstrate whether one treatment is no worse than or equivalent to a proven active control condition by an acceptably small amount within a given degree of confidence.[12]

The Covid-19 setting, characterised by high levels of community distress and remote-delivered mental health services, introduced a key opportunity to apply this study design to address this critical clinical and knowledge gap by harnessing a scalable digital platform. Here, we present the results of the first non-inferiority trial to directly compare the clinical and cost-effectiveness of remote-delivered, online lifestyle therapy using videoconferencing to psychotherapy for depression over an 8-week period as well as the results of the pre-specified within-trial economic evaluation.

Methods

Study design

The Curbing Anxiety and depression using Lifestyle Medicine (CALM) trial was an investigator initiated, two-arm, parallel-group, non-inferiority trial using individually randomised group treatment. This study design did not employ a placebo or other control group as the efficacy of each condition is well established and it was deemed unethical to not provide mental health intervention to Victorians throughout Covid-19 lockdowns (the strictest and longest globally, averaging 200+ days).[13] This was a single site trial recruiting from Barwon Health's Mental Health, Drug and Alcohol Service–a tertiary mental health service in the south western region of Victoria, Australia, and surrounding regions. The trial protocol has been published previously[14] and was approved by the Barwon Health (20/199) and Deakin University (2021-166) Human Research Ethics Committees (HREC). The trial was conducted in accordance with principles of the Declaration of Helsinki, Australian National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95). All participants provided written informed consent. The trial was overseen by Chief and Associate Investigators (Appendix A-Governance Structure) and an independent Data Safety Monitoring Board (DSMB) (Appendix B-Members). All protocol amendments are provided as Supplementary material. Co-authors assume responsibility for data accuracy and completeness, trial fidelity, and manuscript contents. Findings are reported using the 2017 CONSORT Statement Extension for Non-inferiority and Equivalence trials[15] and 2018 Extension for Social and Psychological Interventions[16] and the TIDieR intervention checklist.[17] The trial was registered with the Australian New Zealand Clinical Trials Registry (Registry number: ACTRN12621000387820).

Participants

Participants were adults (aged 18+ years) who: could provide written informed consent; were proficient in verbal English; could attend six 90-min sessions; had basic digital literacy (devices/internet were loaned if required); and who scored Distress Questionnaire-5 (DQ5) score = ≥8.[5] This cutoff was selected as it is a commonly accepted criterion used to identify likely caseness of depression.[5] DQ5 assesses mental health over the past 30-days using 5-point Likert scales. Total scores range from 5 to 25. It is brief, has a low response burden, and external validity, and more accurately

measures distress and common mental disorders than other tools. At their recommended cut off for detecting major depressive disorder, the DQ5 and PHQ9 both have high internal consistency (Cronbach α = 0.86 and α = 0.87 respectively).[5] A DQ5 score of 8+ is equivalent to PHQ9 = 5, indicative of subthreshold depression.[5] Exclusion criteria included: clinically unstable medical disorder; current/past formally-diagnosed eating disorder; severe dietary allergies, intolerances or aversions; socio-cultural, religious, or medical reasons interfering with participation; enrolment in another trial; or planned), pregnancy or breast feeding/lactating. Participants continued taking prescribed pharmacological or other treatments unless commencing new or duplicating treatment in the 4-weeks before baseline. Demographic data including sex assigned at birth (male/female), country of birth, age, postcode, medications, nominated General Practitioner/case manager were self-reported by participants.

Randomisation and masking

Upon enrolment by trial staff, participants were assigned a unique study identification number for randomisation purposes. Randomisation occurred after baseline assessment once sufficient numbers of participants were enrolled to form a group (minimum n = 10 per block, i.e., 5 per group). In each block, participants were assigned their allocation in a 1:1 ratio. An independent statistician conducted this process using computer-generated randomisation inaccessible to investigators. The sequence was concealed until treatments were delegated to participants by the Study Coordinator. The DSMB assessed violations of blinding protocols and mitigation strategies (Appendix C). Treatment commenced within 2–7 days. Data assessments were conducted by blinded Research Assistants (Bachelor psychology with honours) via computer-assisted telephone interview before randomisation (baseline), repeated at program completion (8-weeks). This was a single-blind trial. Participants and interventionists could not be blinded to group allocation. Investigators and the study statistician remained blinded. Participants were instructed to conceal their treatment from data assessors.

Procedures

All procedures except pathology were remote-delivered: Zoom videoconferencing[18] [intervention](group), telephone [assessment](one-on-one), email [enrolment, general communication](one-on-one). Both treatments comprised six group-based sessions (4–10 people) via videoconferencing over 8-weeks, manualised to promote standardisation and reproducibility. Sessions were supplemented with respective workbooks containing resources and homework activities. A hamper containing food produce, a TheraBand, and a Fitbit (lifestyle arm) or self-soothing products (colouring book, head massager, stress ball) and mindfulness apps (psychotherapy arm) were provided. Session scheduling (date/time) was matched for conditions. A mental health research nurse was available to all facilitators for clinical consultation. Sessions were recorded and 10% independently assessed by an interventionist not facilitating that group using fidelity checklists developed for that therapeutic condition (Appendix F) using clinical judgment and training to determine the extent which facilitators adhered to the prescribed modules, content and behavioural techniques.

Intervention protocol development

Intervention development has been described previously.[14] Fig. 1 shows the programs' Curricula. In their design, we acknowledged overlapping techniques across allied health disciplines (e.g., motivational interviewing, goal setting, some behavioural activation) yet clear distinction was made in behavioural content for each. Nutrition and movement (and by association, sleep and alcohol/other drugs) was the strict remit of the lifestyle interventionists. Other areas of behavioural activation (e.g., social support, hobbies) were the remit of psychotherapists. We considered this the most appropriate way to use respective expertise while reducing intervention contamination for the purpose of hypothesis testing.

Experimental condition (lifestyle therapy)

The lifestyle program was co-developed and co-delivered by Dietitians and Exercise Physiologists who were accredited by and current members of Dietitians Australia (DA) or Exercise and Sport Science Australia (ESSA), respectively. Participants' targets/goals centred around nutrition and activity but could integrate alcohol, smoking, substance use, and/or sleep hygiene. All facilitators had advanced training in health coaching, motivational interviewing, goal setting and mindfulness and completed mental health first aid training. Program adaptation and theoretical underpinnings have been published.[19] Body weight was not a focus as the benefits of lifestyle therapies for depression occur independently of weight change.[20] Participants worked with facilitators to establish personal goals for positive lifestyle change. At session commencement, participants could ask questions arising from or since the previous session, discuss their goals and homework. At the final session, goals achieved during the intervention period were discussed and strategies for maintaining changes were identified including sources for additional information and peer support.

Proven active control condition (psychotherapy)

The psychotherapy program used a Cognitive Behavioural Therapy (CBT) approach adapted from the manualised, group-based Mood Management Course.[21] CBT proposes that the cognitive and behavioural factors that maintain mental distress are amenable to change

	Lifestyle Program Content	Psychotherapy Program Content
Session One	1. Meeting guidelines and house keeping 2. Introductions 3. Overview of CALM • CALM goal and objectives. • Program rationale 4. Why, what and how? 5. Program meeting schedule 6. Hamper 7. Nutrition content • ModiMed Diet food pyramid • Serving sizes • Key foods and nutrients for mental health 8. Physical activity content • Physical activity and mental health • Physical activity recommendations • Physical activity safety considerations • Aerobic physical activity • Fitbit and Physitrack app 9. Goal Setting • Goal setting explained • Setting new goals 10. Homework • Complete ModiMed Diet intake checklist • Complete physical activity strategies and track progress	1. Introductions 2. Group guidelines 3. What is CBT? • Brainstorming symptoms of low mood and anxiety – dividing symptoms into feelings, thoughts, behaviors, and physical symptoms. • Psychoeducation regarding CBT model 4. How might I use CBT to help me? • Psychoeducation regarding an individual formulation that identifies predisposing, precipitating, perpetuating, and protective factors 5. Values and Goals • Developing a SMART goal related to top 3 values 6. Mindfulness activity • Complete a mindfulness activity, psychoeducation regarding the value of practicing mindfulness, introduction to Subjective Units of Distress ratings pre-post mindfulness activities to monitor arousal. 7. Wrap up and home practice • Summarize session & suggest ideas to work on during the week
Session Two	1. Discuss questions from previous session, discuss goals and homework, provide feedback and troubleshoot issues 2. Nutrition content • Balanced plate model and activity • Creating healthy meals • BRAINY snacks 3. Physical activity content • Resistance physical activity • Getting started – practical example of movements • Progression using frequency, intensity, time and type principle 4. Goal setting • Setting new goals 5. Homework • Fill in shopping list • Identify ways to achieve 30 minutes of physical activity throughout the day and track progress	1. Mindfulness activity • Body scan 2. Check in • Reflection and feedback on previous session and homework activities. 3. What are feelings? • Play a mix of different songs and reflect on emotional and physiological responses as the songs played and transitioned. • Psychoeducation regarding labelling and accepting feelings. 4. Flipping our lid • Psychoeducation regarding fight-flight response and managing this response through calm breathing. 5. Activators/soothers • Group discussion on activators (mood boosters) and soothers (helpful when feeling anxious) • Introduction to activity scheduling 6. Wrap up and homepractice • Summarize key concepts covered and invite the group to think about what they can work on outside of the session 7. Conclude session with mindfulness activity

Fig. 1: Session Content, by treatment arm.

Session Three	1. Discuss questions from previous session, discuss goals and homework, provide feedback and troubleshoot issues 2. Nutrition content • Dietary fats and practical tips for including in the diet. • Dietary fibre and practical tips for including high-fibre foods • Label reading 3. Nutrition and physical activity content (group discussion) • Barriers and enablers to lifestyle changes • If-then plans. 4. Goal setting • Setting new goals 5. Homework • Download FoodSwitch Australia App and explore healthier alternatives to existing choices • Complete the physical activity tracker	1. Mindfulness activity • Soothing touch 2. Check in • Reflect on previous session 3. Activity logs • Group discussion and sharing of ideas regarding activating and soothing activities completed during the week. 4. Fun activities • Psychoeducation regarding scheduling 'fun' activities as a potential mood booster 5. What are your thoughts and why do they matter? • Psychoeducation on neuroplasticity and how thoughts can influence our feelings and behaviors 6. Thoughts vs. feelings • Group activity identifying thoughts and feelings from a list (e.g., I feel useless, I feel like I will always feel this way, I am scared) 7. The value of noting down thoughts • Introduction to thought logs • Psychoeducation about viewing thoughts objectively and with curiosity to aid perspective taking 8. Wrap up and home practice Mindfulness activity to close session
Session Four	1. Discuss questions from previous session, discuss goals and homework, provide feedback and troubleshoot issues 2. Nutrition content • Hunger and satiety signals • Mindful eating • Addressing non-hungry eating • Tips for managing poor appetite 3. Physical activity content • Sedentary behavior and mental health • Practical examples – "physical activity snacks" • Physical activity and mood • Mindful physical activity 4. Goal setting • Setting new goals 5. Homework • Complete steps to a mindful lifestyle worksheet • Complete physical activity tracker	1. Mindfulness activity • Leaves on a stream 2. Mid-point check in and progress review • Opportunity to review goals and progress made towards goals 3. Thinking traps • Group activity "thinking trap bingo" – to engage in psychoeducation about unhelpful thinking styles. 4. Catch, check, change • Psychoeducation regarding the concept of catching thoughts (through thought logs), checking thoughts (is this a thinking trap? Is this thought helpful to me?) and changing thoughts (cognitive disputation and balanced thinking) 5. Wrap up and home practice 6. Mindfulness activity to close session

Fig. 1: (continued)

through recognising and challenging these unhelpful patterns. This program was co-facilitated by two psychologists (a registered psychologist, provisional psychologist nearing the end of their training, and/or trainee psychologist) with experience facilitating groups and/or training in CBT. Briefly, content focused on promoting self-awareness skills, identifying and managing unhelpful behaviours and thoughts, and adopting and practicing strategies for self-management. The program also incorporated mindfulness practices, as there is evidence that its integration into CBT can improve clinical outcomes.

Session Five	1. Discuss questions from previous session, discuss goals and homework, provide feedback and troubleshoot issues 2. Nutrition content • Recipe modification • Eating out and take-away meals 3. Physical Activity Content • Social support • Physical activity and support groups • Physical activity at home • Local physical activity options 4. Goal setting • Setting new goals 5. Homework • Incorporate household items into daily exercise • Complete physical activity tracker • Complete ModiMed diet weekly checklist	1. Mindfulness activity • Progressive muscle relaxation 2. Check in and homework review (including problem solving any difficulties with thought logs and thought diaries) 3. Putting thoughts to the test • Introduction to behavioral experiments • Group activity brainstorming potential behavioral experiments 4. Pulling together – home practice 5. Mindfulness activity to close session
Session Six	1. Reflection and progress review • Celebrate progress • Dealing with set-backs • Ways to stay motivated and how to maintain changes 2. CALM trial summary • Long term goals setting/ supporting sustainable change (including during future lockdowns) • Sources for additional information and peer support	1. Mindfulness activity • Reflection on how participants felt at the beginning of the program and how they are feeling at the end 2. Check in & homework review • Reflections on the previous fortnight 3. Skills recap • Group activity brainstorming all topics, skills, and concepts covered across previous 5 sessions. Skills were divided into thoughts, feelings, behaviors, and physical symptoms. 4. Lapse and relapse • Psychoeducation regarding the difference between lapsing and relapsing and planning ahead to manage lapses (such as knowing triggers, making new goals, and noticing thought traps) 5. Coping ahead • Explanation of coping ahead and example of using imaginal exposure to manage feared situations. 6. Self-management plan • Group activity completing a self-management plan (this included: what was my goal at the beginning, what skills have I found most helpful, what will I continue using in the future, what goal might I like to work on next) 7. Farewells & goodbye • Facilitators provided feedback to each participant about their unique contribution to the group and shared a collective hope for the group 8. Mindfulness activity to close session • Meditative mindfulness exercise focused on the beginning and ending of all things

Fig. 1: (continued)

Outcomes

The primary outcome was the commonly used Patient Health Questionnaire-9 (PHQ-9).[22] This tool measures depressive symptoms over the preceding 2-weeks with proven diagnostic accuracy against Diagnostic & Statistical Manual (DSM) of Mental Disorders criteria for depression (IV and V). The PHQ-9 was designed for clinicians in real-world settings, like primary care, and is recommended by the US Preventive Services Task Force and the International Alliance of Mental Health Research Funders' Common Measures Board for Mental Health Science. The primary outcome measure (PHQ-9) was different to the eligibility measure (DQ5) to reduce the impact of regression to the mean, which can inflate effect sizes.[23] To further consider possibility of regression to the mean, we present our primary outcomes against population trajectory PHQ9 data for Victorians who did not receive intervention over the trial period.

Secondary outcomes and collection methods are provided in the published protocol[14] and the Results section (Table 2). An additional baseline data collection module (structured clinical psychiatric interview; Mini-International Neuropsychiatric Interview [MINI]) was administered by a psychologist to characterise the sample's psychiatric profile. The AQoL-4D was used to measure participant's preference-based health-related quality of life, with the Australian general population preference weights applied to calculate utility values at each timepoint. These utility values were then used to estimate quality-adjusted life years (QALYs) based on the area-under-the-curve method. A self-reported resource use questionnaire was also completed at each follow-up, capturing healthcare utilisation, time off from paid and unpaid work (absenteeism), and days working at reduced capacity while at paid and unpaid work (presenteeism) due to health problems.

For both arms, group engagement at sessions was measured from facilitators' and participants' perspective by anonymous Zoom poll with Likert scale at completion (How engaged did you feel with others in the group today? 5 = Very to 1 = Disengaged). Participants reported safety events fortnightly and pre- and post-intervention using an adverse events questionnaire (adjudicated by the Study Coordinator, confirmed by medical personnel). General distress was monitored weekly by facilitators using the 10-item Kessler-10 (K10) for safety as it is commonly used in clinical care and promotes real world application (while the DQ5 is accurate as a brief screening tool to identify depression caseness). An escalation of care protocol was activated, where an increase of more than 0.5 standard deviations or a K10 score increase >30 between sessions was detected. Safety events were aggregated and reported to the DSMB by the Study Coordinator; the DSMB was responsible for identifying patterns of safety events and relatedness to either intervention. DSMB members and the HREC were notified of any serious adverse events.

Statistical analysis

The non-inferiority margin was set at ≤2 PHQ-9 points.[11] This margin is commonly used across depression trials[11,24] comparing psychological interventions using PHQ9 as the primary outcome based on its psychometric properties. It is considered by clinicians to not be a clinically important difference.[11] Our target sample size required to detect the non-inferiority margin was $n = 184$ ($n = 92$ per arm) (one-sided type I error = 0.025, 80% power), which was inflated by 15% to allow for attrition. The Intra Class Correlation was set at 0.01. As the final randomised sample was $n = 182$ (n = 91 per arm) for ITT analyses and $n = 132$ completers for PP analyses, we conducted a post-hoc sample size calculation. Based on a one-sided type I error = 0.025 and 80% power, the PP analysis comprising n = 132 had the power to detect a SD 0.54, equivalent to a difference of 2.5 on the PHQ-9 scale, meaning the results of the primary outcome were underpowered and should be interpreted with this in mind. Chi-square and Wilcoxon tests were applied to examine baseline characteristics of treatment arms. Outcomes were analysed using Generalised Estimating Equations (GEE) with Huber Sandwich Estimator of variance to account for clustering (i.e., group blocks). GEE is an ANCOVA-based model that accounts for baseline scores as covariance. When baseline imbalances were identified, we re-ran the main effects model to adjust for variables considered to be on the causal pathway with the outcome as part of sensitivity analyses. Analyses were performed using Stata Version 17.0. Magnitudes of effect were presented as beta values with accompanying 95% Confidence Intervals (95% CIs). In non-inferiority trials, intention-to-treat (ITT) analyses can bias findings to appear that two conditions produce similar results, whereas per-protocol (PP) analyses can offset any theoretical increase in type I error risk that results in erroneously concluding non-inferiority.[25] Here, we include both PP and ITT analyses; the greatest confidence for non-inferiority occurs when results are concordant.[26] ITT analysis was based on multiple imputation chained equations and observed data at 8-weeks follow-up to allow analysis of all 182 randomised individuals. We included fully observed demographic data in the imputation to improve model performance. All analyses were conducted blind to treatment allocation. Because there was no placebo or inactive control, we used data from a nationally representative sample of Australians collected via the Australian National COVID-19 Mental Health, Behaviour and Risk Communication project[27] against which to compare 8-week trajectories of PHQ9 depression scores of both treatment arms. This was a longitudinal cohort study comprising seven fortnightly surveys (including the PHQ9) of a representative sample (n = 1296) from late March 2020 to mid-June 2020. For the purpose of this paper, we derived data from Victorian participants from Wave 3 and Wave 7 who provided PHQ9 responses on both occasions (n = 170). To test the possibility of

spontaneous remission, we tracked the recovery status (achieving a K-10 score of 19 or less) of participants in each treatment arm by week using a Kaplan Meir Curve and by their level of exposure to the intervention (completers = 3+ sessions versus non completers 0–2).

The pre-specified within-trial economic evaluation focused on cost-minimisation due to the non-inferiority study design.[28] Details of the economic evaluation are provided in Supplementary Appendix F, but briefly, a micro-costing approach was used to estimate the economic cost of running the lifestyle and psychotherapy interventions. The intervention costs were estimated using trial data records, which included costs of facilitators' time, workbooks, and all items (e.g., hamper contents) provided to participants. Total costs were analysed from both the health sector and societal perspectives. The health sector perspective included costs related to health professional visits, emergency department visits, hospital admissions, self-help materials, medicines, and intervention costs. The societal perspective comprised the same costs as the health sector perspective with the addition of productivity losses. Base-case analyses were conducted on the PP population and multiple imputation with chained equations was used to handle missing data. The differences in mean costs were estimated using multilevel mixed-effects generalised linear models (meGLM) with the gamma family and log link, with adjustment for baseline covariates (i.e., sex and baseline costs) and accounting for clustering (group blocks). Univariate sensitivity analyses explored the effects of varying the cost of delivering the interventions, analysing the ITT population and complete cases (participants with complete cost and QALY data). All costs are presented in 2021 Australian dollars (AUD). Results are presented in the paper as PP and the ITT analysis provided in Supplementary Table S9.

Role of funder

Funders did not influence trial design, conduct, data analysis, or results.

Results

Key sample characteristics

We enrolled 201 participants between May 2021 and February 2022 and completed the main trial when follow-up assessments were completed in April 2022. Fig. 2 displays reasons for exclusion, drop-out and loss to follow-up. Table 1 displays the key characteristics by treatment arm. Most participants (80%) were female (mean age: 45-years [SD: 13.4]). Overall, participants' mean PHQ-9 score was 10.5 [SD:5.7](moderate depression). Over half were taking psychiatric medication (52.8%) and 40% met criteria for a psychiatric diagnosis on the MINI.

Intervention delivery and engagement

Of those who commenced treatment, 145 (79.6%) completed 3 or more of 6 sessions. There were no between-arm differences in intervention exposure (i.e., session and overall attendance was comparable (data not shown)). Participants receiving lifestyle or

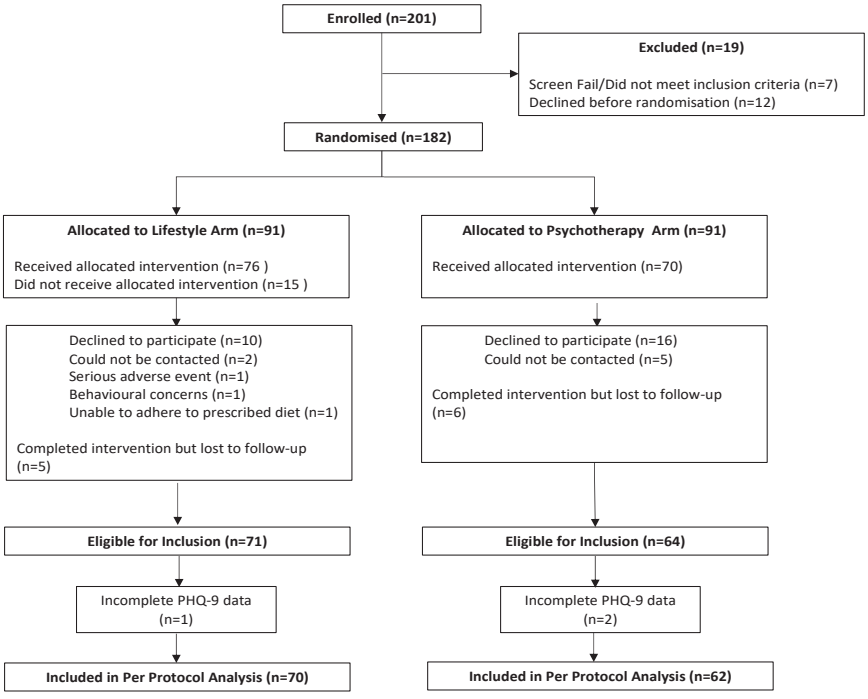

Fig. 2: Participant flow chart.

	Total randomised	Treatment allocation	
	n = 182	Psychotherapy (n = 91)	Lifestyle (n = 91)
Demographics			
Age (years)	45.0 (13.4)	44.5 (13.2)	45.5 (13.7)
Sex			
Female	145 {79.7%}	67 {73.6%}	78 {85.7%}
Currently employed	131 {{72.4%}	50 {54.9%}	61 {67.0%}
Completed high school	155 {85.6%}	65 {71.4%}	69 {75.8%}
Country of birth			
Born in Australia	139 {76.4%}	54 {59.3%}	68 {74.7%}
Ethnicity			
Anglo-Celtic Australian	99 (65.6%)	50 (66.7%)	49 (64.5%)
Indigenous Australian	1 (0.7%)	0 (0%)	1 (1.3%)
South or East Asian	9 (6%)	4 (5.3%)	5 (6.6%)
British or European	31 (20.5%)	15 (20%)	16 (21.1%)
Other	11 (7.3%)	6 (8%)	5 (6.6%)
Psychiatric medication			
Yes	96 {52.8%}	38 {41.8%}	44 {48.4%}
No	82 {45.1%}	33 {36.3%}	37 {40.7%}
Mental health			
MINI diagnostic interview			
Major depressive disorder (MDD)	36 {19.78%}	19 {20.9%}	17 {18.7%}
Generalised anxiety disorder (GAD)	20 {11.0%}	5 {5.5%}	15 {16.5%}
MDD with GAD	4 {2.2%}	1 {1.1%}	3 {3.3%}
Past MDD	32 {17.6%}	15 {16.5%}	17 {18.7%}
Bipolar disorder	5 {2.8%}	2 {2.2%}	3 {3.3%}
Substance or alcohol use disorder	8 {4.4%}	5 {5.5%}	3 {3.3%}
PHQ-9 depression[b]	10.5 (5.7)	10.5 (5.5)	10.4 (6.0)
GAD-7 anxiety	9.1 (4.9)	8.7 (4.3)	9.5 (5.4)
AQoL-4D utility	0.586 (0.213)	0.587 (0.197)	0.584 (0.229)
Coronavirus anxiety scale	2.0 [0.0–4.0]	1.0 [0.0–3.0]	2.0 [0.0–4.0]
Early psychosis score	0.0 [0.0–1.0]	0.0 [0.0–1.0]	0.0 [0.0–1.0]
Cardiometabolic			
Height (cm)	167.9 (7.6)	170.0 (7.8)	166.0 (7.0)
Weight (kg)	77.0 [66.6–92.0]	77.0 [67.5–92.0]	76.5 [66.5–91.5]
BMI kg/m^2	27.4 [23.6–31.6]	26.1 [23.0–31.2]	28.0 [24.8–32.3]
Cholesterol			
LDL (mmol/L)	3.10 (0.81)	3.28 (0.89)	2.91 (0.74)
HDL (mmol/L)	1.67 (0.47)	1.64 (0.42)	1.75 (0.51)
Triglycerides (mmol/L)	1.10 [0.70–1.60]	1.00 [0.70–1.50]	1.00 [0.70–1.50]
Fasting Blood Glucose (mmol/L)	4.80 [4.50–5.20]	4.80 [4.50–5.20]	4.70 [4.50–5.15]
Health behaviours			
SIMPAQ activity score			
Light intensity activity (hours/week)[a]	1.50 [0.00–4.50]	1.50 [0.00–4.50]	1.25 [0.00–4.50]
Moderate intensity activity (hours/week)[a]	0.00 [0.00–2.67]	0.00 [0.00–3.00]	0.00 [0.00–1.83]
Vigorous intensity activity (hours/week)[a]	0.00 [0.00–0.50]	0.00 [0.00–0.75]	0.00 [0.00–0.00]
Nutrition			
Total energy (including from alcohol, kJ/day)	8305.34 [6951.23–10127.75]	8159.23 [6831.71–9741.35]	8627.75 [7124.28–10679.56]
Total saturates (% of FA)	8.10 [5.49–10.31]	7.85 [4.80–9.85]	8.64 [6.30–10.57]
Total monounsaturates (% of FA)	10.13 [7.54–13.34]	9.93 [7.05–12.71]	10.41 [8.42–13.80]
Total polyunsaturates (% of FA)	3.96 [2.70–5.24]	3.93 [2.67–5.45]	4.11 [2.72–5.09]
N6 (% of PUFA)	1.41 [1.01–1.88]	1.63 [1.25–2.48]	1.60 [1.16–2.27]
N3 (% of PUFA)	1.86 [1.31–2.89]	1.45 [0.99–1.88]	1.36 [1.01–1.88]
ASSIST substance use score			
Tobacco	15.0 [8.0–24.0]	15.0 [8.0–24.0]	17.5 [9.0–22.0]

(Table 1 continues on next page)

	Total randomised	Treatment allocation	
	n = 182	Psychotherapy (n = 91)	Lifestyle (n = 91)
(Continued from previous page)			
Alcohol	8.0 [5.0–15.0]	8.0 [5.0–15.0]	8.0 [5.0–14.5]
Cannabis	14.0 [7.0–21.5]	8.5 [2.0–16.0]	17.0 [13.0–22.0]
ISI insomnia score	11.6 (6.1)	12.1 (6.0)	11.1 (6.2)
Psychosocial factors			
MOS-social support scale	15.0 [12.0–17.0]	14.0 [12.0–17.0]	15.0 [12.0–18.0]
General self efficacy	16.7 (3.0)	16.4 (2.8)	16.8 (3.1)
Credibility expectation questionnaire	37.2 (7.5)	36.6 (6.7)	37.6 (7.6)
Readiness to change	23.1 [4.7]	24.0 [21.0–27.0]	23.0 [20.0–25.0]

Mean (standard deviation), median [Q1–Q3], or frequency; Baseline differences were observed for sex (p = 0.04), place of birth (p = 0.03), Generalised Disorder Anxiety (p = 0.02), Height (p = 0.01) and LDL cholesterol (p = 0.02). [a]Intensity of physical activity was determined by the Modified Borg Dyspnoea Scale, and categorised as "sedentary & light" (<3), "moderate" (4–5) and "vigorous & high" (>5). [b]n = 3 participants had missing items meaning an overall score could not be calculated.

Table 1: **Characteristics of participants at baseline, by treatment allocation.**

psychotherapy were 'mostly engaged' or 'very engaged' 82% and 78% of the time, respectively. From the facilitators' perspective, participants in both arms showed comparable engagement (72% of the time, respectively). Retention was higher for lifestyle (78%) than psychotherapy (70%) over the trial period *(p = ns)*. Both programs were delivered with high fidelity (lifestyle 93%; psychotherapy 93%).

Primary outcomes

Table 2 displays means, Standard Errors (SEs) and GEE models for primary outcomes by treatment allocation. Baseline to endpoint reductions in mean PHQ-9 scores were observed for both conditions: lifestyle (n = 70): mean difference: −3.97 [95% CIs:−5.10, −2.84] and psychotherapy (n = 62): mean difference: −3.74 [95% CIs:−5.12, −2.37] (Fig. 3). There was evidence that lifestyle was non-inferior to psychotherapy (β: −0.59; 95% CI:−1.87, 0.70).

Secondary outcomes

Table 2 displays means, SEs and GEE models for all secondary outcomes by treatment arm. Lifestyle participants reported reductions in the percentage of food intake from discretionary items, improvements in diet quality (as measured by Mediterranean Diet Adherence Score; MEDAS) and greater self-reported stool consistency, but fewer improvements in social support than psychotherapy participants. There were no differences in any other health behaviours, dietary or physical activity measures, psychological factors, or other indicators between arms.

Post hoc analyses (exploratory)

Participants with greater baseline depression (PHQ-9 ≥ 10 'moderate depression') (n = 69) reported more pronounced reductions in PHQ-9 scores than the overall sample in both lifestyle (mean difference: −6.8 [95% CIs:−8.4, −5.2]) and psychotherapy (mean difference: −5.4 [95% CIs:−7.5, −3.3]) arms. No differences were observed between arms (GEE β:−0.78 [95% CIs:−2.96, 1.39]). Results were consistent using baseline MINI diagnosis or psychiatric medication use (data not shown). Sensitivity analyses were performed where baseline imbalances were detected and considered to influence the outcome[29] (country of birth, sex, Generalised Anxiety Disorder and Low Density Lipoprotein [LDL] cholesterol) whereby we tested each variable's interaction with treatment allocation for the primary outcome. There was no evidence of interactions between these variables and the primary outcome (p values: Country of birth: 0.49; Sex: 0.07; Anxiety: 0.90; LDL cholesterol: 0.07). Inferences were consistent across PP, ITT and sensitivity models for the primary outcome. Inferences were consistent across PP, ITT and sensitivity models for the primary outcome.

When we examined recovery status of participants using weekly K10 scores, almost half of participants who completed the minimum dose of treatment in either arm fulfilled recovery criteria by program completion (week 6 for lifestyle therapy and week 7 for psychotherapy) (Supplementary Fig. -Appendix H). In contrast, participants who did not complete the minimum dose of treatment, at no time, fulfilled this criteria (Supplementary Fig. -Appendix I).

Economic evaluation

Table 3 shows the PP results of the economic evaluation The lifestyle arm had lower utilities at baseline as calculated from the AQoL-4D, but surpassed the psychotherapy group at 8-weeks. We found no evidence of a difference in utility scores or QALYs between arms (adjusted mean difference: 0.001, 95% CIs: −0.004, 0.005) over 8-weeks. The cost of delivering the therapy was estimated to be marginally lower for lifestyle therapy at approximately AUD $482 per participant, compared to AUD $503 per participant for psychotherapy (Supplementary Appendix Table S7). Health sector

	Psychotherapy	Lifestyle therapy		
	Mean (SE)[a]	Mean (SE)[a]	GEE β (95% CI)[b]	p-value[c]
Primary outcome (PHQ-9; n = 132)				
Baseline	10.53 (0.59)	10.42 (0.62)		
PP (8-weeks)	6.76 (0.62)	5.94 (0.54)	−0.59 (−1.87, 0.70)	0.187
ITT (8-weeks)	6.66 (0.62)	6.00 (0.52)	−0.49 (−1.73, 0.75)	0.219
Secondary outcomes—mental health				
GAD-7 (Anxiety symptoms; n = 132)				
Baseline	8.74 (0.45)	9.47 (0.56)		
PP (8-weeks)	6.13 (0.55)	5.23 (0.52)	−0.99 (−2.51, 0.53)	0.102
ITT (8-weeks)	6.03 (0.55)	5.27 (0.50)	−1.01 (−2.50, 0.49)	0.093
CAS (COVID-related distress; n = 131)				
Baseline	2.28 (0.31)	2.77 (0.33)		
PP (8-weeks)	0.89 (0.20)	0.96 (0.23)	−0.06 (−0.53, 0.40)	0.393
ITT (8-weeks)	0.87 (0.19)	0.93 (0.21)	−0.12 (−0.57, 0.34)	0.308
K10 (Psychological distress; n = 131)				
Baseline	25.54 (0.82)	25.86 (0.85)		
PP (8-weeks)	20.84 (0.90)	19.35 (0.85)	−1.09 (−2.98, 0.79)	0.128
ITT (8-weeks)	20.68 (0.90)	19.50 (0.81)	−1.00 (−2.78, 0.77)	0.134
MOS-SSS (Social support; n = 132)				
Baseline	14.23 (0.39)	14.65 (0.41)		
PP (8-weeks)	15.24 (0.47)	15.00 (0.50)	−0.73 (−1.30, −0.17)	**0.011**
ITT (8-weeks)	15.27 (0.46)	14.84 (0.49)	−0.69 (−1.18, −0.20)	**0.003**
WHO ASSIST (Smoking; n = 132)				
Baseline	3.65 (0.92)	2.57 (0.72)		
PP (8-weeks)	2.22 (0.80)	1.33 (0.59)	0.01 (−0.29, 0.30)	0.519
ITT (8-weeks)	2.26 (0.85)	1.38 (0.63)	−0.13 (−0.43, 0.17)	0.198
WHO ASSIST (Alcohol; n = 132)				
Baseline	10.19 (0.99)	8.88 (0.91)		
PP (8-weeks)	8.10 (0.98)	7.33 (0.93)	−0.23 (−1.53, 1.07)	0.366
ITT (8-weeks)	8.05 (0.97)	7.17 (0.87)	−0.21 (−1.42, 0.99)	0.365
WHO ASSIST (Cannabis; n = 131)				
Baseline	0.98 (0.53)	2.12 (0.73)		
PP (8-weeks)	0.54 (0.26)	1.39 (0.69)	−0.21 (−0.64, 0.21)	0.163
ITT (8-weeks)	0.56 (0.30)	1.39 (0.65)	−0.27 (−0.64, 0.10)	0.078
ISI (Sleep difficulties; n = 132)				
Baseline	12.06 (0.63)	11.09 (0.65)		
PP (8-weeks)	9.35 (0.70)	7.99 (0.66)	−0.68 (−2.52, 1.17)	0.235
ITT (8-weeks)	9.20 (0.70)	7.94 (0.63)	−0.66 (−2.48, 1.16)	0.239
AQoL (Quality of life; n = 132)				
Baseline	19.62 (0.33)	19.86 (0.38)		
PP (8-weeks)	18.56 (0.39)	18.22 (0.48)	−0.47 (−1.28, 0.34)	0.129
ITT (8-weeks)	18.48 (0.39)	18.19 (0.46)	−0.47 (−1.28, 0.33)	0.126
Early psychosis (n = 129)				
Baseline	1.06 (0.24)	0.90 (0.21)		
PP (8-weeks)	0.94 (0.30)	0.94 (0.26)	0.28 (−0.18, 0.74)	0.882
ITT (8-weeks)	0.92 (0.29)	0.96 (0.25)	0.32 (−0.18, 0.83)	0.105
Secondary outcomes—cardiometabolic				
Weight (kg) (n = 94)				
Baseline	80.49 (2.22)	80.34 (2.08)		
PP (8-weeks)	79.65 (2.66)	75.95 (2.42)	−0.83 (−2.08, 0.43)	0.099
ITT (8-weeks)	79.13 (2.66)	76.16 (2.43)	−0.76 (−1.98, 0.47)	0.114
Stool consistency (n = 130)				
Baseline	3.72 (0.14)	3.68 (0.16)		

(Table 2 continues on next page)

	Psychotherapy	Lifestyle therapy		
	Mean (SE)[a]	Mean (SE)[a]	GEE β (95% CI)[b]	p-value[c]
(Continued from previous page)				
PP (8-weeks)	3.40 (0.13)	3.88 (0.12)	1.13 (1.04, 1.23)	**0.003**
ITT (8-weeks)	3.43 (0.14)	3.82 (0.12)	0.38 (0.09, 0.66)	**0.005**
IBS diagnosis (yes/no) (n = 130)				
Baseline	15.00 [16.67%]	13.00 [14.29%]		
Relative difference (risk ratio) PP (8-weeks)	12.00 [19.05%]	8.00 [11.94%]	1.01 (0.66, 1.55)	0.961
Absolute difference (risk difference) PP (8-weeks)			−0.00 (−0.06, 0.05)	0.915
Relative difference (risk ratio) ITT (8-weeks)	16.96 [18.64%]	11.42 [12.55%]	0.98 (0.61, 1.56)	0.925
Absolute difference (risk difference) ITT (8-weeks)			−0.00 (−0.08, 0.07)	0.922
Fasting blood glucose (mmol/L) (n = 86)				
Baseline	4.94 (0.07)	5.05 (0.14)		
PP (8-weeks)	4.86 (0.07)	5.05 (0.15)	0.11 (−0.02, 0.24)	0.954
ITT (8-weeks)	4.87 (0.07)	5.05 (0.15)	0.11 (−0.03, 0.24)	0.058
LDL Cholesterol (mmol/L) (n = 85)				
Baseline	3.28 (0.11)	2.95 (0.08)		
PP (8-weeks)	3.17 (0.12)	2.92 (0.12)	−0.02 (−0.23, 0.20)	0.440
ITT (8-weeks)	3.17 (0.12)	2.92 (0.12)	−0.02 (−0.23, 0.20)	0.439
HDL Cholesterol (mmol/L) (n = 85)				
Baseline	1.61 (0.05)	1.72 (0.06)		
PP (8-weeks)	1.60 (0.06)	1.74 (0.08)	−0.01 (−0.10, 0.08)	0.392
ITT (8-weeks)	1.60 (0.06)	1.74 (0.08)	−0.01 (−0.10, 0.07)	0.394
Total Cholesterol (mmol/L) (n = 85)				
Baseline	5.44 (0.12)	5.25 (0.10)		
PP (8-weeks)	5.30 (0.14)	5.20 (0.15)	0.03 (−0.19, 0.24)	0.593
ITT (8-weeks)	5.30 (0.14)	5.20 (0.15)	0.03 (−0.19, 0.24)	0.408
Triglycerides (mmol/L) (n = 85)				
Baseline	1.24 (0.10)	1.26 (0.07)		
PP (8-weeks)	1.15 (0.08)	1.15 (0.09)	0.09 (−0.07, 0.24)	0.853
ITT (8-weeks)	1.15 (0.08)	1.15 (0.09)	0.08 (−0.08, 0.24)	0.153
Secondary outcomes—physical activity[e]				
Low intensity activity (hours/week) (n = 128)				
Baseline	2.42 (0.31)	2.57 (0.31)		
PP (8-weeks)	3.28 (0.40)	3.08 (0.37)	−0.36 (−1.32, 0.59)	0.227
ITT (8-weeks)	2.34 (0.32)	2.50 (0.32)	0.08 (−0.73, 0.88)	0.428
Medium intensity activity (hours/week) (n = 132)				
Baseline	1.09 (0.24)	1.18 (0.22)		
PP (8-weeks)	1.63 (0.30)	1.48 (0.24)	−0.14 (−0.81, 0.54)	0.344
ITT (8-weeks)	1.11 (0.22)	1.17 (0.20)	0.06 (−0.46, 0.58)	0.410
High intensity activity (hours/week) (n = 119)				
Baseline	0.39 (0.10)	0.53 (0.11)		
PP (8-weeks)	0.61 (0.16)	0.50 (0.12)	−0.30 (−0.71, 0.11)	0.074
ITT (8-weeks)	0.42 (0.11)	0.41 (0.10)	−0.18 (−0.52, 0.17)	0.159
Intensity of physical activity (n = 119)				
Baseline	2.53 (0.13)	2.95 (0.16)		
PP (8-weeks)	2.98 (0.13)	2.84 (0.16)	−0.25 (−0.66, 0.15)	0.110
ITT (8-weeks)	2.95 (0.13)	2.89 (0.16)	−0.18 (−0.57, 0.22)	0.189
Secondary outcomes—nutrients/dietary intake				
MEDAS diet quality score (n = 74)[d]				
Baseline	5.04 (0.22)	4.52 (0.20)		
PP (8-weeks)	4.74 (0.26)	5.50 (0.29)	0.82 (0.32, 1.31)	**0.001**
ITT (8-weeks)	4.74 (0.26)	5.45 (0.28)	0.78 (0.31, 1.26)	**<0.001**

(Table 2 continues on next page)

	Psychotherapy	Lifestyle therapy		
	Mean (SE)[a]	Mean (SE)[a]	GEE β (95% CI)[b]	p-value[c]
(Continued from previous page)				
Dairy (serves/day; n = 74)[f]				
Baseline	1.80 (0.15)	1.80 (0.11)		
PP (8-weeks)	1.85 (0.18)	1.93 (0.12)	−0.13 (−0.44, 0.18)	0.199
ITT (8-weeks)	1.87 (0.20)	1.90 (0.14)	−0.13 (−0.42, 0.16)	0.185
Discretionary (% of total energy) (n = 74)				
Baseline	38.92 (2.74)	36.49 (2.19)		
PP (8-weeks)	36.20 (3.28)	29.17 (2.72)	−5.48 (−10.86, −0.09)	**0.023**
ITT (8-weeks)	36.21 (3.28)	28.66 (2.61)	−5.39 (−10.71, −0.07)	**0.024**
Fat (serves/day; n = 74)[f]				
Baseline	1.38 (0.24)	1.50 (0.12)		
PP (8-weeks)	1.24 (0.11)	1.59 (0.14)	0.20 (−0.22, 0.62)	0.826
ITT (8-weeks)	1.24 (0.11)	1.60 (0.14)	0.23 (−0.15, 0.61)	0.120
Fruit (serves/day; n = 74)[f]				
Baseline	1.66 (0.15)	1.73 (0.14)		
PP (8-weeks)	1.66 (0.17)	1.80 (0.14)	−0.12 (−0.33, 0.09)	0.137
ITT (8-weeks)	1.66 (0.17)	1.70 (0.14)	−0.12 (−0.32, 0.08)	0.125
Grains/cereals (serves/day; n = 74)[f]				
Baseline	2.97 (0.19)	3.34 (0.19)		
PP (8-weeks)	3.06 (0.29)	3.48 (0.25)	−0.23 (−1.01, 0.56)	0.285
ITT (8-weeks)	3.06 (0.29)	3.47 (0.25)	−0.17 (−0.94, 0.59)	0.330
Vegetable (serves/day) (n = 74)[f]				
Baseline	3.32 (0.23)	2.97 (0.20)		
PP (8-weeks)	3.53 (0.26)	4.00 (0.33)	0.36 (−0.37, 1.09)	0.834
ITT (8-weeks)	3.52 (0.26)	3.86 (0.33)	0.35 (−0.34, 1.04)	0.162
Energy, total, including from alcohol (kJ/day) (n = 74)				
Baseline	8469.95 (303.92)	9383.32 (414.71)		
PP (8-weeks)	8022.73 (325.24)	9020.64 (416.45)	690.72 (−453.11, 1834.55)	0.882
ITT (8-weeks)	8005.10 (331.73)	8831.41 (418.19)	660.21 (−428.81, 1749.21)	0.118
Energy, total, excluding from alcohol (kJ/day) (n = 74)				
Baseline	8109.63 (297.89)	9019.04 (378.61)		
PP (8-weeks)	7806.51 (339.29)	8891.91 (430.39)	579.47 (−589.80, 1748.74)	0.834
ITT (8-weeks)	7811.77 (340.46)	8697.21 (430.17)	558.89 (−549.87, 1667.66)	0.162
Fibre intake (g/day) (n = 74)[f]				
Baseline	24.46 (1.11)	25.10 (1.03)		
PP (8-weeks)	24.82 (1.40)	27.83 (1.41)	−0.08 (−2.57, 2.41)	0.475
ITT (8-weeks)	24.77 (1.36)	27.00 (1.43)	−0.04 (−2.44, 2.37)	0.488
Monounsaturates (% of FA) (n = 74)[f]				
Baseline	10.57 (0.60)	11.06 (0.50)		
PP (8-weeks)	10.54 (0.86)	9.48 (0.68)	−0.41 (−2.16, 1.33)	0.321
ITT (8-weeks)	10.80 (0.93)	9.90 (0.70)	−0.09 (−1.81, 1.63)	0.458
N6 (% of PUFA) (n = 74)[f]				
Baseline	1.47 (0.07)	1.56 (0.10)		
PP (8-weeks)	1.38 (0.09)	1.41 (0.10)	−0.02 (−0.19, 0.15)	0.393
ITT (8-weeks)	1.41 (0.09)	1.44 (0.10)	−0.04 (−0.20, 0.13)	0.331
N3 (% of PUFA) (n = 74)[f]				
Baseline	2.31 (0.19)	2.09 (0.14)		
PP (8-weeks)	2.37 (0.25)	2.52 (0.22)	0.06 (−0.23, 0.36)	0.665
ITT (8-weeks)	2.39 (0.25)	2.44 (0.22)	−0.01 (−0.29, 0.28)	0.486
Polyunsaturates (% of FA) (n = 74)[f]				
Baseline	4.21 (0.25)	4.45 (0.27)		
PP (8-weeks)	4.33 (0.37)	3.81 (0.26)	−0.39 (−1.22, 0.45)	0.183

(Table 2 continues on next page)

	Psychotherapy	Lifestyle therapy		
	Mean (SE)[a]	Mean (SE)[a]	GEE β (95% CI)[b]	p-value[c]
(Continued from previous page)				
ITT (8-weeks)	4.25 (0.36)	3.96 (0.28)	−0.23 (−1.03, 0.57)	0.283
Saturates (% of FA) (n = 74)[f]				
Baseline	8.12 (0.49)	8.63 (0.44)		
PP (8-weeks)	7.64 (0.56)	6.66 (0.55)	−0.51 (−1.66, 0.63)	0.190
ITT (8-weeks)	8.47 (1.08)	6.84 (0.57)	−0.32 (−1.48, 0.85)	0.298

Bold indicates significant between arm differences based on the standard p value cut off of <0.05. PP=Per-protocol, based on participants with observed data at 8-weeks follow-up, ITT=Intention to treat, based on multiple imputation chained equations and observed data at 8-weeks follow-up to allow analysis of all 182 randomised individuals. [a]Results are mean (standard error) or frequency [%]. [b]Regression models are adjusted for the baseline counterpart for each outcome variable. [c]One-tailed p-value. [d]MEDAS score was modified to remove question 14 as sofrito was not measured in the food frequency questionnaire. The MEDAS score for the CALM trial therefore had a maximum of 13. [e]Intensity of physical activity was determined using the Modified Borg Dyspnoea Scale, number of active hours were determined using the Simple Physical Activity Questionnaire (SIMPAQ). [f]Results are adjusted for energy intake using Willett's residual method. Outcomes for Binary variables are presented as risk ratios on the ratio scale.

Table 2: **Primary outcomes.**

costs over the 8-week period were comparable across the two arms, with no statistically significant differences detected (adjusted mean difference: AUD$156 [95% CIs: −$182, $611]). The addition of productivity losses led to similar results (adjusted mean difference in total societal costs: AUD $350 [95% CIs: −$222, $1152]). Furthermore, no major changes were observed in the incremental costs between conditions when conducting the different sensitivity analyses, except when complete cases were analysed. In the complete case sensitivity analysis, mean difference in societal costs were higher in the lifestyle arm (adjusted mean difference: AUD$1066 [95% CIs: $244, $2191]). Results from the ITT analysis were comparable to the PP analysis (Supplementary Table S9).

Safety & integrity

Protocol deviations are detailed in Supplementary Appendix F. More safety events were reported for lifestyle (204) than psychotherapy participants (147); 46% occurred prior to randomisation, with the most common being hypercholesterolemia (67 versus 59 respectively using High Density Lipoprotein, Low Density Lipoprotein and Triglyceride ranges of >1.0, <2.5 and < 3.9 mmol/L). Of the 54% that occurred after randomisation (Lifestyle 121, Psychotherapy 72), the most common was elevated distress (39 versus 12 respectively) and low mood (25 versus 17 respectively). Three serious adverse events were recorded (two versus one respectively) one of which was rated as probably related to the intervention (hospitalisation for anaemia).

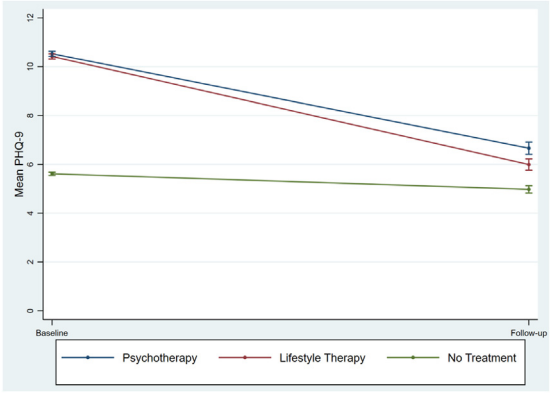

Fig. 3: Mean (and Standard Error) PHQ9 depression scores over 8 weeks by treatment arm against representative sample of the Victorian population over comparable time period.

Discussion

This trial provides novel evidence that remote-delivered, online lifestyle therapy may be as clinically and cost-effective as psychotherapy for reducing depression when administered comparably over 8-weeks. If replicated in a fully powered RCT, this could be a new treatment option for individuals experiencing indicative depression, especially where psychological services are unavailable, inaccessible (e.g., areas outside metropolitan settings where social disadvantage is more prevalent), or not preferred. The scalability, low cost, and efficiency of videoconferencing group programs is noteworthy from a resourcing perspective and it is well-accepted by service-users and health professionals. Some public and private insurers and health care services reimburse its ongoing use beyond the pandemic setting, providing an avenue for translation.

There may be scope to accrue, train and redeploy a new mental health workforce by harnessing the abilities of accredited dietitians and exercise physiologists, which, in conjunction with specialised mental health training and evidence-based guidelines, could support widespread implementation. Our economic evaluation demonstrated that therapy cost alone was lower for the

	Psychotherapy mean (SE)	Lifestyle mean (SE)	Adjusted mean difference	95% CI	p-value
Health sector costs					
Baseline	$868 ($100)	$1306 ($253)	**$838**	$131–$1902	**0.032**
8-weeks	$1323 ($186)	$1709 ($223)	$156	−$182 to $611	0.404
Societal Costs					
Baseline	$2018 ($269)	$2724 ($409)	$1148	−$165 to $3187	0.090
8-weeks	$2007 ($346)	$2436 ($302)	$350	−$222 to $1152	0.263
Utilities					
Baseline	0.607 (0.021)	0.595 (0.027)	−0.029	−0.088 to 0.029	0.168
8-weeks	0.649 (0.025)	0.656 (0.027)	0.007	−0.049 to 0.062	0.369
QALYs					
8-weeks	0.097 (0.003)	0.096 (0.004)	0.001	−0.004 to 0.005	0.484

Note: Costs data are 2021 Australian dollars. Analysis conducted in the per-protocol population. Adjusted mean difference calculated using mixed-effects models accounting for group clustering and with adjustment for baseline covariates. Bold indicates significant between arm differences; p value < 0.05.

Table 3: **Total costs, utilities and QALYs.**

lifestyle arm, primarily due to the lower wage rate of the dietitian and exercise physiologist compared to psychologists. However, when total health sector and societal costs were analysed, there was no distinction in costs. Given that the total University course and clinical training costs of dietitians (AUD $153,039) is cheaper and of shorter duration than psychologists (AUD $189,063) in Australia,[30] there may be opportunity for dietitians for example, with appropriate support, to relieve some service provision burden on the mental health care system without additional financial cost to Governments. While we acknowledge global shortages of nutrition and exercise experts which may affect sustainability of this approach, a WHO report revealed that in 2017 that the Western Pacific region has one of the highest trained nutrition workforces in the world.[31] This suggests our region may be well placed to lead the testing of such innovative approaches especially given the group-based, internet delivered nature of our model, which can be delivered centrally to a variety of populations across various jurisdictions. Investment in comprehensive undergraduate curriculum and/or postgraduate degrees that focuses on mental health risk assessment and management will form an essential part of education and training to equip the dietetic and exercise physiology workforce in contributing to mental health care. The higher number of safety events in the lifestyle intervention, especially as they relate to mental health, should be considered in this context. The one serious adverse event which was deemed as probably related to the lifestyle intervention (hospitalisation after exercise with diagnosis of anaemia) underscores the need for multi-disciplinary oversight from allied health professionals and GPs to ensure patient safety.

The average mental health profile of trial participants (mean PHQ-9 score = 10.6, indicating moderate depression) was 5 points above the Australian population during this time (mean PHQ-9 score = 5.6).[27] At completion, lifestyle and psychotherapy participants experienced improvements of 42% and 37% respectively. The general population reported an 11% reduction over an 8 week period. A clinically meaningful change on this instrument is a post-treatment score ≤9 and improvement by 50%, but recent analyses suggest a minimum clinically important difference is 20%.[32] As the study sample was not a clinically defined psychiatric population, this trial may be more vulnerable to the phenomenon of spontaneous remission. On the other hand, it may be reflective of a broader help seeking population. To address this limitation, we are conducting a larger trial with a newly established clinical trial network[33] to confirm whether results are reproducible for those with severe mental illness. These findings are nonetheless promising as a potential new treatment option to address the lack of available services for individuals whose mental health concerns are not sufficiently acute or complex for tertiary care, who cannot or do not want to access psychological-based services or as interim treatment until psychological care is available.

While secondary outcome analysis and effect modification did not illuminate individual-level candidate mechanisms driving respective treatment effects, lifestyle participants reduced their discretionary food intake (those high in saturated fat, added sugar and/or salt, e.g., commercial cakes, desserts, processed meats) and improved their diet quality. As the gut microbiome may be an important regulator of mental health and diet influences gut microbiota composition and function, it is a plausible mechanism of action by which diet influences mental health; a hypothesis we are investigating using biospecimens. We did not observe any differences in physical activity outcomes by arm. It is possible that lifestyle participants improved the quality

or enjoyment of activity while the dose remained unchanged. Quality and context of physical activity may be more important than dose itself for mental health.[34] Psychotherapy participants subtlety changed their activity, possibly a secondary consequence of techniques learned from CBT (e.g., of which behavioural activation is a core principle and alone is a highly effective therapeutic strategy for depression[24]) or from knowing they were enrolled in a lifestyle-related trial.

Study strengths

The study's strength is the evaluation of a scalable, reproducible digitally-delivered intervention that used a robust, randomised design and incorporated an economic evaluation concordant with gold standard reporting and governance frameworks. While overall trial attrition was higher than anticipated, engagement with both therapies was high; 79.6% of participants completed 3+ of 6 sessions. We took suitable lengths to uphold the constancy assumption of non-inferiority trials and specifically our CBT control, by: ensuring our content was created by an experienced clinical psychologist based on the Mood Management Course[21]; using an intervention manual to promote adherence with delivery; assessing a random 10% of sessions for fidelity using a checklist aligned with content modules; ensuring conditions were matched in terms of group size, frequency and intensity. Participants in the psychotherapy arm experienced a mean 37% reduction in PHQ9 scores over 8-weeks which exceeds efficacy trials of similar group-based, video conferencing-delivered CBT interventions for people with mild-moderate depression which reduced PHQ9 scores by 30% (10.45–7.37) over 7 weeks compared to a waitlist control (7%; 10.76–10.01).[35]

Another strength was how we mitigated the risks associated with single blinding by using the Cochrane Risk of Bias 2 whereby we: (1) assessed participants' treatment expectations using a validated scale and eliminated expectation bias as a driver of treatment effects; (2) recorded and reported protocol deviations to the DSMB when unblinding occurred and ensured blinding was maintained for all outcome data; and (4) conducted all analyses blind to treatment allocation.

Study limitations

First, the generalisability of the findings is limited by the sample's demographics: middle aged, educated, Anglo-Celtic women born in Australia. By chance, the small number of men were more commonly randomised to psychotherapy, creating some imbalances in baseline characteristics. Psychotherapy participants had lower anxiety, had higher LDL cholesterol, were more likely to be born outside of Australia and also had a higher dropout rate (30%). We recognise that the program and trial recruitment more broadly may not have been sufficiently tailored to all people, especially men and those of diverse cultural backgrounds. Efforts should be made to attract these populations and retain men as historically their representation has been low[6] despite them benefiting from these approaches.[36] Second, the overall attrition rate was high compared to trials of internet-based therapies for depression especially brief interventions of shorter duration.[37] This could be attributed to (i) the group setting (perceived lack of privacy), (ii) the Covid-19 setting (a novelty early in the pandemic when participants had fewer competing commitments that subsequently dissipated), (iii) personality, scheduling or the presence of psychiatric comorbidities (avoidance, social anxiety) which resulted in 7% attrition prior to session 1 or (iv) program length (average drop out occurred at week 4) where some may prefer a briefer intervention. Third, our final randomised and completing sample sizes (n = 182 and n = 132) were underpowered for the primary outcome. The overall between-arm difference of −0.59 PHQ9 points (corresponding 95% CIs of −1.87 and 0.7) did however fall below our NI margin of 2 PHQ9 points. Our results were consistent using both PP and ITT analyses and also following sensitivity analyses.

Finally, the lack of control or placebo arm in this trial cannot eliminate the possibility of regression to the mean or the Hawthorne effort in either arm, whereby simply observing participants' behaviours can results in improvements regardless of the intervention they receive. We also acknowledge that spontaneous remission can affect 20% of people with recent depression.[38] This phenomenon may have inflated the effects sizes of either program and been wrongly attributed to that therapy (assuming equal distribution across arms) or influenced drop out if a participant saw no value in participating. Results should be interpreted with this consideration. While it is also possible that mental health benefits came from structured, regular social interaction especially during lockdowns when many were socially isolated, trials show that treatment effects of dietary interventions go beyond the mental health benefits of a generic social support intervention.[39] Inclusion of population level PHQ9 scores over a comparable period show despite minor reductions in depression over 8-weeks in those 'untreated', these were not nearly as pronounced as those in each treatment arm, suggesting they may not simply be a product of regression to the mean. Further, almost half of participants who completed the minimum course of treatment fulfilled recovery criteria by program completion, whereas participants who did not complete the minimum treatment course did not fulfil this criteria at any point. This is suggestive of treatment effects and not spontaneous recovery.

In conclusion, we demonstrate the non-inferiority of remote-delivered, online lifestyle therapy-that focuses on nutrition and physical activity-to psychological care

that uses a CBT approach with respect to mental health and cost outcomes. While a fully powered RCT to confirm these results is required, appropriately trained dietitians and exercise physiologists may be well-placed to provide remote mental health care to help alleviate the current burden on mental health care services.

Contributors

Conceptualisation: SMo, MTey, SR, FJ, MY, JS, PA, VV, MLC, MBe, SMa, MMoh, MMor, AC, CBe, MO, TR, AO. Study development and delivery: LMY, TJ, MTu, RO, MH, DS, CBr, KB, SMa, MTem, JL, NLM, GM, MBr, JD, ID, Sar, LP. Original draft preparation: AO, MBr, JP, MLC. All authors provided feedback on the draft and subsequent revisions. All authors read and approved and take responsibility for the final manuscript. DNA, MBr, JP, MLC and AO and verified the dataset and have access to the raw data. AO and MLC take final responsibility for the decision to submit for publication.

Data sharing statement

A minimum dataset (including biological specimens) of individual participant data collected during the trial will be available after de-identification (including data dictionaries, study protocol, statistical analysis plan, analytic code) for any purpose that is approved by the applicant's Human Research in Ethics Committee and the CALM Chief Investigator Team via https://researchdata.edu.au/health/. This will be available immediately following publication with no end date.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101142.

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Further reading

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