Restoring Emotional Needs with Exogenous ketones for Women (RENEW)
The Ohio State University
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Protocol Title: Restoring Emotional Needs with Exogenous ketones for Women (RENEW)

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1. Abbreviations and Definitions (enter N/A if not needed)

ASA24 - Automated Self-administered 24-hour Dietary Assessment Tool, one of the questionnaires provided to participants.
DEXA or DXA - Dual-Energy X-Ray Absorptiometry, Analyze Body Composition Outcomes Measure alterations in body fat percentage, lean body mass, and visceral fat distribution using validated methods.
GMCB - Group Mediated Cognitive Behavioral
POMS - Profile of Mood States.
PPD- Postpartum Depression
Ultrasonography (USG) - performed during visits performed to ensure consistent hydration status

2. Background and Rationale

Summarize and synthesize the available research, including published data, to provide justification for the study.

Importance of the Problem to be Addressed. PPD) is the most common psychological condition following childbirth, affecting 1 in 5 women (17.22%) globally [1]. PPD is a Major Depressive Disorder (MDD) characterized by depressed mood states, extreme withdrawal from family and friends, difficulty establishing bonds with the infant, anxiety, and feelings of hopelessness. Infants of mothers who suffered from PPD are at increased risk for developing insecure attachments, cognitive delays, adolescent behavior problems, and future mood disorders [2]. Suicide is the leading cause of maternal death in industrialized countries, underscoring the urgent need for more effective approaches to treat PPD [3]. The severity of this outcome further highlights the importance of advancing treatment strategies to address PPD comprehensively. Traditionally, PPD has been treated using psychotherapy and antidepressants such as selective serotonin reuptake inhibitors and anti-anxiety medications such as benzodiazepine. However, these drugs have devastating side effects such as anxiety, decreased libido, nausea, and insomnia, which may exacerbate the same depressive symptoms they are intended to treat and the risks associated with taking antidepressants while breastfeeding [2]. This warrants the demanding need for more holistic approaches for the treatment of PPD.

Integrative Framework for Addressing Postpartum Depression

Emerging evidence supports the integration of nutritional, physical activity, and behavioral strategies as a comprehensive approach to PPD. Women experiencing PPD often face interconnected disruptions in energy metabolism, sleep, social connection, and stress regulation, each of which contributes to the persistence or worsening of depressive symptoms. Growing evidence demonstrates that combining exercise and cognitive behavioral therapy (CBT) can yield greater reductions in depressive symptoms than either intervention alone (7). These complementary interventions enhance neuroplasticity, sleep quality, and self-efficacy—mechanisms that overlap with those influenced by circulating β-hydroxybutyrate (BHB).

The Group-Mediated Cognitive Behavioral (GMCB) model provides an evidence-based framework for facilitating sustained lifestyle behavior change through group dynamics and social cognitive mechanisms (8–10). When applied to postpartum women, the GMCB format offers a structured, supportive environment for developing coping skills, building social connection, and reinforcing adherence to health behaviors that can mitigate depressive symptoms. Similarly, exercise training remains one of the most consistently effective non-pharmacologic strategies for improving mood, reducing inflammation, and restoring metabolic regulation. Regular resistance and aerobic activity elevate neurotrophic factors, modulate hypothalamic–pituitary–adrenal (HPA) axis activity, and increase endogenous ketone production, complementing the proposed exogenous ketone supplementation. Collectively, these mechanisms may converge to improve both mood and physiological recovery in the postpartum period.

Ketone bodies, primarily Beta-Hydroxybutyrate (BHB), may benefit individuals suffering from PPD through multiple mechanisms including: increased concentrations of GABA [4], a key neurotransmitter targeted by benzodiazepine, BHBs ability to cross over the blood brain barrier, and potential signaling mechanisms. Increases in circulating BHB have been shown to be feasible for populations with MDD and may provide psychological benefits, demonstrating a possible favorable relationship between ketones and symptoms of depression. Preliminary evidence from our group suggests that exogenous ketones may hold promise as an adjuvant therapy for PPD, menses regulation [5], and cognitive function [6]. In a trial with college-aged students (n = 19) diagnosed with Major Depressive Disorder (MDD) and receiving standard

care, participants followed a well-formulated ketogenic diet (WFKD) for 10-12 weeks. The study showed significant improvements in depression symptoms, with PHQ-9 and HAM-D scores decreasing by 67-71%. These findings indicate that a ketogenic approach may be a feasible adjuvant therapy for improving mental health problems.

In our proposed project, Restoring Emotional Needs with Exogenous ketones for Women (**RENEW**), we aim to investigate the effect of exogenous ketones on mothers suffering from PPD. Because of its prevalence and potential for severe consequences in the mother, infant, and family, PPD demands greater attention in the sphere of clinical research. We believe that the use of exogenous ketones will improve symptoms of PPD.

3. Objectives

Describe the purpose of the study.

The purpose of this study is to evaluate the feasibility, acceptability, and preliminary efficacy of a 16-week, fully remote, multimodal intervention combining exogenous ketone supplementation (Qitone™) with group-mediated cognitive behavioral (GMCB) counseling with structured exercise for women diagnosed with postpartum depression (PPD). The study aims to determine whether integrating biochemical, behavioral, and physical activity strategies can improve depressive symptoms, metabolic health, and psychosocial functioning during the postpartum period.

Primary Objectives and Outcome Measures

Describe the study objectives and outcomes.

Primary Objective:
To determine the feasibility (e.g., recruitment, retention, adherence, and safety) and preliminary efficacy of a GMCB + Exercise intervention on depression scores in participants diagnosed with PPD.

Primary Outcome Measure:

- Change in Edinburgh Postnatal Depression Scale (EPDS) scores from baseline to Week 16.

Secondary Objectives and Outcome Measures

Describe any secondary objectives and outcomes.

Secondary Objectives:
To examine the preliminary efficacy of the GMCB (Exercise + Nutrition) framework, when combined with exogenous ketone supplementation versus placebo, on:
Physical and metabolic outcomes, including:
-Body composition assessed by DEXA (lean mass, fat mass, % body fat).
-Anthropometric measures (waist/hip circumference, weight, BMI).
-Blood biomarkers related to metabolic and neuroendocrine function (e.g., β-hydroxybutyrate, glucose, insulin, cortisol, CRP).
Behavioral and psychosocial outcomes, including:
-Physical activity engagement and sleep metrics (Ultrahuman Ring data).

-Self-efficacy (Exercise Self-Efficacy Scale; ESES)
-Self-regulation (Physical Activity Self-Regulation Scale; PASR-12).
-Perceived Competence (Maintaining a Healthy Diet; PCS-D; Exercising Regularly; PCS-E)
-Maternal functioning (Barkin Index of Maternal Functioning; BIMF).
-Quality of life and perceived stress (PROMIS Global Health; PSS).
-Dietary Recall (DHQ-III Diet History Questionnaire)
Secondary Outcome Measures: Percent change from baseline to Week 16 in each listed physiological and psychosocial measure. Adherence rates to supplementation, exercise, and behavioral sessions. Safety and tolerability of exogenous ketone supplementation in postpartum women.

4. Study Design & Procedures

	Y	N	Comments
1. Is this a multi-site study?	☐	☒	If yes, complete the Multi-Site Research appendix.
2. Does the research involve the use of an approved drug or biologic, use of an unapproved drug or biologic, or use a food or dietary supplement intended to diagnose, cure, treat, or mitigate a disease or condition?	☐	☒	If yes, complete the Drug appendix.
3. Does the research involve the use of a device to evaluate its safety or effectiveness or use a humanitarian use device (HUD)?	☐	☒	If yes, complete the Device appendix.

Provide information about all research interventions and activities that are to be performed.

The **RENEW (Restoring Emotional Needs with Exogenous Ketones for Women)** study is a 16-week, randomized, double-blind, placebo-controlled behavioral and nutritional intervention designed to evaluate the feasibility and preliminary efficacy of combining **exogenous ketone supplementation (Qitone™)** with **Group-Mediated Cognitive Behavioral (GMCB)** exercise and nutrition counseling in women diagnosed with **postpartum depression (PPD)**.

Screening and Enrollment

Participants will complete a screening questionnaire to confirm eligibility based on inclusion/exclusion criteria (age, postpartum status, Edinburgh Postnatal Depression Scale [EPDS] score, medical clearance for light-to-moderate exercise, and absence of contraindicated medications or conditions). Eligible participants will provide informed consent prior to any study activities.

Randomization and Blinding

Following baseline assessments, participants will be randomized (1:1) into one of two groups:

1. **Ketone Supplement + GMCB (Exercise + Nutrition)**

2. **Placebo + GMCB (Exercise + Nutrition)**
   Both participants and study staff involved in outcome assessments will be blinded to group allocation.

Interventions

- **Supplementation:** Participants will consume either **Qitone™ exogenous ketone supplement** or a matched **placebo** twice daily for 16 weeks. Supplements will be pre-packaged and labeled by ID code to maintain blinding. Compliance will be tracked via self-report logs and returned packaging counts.
- **Behavioral Counseling (GMCB):** All participants will attend **one weekly 30–45-minute virtual GMCB session** via secure videoconferencing. The sessions, led by trained behavioral specialists, will follow the **Group-Mediated Cognitive Behavioral (GMCB)** framework to foster self-regulation, social support, and adherence to exercise and nutrition recommendations. Session content will progress through three phases—intensive, transition, and maintenance—targeting reflective, regulatory, and reflexive behavior change processes.
- **Exercise Component:** Participants will engage in **two virtual group exercise sessions per week**, combining resistance- and interval-based training led by certified instructors. Exercise intensity and progression will be individualized based on perceived exertion (RPE 3–6), postpartum safety, and ACSM (2025) guidelines. Participants will also be encouraged to meet national aerobic activity recommendations (≥150 minutes of moderate-to-vigorous activity per week).
- **Home Monitoring:** Participants will complete **daily ketone and glucose measurements** using handheld meters and **sleep/activity tracking** via wearable devices. Adherence and feedback will be monitored through the study's secure digital platform.

Monthly Laboratory Visits

Participants will visit the research laboratory **once per month (Weeks 0, 4, 8, 12, and 16)** for in-person assessments, including:

- Anthropometrics (height, weight, waist/hip circumference)
- **DEXA** for body composition
- **Blood draws** for fasting glucose, insulin, β-hydroxybutyrate (BHB), cortisol, and inflammatory markers
- **Questionnaires** on depression (EPDS), self-efficacy (ESES), self-regulation (PASR-12), Perceived Competence (PCS-E / PCS-D), maternal functioning (BIMF), perceived stress (PSS), quality of life (PROMIS Global Health), and Dietary Recall (DHQ-III Diet History Questionnaire)

Qualitative Interviews

At study completion, participants will complete a **semi-structured interview** (~30-60 minutes) followed by secondary, optional **focus group interview** (~60-90 minutes)**.** Both interviews will be used to explore perceived changes in mood, motivation, group support, and well-being, and to

identify the intervention component's (supplementation, group sessions, and exercise) impact, feasibility, barriers, enablers, delivery method and overall perception of quality.

Duration and Compensation

Total participation time is approximately **18 weeks**, including screening and final assessments. Participants will receive compensation commensurate with time and travel, with prorated payment for partial completion.

Research Design

Identify the research design appropriate to answer the question(s) under study.

Research Design This study uses a **randomized, double-blind, placebo-controlled, parallel-group, mixed-methods design** to evaluate the feasibility and preliminary efficacy of a **16-week multimodal behavioral and nutritional intervention** for women diagnosed with postpartum depression (PPD).
The research is **experimental** in nature and will employ a **prospective pre-test/post-test control group design**. Participants will be randomly assigned (1:1) to one of two groups:
1) **Qitone™ + Group-Mediated Cognitive Behavioral (GMCB) Intervention (Exercise + Nutrition)**
2) Placebo + Group-Mediated Cognitive Behavioral (GMCB) Intervention (Exercise + Nutrition)

Both groups will receive identical behavioral and exercise components to isolate the additive effect of exogenous ketone supplementation on depressive symptoms and related outcomes.

The study will examine changes from baseline to Week 16 in psychological, behavioral, and physiological outcomes, including:
-Depressive symptoms (Edinburgh Postnatal Depression Scale; EPDS)
-Physical activity and sleep metrics (Ultrahuman Ring data)
-Body composition (DEXA, anthropometrics)
-Blood biomarkers (β-hydroxybutyrate, glucose, insulin, cortisol, CRP)
-Psychosocial outcomes (self-efficacy, self-regulation, perceived competence, maternal functioning, perceived stress, quality of life, and dietary recall)

-Daily home-based monitoring (glucose, ketones, and sleep) and monthly laboratory visits will capture longitudinal change.

The behavioral framework follows the Group-Mediated Cognitive Behavioral (GMCB) model (Brawley et al., 2016; Bandura, 1997), which emphasizes group dynamics and self-regulation to support adherence to lifestyle changes. Integration of exercise, nutrition, and psychosocial support is designed to address the metabolic, psychological, and social contributors to PPD in a comprehensive, fully remote, and scalable model.

Quantitative data will assess feasibility, adherence, and preliminary efficacy, while qualitative data will capture participants' perceptions of behavioral and biochemical change mechanisms.

Findings will inform the design of a larger, fully powered randomized controlled trial for postpartum women with depression.

Detailed Study Procedures

	Y	N	Comments
1. Are you requesting expedited IRB review? Note: The federal regulations establish two main criteria for an expedited review: **a.** The research may not involve more than "minimal risk" (refer to appendix). **b.** The entire research project must be consistent with one or more of the federally defined categories (refer to appendix).	☐	☒	If yes, complete the Expedited Review appendix.
2. Does the research involve genetic testing?	☐	☒	If yes, complete the Genetic Testing appendix.

Describe the selected procedures sufficiently to justify their use in answering the defined research question(s).

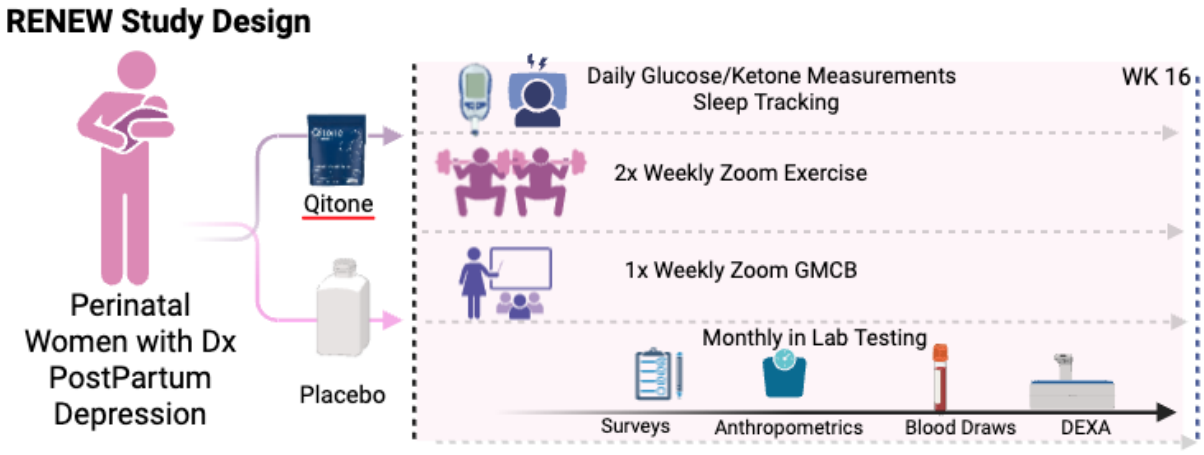


Figure 1 | KAPTIVATE Study Design

Detailed Study Procedures

1. **Screening and Baseline Assessments**
   Participants will complete a **medical intake questionnaire** and **dietary assessment questionnaire**. Anthropometric data will include **height, weight, BMI, and waist and hip circumference**. Eligible participants will provide written informed consent prior to any study procedures.

2. **Randomization**
   Following baseline assessments, participants will be **randomly assigned (1:1)** to one of two conditions:
   - **Ketone Supplement (Qitone™) + Group-Mediated Cognitive Behavioral (GMCB) Intervention (Exercise + Nutrition)**
   - **Placebo + Group-Mediated Cognitive Behavioral (GMCB) Intervention (Exercise + Nutrition)**
     Randomization and blinding will be managed by an independent research coordinator.
3. **Exogenous Ketone Supplementation**
   Participants assigned to the intervention group will consume **Qitone™ exogenous ketone supplement** twice daily for 16 weeks. The placebo group will receive a visually and taste-matched inert beverage. Supplements will be pre-packaged and coded to maintain double-blind conditions. Adherence will be tracked via self-report logs and return of packaging.
4. **Behavioral and Exercise Intervention**
   All participants will engage in:
   - **Two virtual group exercise sessions per week** (30 minutes each), combining resistance and interval-based training tailored to postpartum safety and ACSM guidelines (2025).
   - **One virtual Group-Mediated Cognitive Behavioral (GMCB) session per week** (30–45 minutes), delivered via HIPAA-compliant videoconferencing. Sessions follow the GMCB model (Brawley et al., 2016), emphasizing group support, cognitive reframing, self-regulation, and motivation.
5. **Daily Home Monitoring**
   Participants will perform **daily fasting glucose and ketone measurements** using a handheld finger-stick device (KetoMojo). A small drop of capillary blood (size of a grain of rice) will be analyzed each morning in the fasted state. Data will be stored within the device until downloaded during in-lab visits.
6. **Wearable Sleep and Activity Monitoring**
   Participants will be provided with a **digital wearable ring (FEMOMETER or equivalent)** for continuous measurement of **sleep duration, sleep quality, and physical activity** throughout the 16-week period. Devices will be worn continuously except during bathing or charging.
7. **Monthly In-Lab Visits**
   Participants will attend in-person testing sessions at baseline (Week 0) and every four weeks (Weeks 4, 8, 12, and 16). At each visit, the following will be performed:
   - **Anthropometrics:** Height, weight, BMI, waist and hip circumference.
   - **Body Composition: Dual-energy X-ray Absorptiometry (DEXA)** to assess fat mass, lean mass, and bone density (conducted at Weeks 0 and 16).
   - **Blood Sampling:** Venous blood will be collected (~10 mL per draw) to assess β-hydroxybutyrate (BHB), glucose, insulin, cortisol, and C-reactive protein (CRP).
   - **Pregnancy and Hydration Testing:** Urine specific gravity (USG <1.025) will confirm hydration; pregnancy tests will be conducted as a safety measure prior to blood draws.
8. **Psychological and Behavioral Surveys**
   On each testing day, participants will complete validated questionnaires assessing mood, behavior, and psychosocial outcomes, including:

- **Edinburgh Postnatal Depression Scale (EPDS)** – depressive symptoms (primary outcome)
- **Exercise Self-Efficacy Scale (ESES)**
- **Physical Activity Self-Regulation Scale (PASR-12)**
- **Perceived Competence (Maintaining a Healthy Diet; PCS-D; Exercising Regularly; PCS-E)**
- **Barkin Index of Maternal Functioning (BIMF)**
- **Quality of Life (PROMIS Global Health)** and **Perceived Stress Scale (PSS)**
- **Dietary Recall (DHQ-III Diet History Questionnaire)**

9. **Qualitative Interviews**
   At the conclusion of the 16-week intervention, participants will complete a **semi-structured interview** (~30-60 minutes) followed by secondary, optional **focus group interview** (~45-90 minutes)**.** Both interviews will be used to explore perceived changes in mood, motivation, group support and well-being, and to identify the intervention component's (supplementation, group sessions, or exercise) impact, feasibility, barriers, enablers, delivery method and overall perception of quality.
10. **Follow-Up and Data Review**
    Data from all wearable devices, glucose/ketone meters, and surveys will be securely uploaded to the study database. Adherence and safety will be monitored weekly by the study team. Participants will receive a debriefing and compensation upon study completion.

Describe procedures for data collection. Be sure to specify the source records that will be used to collect data about participants. Upload all surveys, scripts, and data collection forms/spreadsheets to the Other Attachments section of the SmartForm.

All data collection methods align with the study objectives to assess the feasibility and preliminary efficacy of **Qitone™ ketone supplementation** combined with **Group-Mediated Cognitive Behavioral (GMCB)** exercise and nutrition counseling in postpartum women with depression.

1. Blood Collection and Processing

Venous blood samples (~10 mL) will be collected at **baseline (Week 0)** and at **Weeks 4, 8, 12, and 16** following an overnight fast.

- **Processing:** Whole blood will be separated into plasma (EDTA tubes) and serum (clot activator tubes) via centrifugation. Aliquots will be stored in labeled cryovials at −80°C until batch analysis.
- **Capillary Sampling:** Participants will also collect daily fasting **capillary blood samples** using a handheld analyzer (**KetoMojo, USA**) to measure β-hydroxybutyrate (BHB) and glucose concentrations. These data will provide insight into individual variability in ketone response and adherence to supplementation.

2. Blood Sample Analytical Methods

- Capillary glucose and BHB concentrations will be obtained via enzymatic test strips analyzed by handheld device (KetoMojo, USA).

- Serum assays for glucose, insulin, cortisol, and **C-reactive protein (CRP)** will be analyzed using validated commercial kits (Roche Diagnostics, Indianapolis, IN).
- Remaining serum and plasma samples will be stored for secondary analyses related to endocrine and inflammatory markers.

3. Anthropometrics and Body Composition

Anthropometric measurements (height, weight, waist and hip circumference) will be collected during each lab visit to monitor changes in body composition and weight stability.
DEXA scans will be performed at **Weeks 0 and 16** to assess total and regional fat mass, lean mass, and bone mineral density. Each scan requires approximately 7–10 minutes, and participants will be asked to remove all metal jewelry prior to scanning.

4. Wearable Device Data

Participants will be provided with a Femometer (or equivalent) smart ring to continuously monitor sleep duration, quality, and physical activity throughout the 16-week study. Data are stored locally on the device and synced via the accompanying secure application. These data will allow for longitudinal tracking of rest–activity patterns and adherence to physical activity recommendations.

5. Exercise and Behavioral Session Data

All virtual exercise and GMCB sessions will be conducted via a HIPAA-compliant video platform. Attendance, completion logs, and qualitative notes from the facilitator will be recorded as fidelity measures. Participants' self-reported session satisfaction and perceived exertion (RPE scale) will also be collected to evaluate adherence and tolerability.

6. Psychosocial and Behavioral Surveys

Participants will complete the following validated self-report instruments during each laboratory visit:

- Edinburgh Postnatal Depression Scale (EPDS) – primary outcome for depressive symptoms.
- Exercise Self-Efficacy Scale (ESES) – confidence in engaging in exercise.
- Physical Activity Self-Regulation Scale (PASR-12) – physical activity self-regulation.
- Perceived Competence (PCS-D; PCS-E) maintaining a healthy diet; exercising regularly
- Barkin Index of Maternal Functioning (BIMF) – postpartum maternal role functioning.
- PROMIS Global Health and Perceived Stress Scale (PSS) – overall well-being and stress perception.
  All surveys will be administered electronically through REDCap and securely stored on password-protected OSU servers.

7. Qualitative Data Collection

At the end of the 16-week intervention, participants will complete a semi-structured qualitative interview (30-60 minutes, via Zoom) followed by an optional focus group interview (45-90 minutes,

via Zoom) to explore perceived program impact, enablers, barriers, and facilitators of change. Interviews will be audio-recorded and transcribed verbatim for thematic analysis using de-identified participant codes.

8. Data Management and Source Records

All collected data (survey responses, lab results, wearable exports, exercise logs, and qualitative transcripts) will be de-identified and linked using a unique participant ID.

- Primary source records: digital survey forms, lab assay reports, wearable device data exports, Zoom attendance logs, and interview transcripts.
- Data will be stored in REDCap and on secure, password-protected OSU servers accessible only to authorized study personnel.
- All survey instruments, interview guides, and source documents are uploaded in the Other Attachments section of the SmartForm.

Describe the timeline for participant evaluations and the duration of project participation, for both individual study activities and total study participation, when applicable.

Study Week	Activity Type	Specific Procedures and Assessments	Frequency / Duration
Week –1 to 0	**Screening & Baseline**	• Informed consent • Medical intake & diet questionnaires (DHQ-III • Eligibility verification (EPDS, inclusion/exclusion) • Anthropometrics (height, weight, BMI, waist/hip) • Baseline blood draw (BHB, glucose, insulin, cortisol, CRP) • DEXA scan (body composition) • Pregnancy & hydration check (USG) • Survey battery: EPDS, ESES, PASR-12, PCS-D, PCS-E, BIMF, PROMIS, PSS	~90–120 minutes
Weeks 1–4	**Adoption Phase**	• Begin supplementation (Qitone™ or placebo) • 2× weekly virtual group exercise sessions (resistance + interval) • 1× weekly GMCB behavioral counseling session (Zoom) • Daily glucose/ketone monitoring (KetoMojo) • Continuous sleep/activity tracking (ring) • Monthly lab visit (Week 4): blood draw, anthropometrics, surveys	3–4 contacts/week + 1 lab visit
Weeks 5–8	**Transition Phase**	• Continued supplementation • 2× weekly virtual exercise (progression	3–4 contacts/week + 1 lab visit

Study Week	Activity Type	Specific Procedures and Assessments	Frequency / Duration
		individualized) • 1× weekly GMCB behavioral counseling • Daily glucose/ketone and sleep tracking • Monthly lab visit (Week 8): blood draw, anthropometrics, surveys	
Weeks 9–12	**Maintenance Phase I**	• Continued supplementation • 2× weekly virtual exercise • 1× weekly GMCB session • Daily home monitoring (glucose, ketones, sleep) • Monthly lab visit (Week 12): blood draw, anthropometrics, surveys	3–4 contacts/week + 1 lab visit
Weeks 13–16	**Maintenance Phase II & Exit Testing**	• Continued supplementation • 2× weekly virtual exercise • 1× weekly GMCB session • Daily home monitoring (glucose, ketones, sleep) • Final lab visit (Week 16): blood draw, anthropometrics, DEXA, surveys, diet questionnaire (DHQ-III) • Qualitative exit interviews (Zoom)	3–4 contacts/week + final testing visit (~120 min)

Timeline for Participant Evaluations and Duration of Project Participation

Each participant's total involvement in the **RENEW** study will span approximately **17–18 weeks**, including screening, enrollment, baseline testing, the 16-week intervention period, and final assessments. The evaluation timeline is as follows:

- **Screening Call (Week –2 to –1):**
  Interested women will be contacted by research staff to assess preliminary eligibility based on inclusion/exclusion criteria (diagnosis of postpartum depression, postpartum status <12 months, age 18–45, medically cleared for light-to-moderate exercise). Eligible individuals will be scheduled for a consent visit.
- **Consent Visit (Week –1):**
  Conducted in a private space at The Ohio State University Exercise Science Laboratory. The study will be described in full, and participants will review and sign the informed consent form. Baseline demographic, medical history, and lifestyle information will be collected, including dietary assessment and postpartum status.
- **Baseline Testing Day (Week 0):**
  Participants will arrive in a fasted state (>10 hours). Assessments include:
  - Anthropometrics (height, weight, BMI, waist/hip circumference)
  - **DEXA** scan for body composition
  - Fasting blood draw (glucose, insulin, β-hydroxybutyrate, cortisol, CRP)

  - Pregnancy and hydration testing (urine USG <1.025)
  - Completion of baseline psychosocial surveys (EPDS, ESES, PASR-12, PCS-D, PCS-E BIMF, PROMIS, PSS)
  - Device onboarding for glucose/ketone meter and wearable ring setup
- **Weeks 1–4 (Adoption Phase):**
  Participants begin assigned supplementation (Qitone™ or placebo) and start the structured intervention schedule:
  - 2× weekly virtual exercise sessions
  - 1× weekly GMCB behavioral counseling session
  - Daily fasting glucose/ketone readings
  - Continuous sleep/activity tracking via wearable ring
  - Monthly in-lab testing (Week 4): blood draw, anthropometrics, survey battery
- **Weeks 5–8 (Transition Phase):**
  Participants continue supplementation and intervention schedule.
  - Progression of exercise intensity individualized per postpartum safety guidelines
  - Ongoing weekly GMCB sessions and home monitoring
  - Monthly in-lab testing (Week 8): blood draw, anthropometrics, survey battery
- **Weeks 9–12 (Maintenance Phase I):**
  Continued supplementation and behavioral support with maintained session frequency.
  - 2× weekly exercise and 1× weekly GMCB sessions
  - Monthly in-lab testing (Week 12): blood draw, anthropometrics, survey battery
- **Weeks 13–16 (Maintenance Phase II / Exit Phase):**
  Continued supplementation and behavioral sessions.
  - Final in-lab testing (Week 16): blood draw, anthropometrics, DEXA, survey battery, dietary recall
  - Completion of qualitative exit interviews (Zoom, ~30–60 minutes)
- **Week 17–18 (Data Verification and Debrief):**
  Study team verifies device data downloads and survey completion. Participants receive debriefing and compensation following completion of all study procedures.

Total Participant Time Commitment: ~4–5 hours per week including all virtual and self-monitoring activities.

Describe plans for long-term follow-up once all research related procedures are complete, if any, and specify what data will be collected during this period.

No formal long-term follow-up procedures are planned after completion of the 16-week intervention. Once all study-related activities are completed, participants will not be contacted for additional data collection. All data collected during the active study period—including biological samples, body composition data, psychosocial measures, and device-generated metrics—will be securely stored and analyzed in de-identified form. Any future contact or follow-up research involving these participants would require a separate IRB-approved protocol and consent process.

Alternatives to Participation

Indicate any alternatives to participating in the research, if applicable, including available procedures or treatments outside the research that may be advantageous to the participant.

Participants are not required to participate in this research to receive care. Alternatives to participation include seeking PPD) treatment through standard clinical pathways. This may include care from an obstetrician/gynecologist, primary care provider, psychiatrist, psychologist, licensed therapist, or other qualified mental health professional.

Standard treatments for PPD available outside of this study include individual psychotherapy (e.g., cognitive behavioral therapy or interpersonal therapy), pharmacologic treatment (e.g., antidepressant medication), support groups, structured exercise programs, and community-based maternal support services.

Participants may also independently pursue nutritional counseling or exercise programming outside of the research setting.

Choosing not to participate in this study will not affect access to medical care, mental health services, or other community resources.

5. Institutional Approvals

1. Check all institutional approvals that apply to research being conducted at Ohio State.
☐ Comprehensive Cancer Center (CCC) Clinical Scientific Review Committee (CSRC): Approval or exemption required prior to IRB review for all cancer-related research. Upload a copy of the approval letter to the Other Attachments section of the SmartForm.
☐ Institutional Biosafety Committee (IBC): Approval required prior to IRB review for research involving biohazards (recombinant DNA, infectious or select agents, viruses, toxins), gene transfer, or xenotransplantation. Upload a copy of the approval letter to the Other Attachments section of the SmartForm.
☒ Human Subject Radiation Committee (HSRC): Approval required for research involving radiologic procedures for research purposes (e.g., non-clinical care X-rays, DEXA or CT scans, nuclear medicine procedures). Complete the Radiation appendix and upload a copy of the HSRC approval letter to the Other Attachments section of the SmartForm.

6. Participant Population

1. Specify the participant population(s). Check all participant groups that apply. For any population other than adults, complete the applicable appendix.
☒ Adults

☐ Adults with impaired decision-making capacity
☐ Children
☐ Neonates of uncertain viability
☐ Nonviable neonates
☐ Non-English-speaking individuals
☐ Pregnant women/fetuses (only if pregnant women will be intentionally recruited and/or studied)
☐ Prisoners

Describe the sample population from which the study team plans to either recruit or access private, identifiable information for the research.

This study aims to recruit 40 female participants between the ages of 18 to 45 years who are in the postpartum period (≤12 months following childbirth) and have been clinically diagnosed with postpartum depression (PPD). Each participant must meet all inclusion criteria and none of the exclusion criteria at screening to be eligible for participation.

The target sample size (n = 40) was determined to ensure sufficient feasibility data and to estimate preliminary effect sizes for depressive symptoms, behavioral adherence, and metabolic outcomes across both study arms (20 participants per condition: Ketone Supplement + GMCB vs. Placebo + GMCB).

Participants will be recruited through obstetric and women's health clinics, social media advertisements, and community postings targeting postpartum support networks. Recruitment will continue until the desired sample size has been achieved, allowing for an anticipated 10–15% attrition rate across the 16-week intervention period.

Create a numbered list of the eligibility criteria that define who will be included in the final study sample (e.g., age, gender, condition).

Inclusion Criteria

Participants must meet **all** of the following criteria to be eligible for enrollment:

1. Identify as **female** and are between **18–45 years of age**.
2. Are within **12 months postpartum** following a live birth.
3. Have a **clinical diagnosis of Postpartum Depression (PPD)** confirmed by a healthcare provider and/or an **EPDS score ≥10** at screening.
4. Are **medically cleared** by their healthcare provider for light-to-moderate physical activity.
5. Are **willing and able** to participate in virtual group exercise sessions (2× weekly) and behavioral counseling sessions (1× weekly) for 16 weeks.
6. Are **willing to consume** the study supplement (Qitone™ exogenous ketone or placebo) twice daily for the duration of the study.
7. Have **access to reliable internet** and a device capable of participating in Zoom-based sessions.

8. Are **not currently following** a ketogenic or low-carbohydrate diet.
9. Are **able and willing** to complete daily glucose and ketone monitoring and wear a sleep/activity tracking ring.
10. Are **fluent in English** and able to read and provide informed consent.

Exclusion Criteria

Participants will be **excluded** from the study if any of the following apply:

1. Current **pregnancy** or planning to become pregnant during the study period.
2. **Breastfeeding exclusively** if determined by their healthcare provider to be at risk for dietary modification or supplement use.
3. Diagnosed with a **severe psychiatric disorder** (e.g., bipolar disorder, psychosis, schizophrenia) or current suicidal ideation requiring crisis intervention.
4. History of **seizure disorders**, **uncontrolled hypertension**, or **cardiovascular disease** that would preclude participation in exercise.
5. Current use of **ketone supplements**, **GLP-1 receptor agonists**, or **weight loss medications**.
6. Known **metabolic, renal, or hepatic disorders** that may interfere with ketone metabolism or supplement safety.
7. Participation in another **interventional study** within the past 30 days.
8. Any condition that, in the judgment of the investigators, would make participation unsafe or compromise study integrity (e.g., inability to adhere to study schedule).

If appropriate, describe why certain populations may be excluded (e.g., non-English speaking individuals for studies involving informed consent).

Certain populations are excluded from participation in the RENEW study to ensure participant safety, data quality, and intervention fidelity. Non-English-speaking individuals are excluded because the study materials, informed consent forms, and behavioral counseling sessions are currently available only in English, and accurate comprehension is essential for informed participation and adherence to intervention components. Pregnant women and those planning pregnancy are excluded to minimize risk associated with hormonal changes and supplement exposure during gestation. Individuals with severe psychiatric disorders or current suicidal ideation are excluded to prevent potential worsening of symptoms that require specialized mental health care beyond the scope of this study. Participants with metabolic, renal, or hepatic disorders are excluded due to possible contraindications to ketone metabolism and supplement safety. These exclusions are designed to protect vulnerable populations and maintain the internal validity of the study's outcomes.

Number of Participants

The number of participants is defined as the number of individuals who agree to participate (i.e., those who provide consent or whose records are accessed) even if all do not prove eligible or complete the study. The total number of research participants may be increased only with prior IRB approval.

1. Indicate the number of participants to be enrolled locally.	40
2. For multi-site studies, indicate the total number of participants to be enrolled across all sites.	N/A

Explain how this number was derived (e.g., meets statistical power, limited population). If applicable, explain how many individuals are expected to agree to participate and how many evaluable participants are needed to conduct the study (excluding screen failures).

A total of 40 participants (20 per arm) will be enrolled in this pilot, feasibility-focused randomized controlled trial. This sample size allows for **estimation** of feasibility outcomes (e.g., recruitment, adherence, and retention) with acceptable precision and provides preliminary data on depressive symptom change.
Assuming ~15–20% attrition, 32–34 evaluable participants are expected. With an SD of 5 on the Edinburgh Postnatal Depression Scale (EPDS) and correlation of 0.6 between time points, this sample provides ~80% power (α=0.05) to detect a 3–3.5 point between-group difference—approximately the minimal clinically important difference for PPD.
Enrollment targets also account for expected screening yield (~80% eligible, 60% consented). The proposed number balances feasibility, resource constraints, and the need to obtain reliable estimates for a future larger-scale trial.

Participant Identification

Describe how potential participants will be identified (e.g., advertising, individuals known to the investigators, record review).

Participants will be recruited through posted flyers throughout the Ohio State College Campus in locations visible to Ohio State faculty and the Wexner medical center. This includes but is not limited to faculty labeled buildings, administrative offices, research buildings, parking areas, faculty lounges, lecture halls and classrooms, health sciences buildings, and common spaces. Planned methods of recruitment include the study team telling others about the study via word of mouth, then handing them a flyer if they are interested, or putting them in touch with the scheduling team by relaying the scheduling team member's email. Recruitment fliers will also be posted on social media, such as Meta ads. Recruitment flyers will instruct interested individuals to email the study team for additional information about the study. The ResearchMatch and Study Search database will also be used to recruit participants.

Explain how the investigator(s) will gain access to this population, as applicable, and provide evidence that you will be able to recruit the necessary number of participants to complete the study.

The study team will recruit participants from the local Columbus, Ohio community, including individuals affiliated with The Ohio State University and the broader surrounding area. Investigators

will gain access to the target population—women in the perinatal women diagnosed with PPD—through IRB-approved recruitment strategies, including:

- Posting flyers in campus buildings, health centers, and community spaces
- Using digital advertisements via social media platforms and university-affiliated listservs
- Potential participants will contact the study team directly, after which a screening call will be conducted to assess eligibility.

Feasibility of Recruitment: Based on prior recruitment success in similar dietary intervention studies conducted by the research team and affiliated laboratories, including those led by Dr. Madison Kackley, there is strong evidence that the target sample size is feasible. The study's inclusion criteria are broad enough to capture a representative segment of women in the perinatal stage with diagnosed PPD, and the research team has existing infrastructure for outreach and community engagement. Recruitment progress will be monitored continuously, and additional outreach methods will be implemented if necessary to meet enrollment goals.

Participant Recruitment and Selection

Describe how potential participants will be screened or otherwise determined to be eligible.

Potential participants will be identified through, social media advertisements, health center and community postings targeting postpartum support networks. Interested individuals will complete an initial phone prescreening conducted by trained study staff to assess basic eligibility, including postpartum status, age, medical history, and current depressive symptoms.

Eligible candidates will be scheduled for a consent visit, during which the study purpose, procedures, and expectations will be reviewed in detail. After providing informed consent, participants will complete a brief medical history questionnaire, lifestyle and dietary assessment, and the Edinburgh Postnatal Depression Scale (EPDS). A score of ≥10 on the EPDS and/or a clinical diagnosis of postpartum depression by a healthcare provider will confirm eligibility. Eligibility will be verified by the principal investigator or designated research staff prior to study enrollment.

Describe the recruitment process, including the setting in which recruitment will take place.

Print advertisements will instruct interested potential participants to contact the study center for any additional information. Participants may either respond to the email address to set up a phone call or may call during the phone-in hours. One of the key personnel involved in the project will describe the study and determine preliminary qualifications by conducting a scripted phone interview. Participant answers to qualifying criteria questions will be recorded to assess whether or not the person calling meets the initial qualifying criteria. If it is determined that the interested participant meets qualifying criteria, an appointment will be made for the interested participant to visit the study center for a screening meeting. During the screening meeting the study will be described to the interested participant in full detail, an informed consent form will be signed, any questions the interested participant has will be responded to and health history information will be collected to determine final eligibility.

Explain how the recruitment process respects potential participants' privacy.

Potential participants who see the recruitment material will be directed to reach out to study team. The study team will not reach out to any potential participants. All data collected with the exception of the medical history questionnaire, consent form and the responses to the phone script will use a unique subject identifier instead of the subject name. All files will be protected by the previously stated privacy/confidentiality measures. We will only make inquiries about information required for the study. As stated in the informed consent form, subjects can withdraw at any time.

7. Cost to Participants and Incentives to Participate

Potential Costs/Reimbursements

Describe any potential costs participants or their insurer will incur as a result of study participation (e.g., parking, study drugs, diagnostic tests). Indicate here which costs, if any, will be reimbursed or covered by the study.

Participants will not be expected to pay for any study-related procedures, materials, or interventions. All costs associated with the intervention—including ketone supplements, nutritional counseling, DXA scans, blood tests, ovulation tracking devices, and other study assessments—will be covered by the study.

Incentives

Describe any compensation or other incentives (e.g., free services, cash payments, gift cards, classroom credit) that will be offered to potential participants. Include the amount and timing of all incentives or compensation, the form of compensation (e.g., cash, check, gift card), and how the compensation will be received (e.g., mailed, in person, online). This information must also be included in the consent form.

Participants will receive a total of $150 for their time and participation in the RENEW study. Compensation will be provided in electronic gift cards (e.g., Visa or Amazon) distributed in two installments to encourage continued participation and completion of study procedures.

- $75 will be provided after completion of the midpoint (Week 8) assessments.
- $75 will be provided after completion of the final (Week 16) assessments.

Gift cards will be sent electronically via email within two weeks of completing each assessment milestone. Participants who withdraw early will receive prorated compensation for the portions of the study they have completed (e.g., partial participation through Week 8).

This compensation amount reflects reasonable reimbursement for participant time, effort, and commitment across the 16-week intervention period and associated assessments.

8. Compensation for Research-Related Injury

If the research involves greater than minimal risk to participants, describe the available compensation in the event of research related injury or explain why no compensation is available.

In the event of a research-related injury resulting from participation in this study, medical treatment will be made available to the injured participant. However, there is no formal program for financial compensation or payment for medical costs or other expenses incurred due to such an injury. Treatment may be provided at the participant's own expense, or billed to their insurance company if applicable.

The lack of compensation is due to institutional policy and the nature of research funding. Participants will be informed that they are not waiving any legal rights by agreeing to participate, and they retain the right to seek legal remedies as permitted by law.

9. Informed Consent Process

1. Specify the consent process(es) to be used for the study. Check all processes that apply. For any waivers or alterations, complete the applicable appendix.

- ☒ Informed Consent with Written Signature (e.g., on paper)
- ☐ Informed Consent with Electronic Signature
  Note: If the method used to obtain electronic signatures does not qualify as a legally valid signature, also check "Waiver of Consent Documentation." See guidance provided by the Office of Technology and Digital Innovation.
- ☐ Waiver of Consent/Parental Permission Documentation
- ☐ Deception (i.e., procedure in which investigators deliberately mislead participants during research by withholding information or providing false information).
  Note: If this is selected, also check "Waiver or Alteration of the Consent Process."
- ☐ Waiver or Alteration of the Consent Process
- ☐ Waiver of the Parental Permission Process

Describe the consent process. Explain when and where consent will be obtained and how participants or their legally authorized representatives will be provided sufficient opportunity to consider participation.

Informed consent will be obtained in person during a scheduled visit at the Kinesiology Laboratory at The Ohio State University (305 Annie and John Glenn Avenue, Columbus, OH). During this visit, a trained member of the research team will meet with the participant in a private office setting to review the study in detail. Participants will be provided with the written informed consent form in advance or at the visit and given ample time to review it, ask questions, and consider participation

without pressure. The study procedures, risks, benefits, and alternatives will be explained verbally, and participants will be encouraged to ask questions to ensure understanding. Only after all questions have been addressed and the participant confirms understanding and willingness to participate will they be asked to sign the consent form. Participants will be reminded that their participation is voluntary, and that they may withdraw at any time without penalty.

Specify who will provide consent or permission (i.e., participant, legally authorized representative, parent and/or guardian).

The participant will provide consent.

Explain how the possibility of coercion or undue influence will be minimized in the consent process.

To minimize coercion or undue influence, the consent process will occur in a private setting, and participants will be clearly informed that participation is entirely voluntary. They will be given sufficient time to review the consent form, ask questions, and make an independent decision without pressure. Research staff will emphasize that declining or withdrawing from the study will not result in any penalty or loss of benefits.

10. Privacy of Participants

Describe the steps that will be taken to protect participants' privacy and make them feel at ease with the research situation in terms of the questions being asked and the procedures being performed.

Participant privacy will be protected during the recruitment process by ensuring that initial contact is participant-initiated whenever possible. Recruitment materials (e.g., flyers, email announcements, social media posts) will provide study information and direct interested individuals to contact the research team voluntarily via a secure university email address or study phone line. The research team will not publicly identify or approach individuals regarding their potential eligibility.

Any responses from interested individuals will be handled confidentially. Communications will occur through secure OSU email systems or private phone calls, and no protected health information will be requested in public settings. Screening conversations will be conducted privately (via secure phone call or private office space) to prevent inadvertent disclosure of personal or health-related information.

If recruitment occurs through clinics or partner organizations, providers will share study information directly with potential participants, and only individuals who independently express interest will have their contact information shared with the research team (with permission).

No participant names or identifying information will be collected until individuals voluntarily initiate contact and provide consent to proceed with screening. All recruitment records will be stored securely and accessible only to authorized study personnel.

11. Confidentiality and Management of Study Materials

	Y	N	Comments
1. Does the research involve obtaining and storing participants' data and/or biospecimens for future, unspecified, research?	☐	☒	If yes, complete the Repositories appendix.

Describe the steps that will be taken to secure study data.

Each participant will be assigned a unique subject identifier (Study ID) that replaces any personally identifying information in study records. For example, participants will be labeled using a coded identifier (e.g., RENEW-01, RENEW-02). These codes will be used on all biological samples, surveys, and electronic data.

The link between participant names and study IDs will only appear on the signed informed consent form and the master code key, both of which will be stored separately from study data. These materials will be kept either in a locked file cabinet located in the Kinesiology Laboratory file storage room (PAES A4) or in password-protected electronic folders on secure OSU servers accessible only to the research team. Biological specimen will be stored in -80 degree freezer units in the PAES Laboratory (A035). This room is locked and required Kinesiology Lab swipe access.

All study-related electronic files, including survey data and biological sample results, will be stored in password-protected, access-restricted directories. Hard copies (if any) will be securely maintained in locked cabinets within restricted-access lab spaces. Data will be retained for up to ten years following publication or final study completion, after which all identifiable data will be securely destroyed.

Participants will be informed that participation is voluntary and that they may withdraw at any time without penalty. All participants who sign the informed consent form will be considered enrolled in the study. Data collected after consent, including for participants deemed ineligible after screening, will be handled with the same confidentiality measures. Prescreening data from ineligible individuals will be deleted.

Any incidental findings (e.g., unexpected health-related indicators) discovered during study procedures will be shared directly with the participant in a non-diagnostic format, allowing them to consult their healthcare provider for further evaluation if desired. All unpublished data and findings will remain strictly confidential.

Describe any procedures that will be used for quality control of collected data.

All research staff will be trained on standard operating procedures for data collection, storage, and entry to ensure consistency across all study visits. For all the data collected over the course of the study for each participant (i.e., records, biological samples and questionnaires) a unique subject identifier (i.e., a code) will be assigned and used instead of the subject's name. The code for each participant which links the subject name with their identifier will only be available to research personnel. Electronic CRFs or other documents will identify participants by initials, number, or code, and not by name. The Investigator will keep a separate log showing codes, names, and addresses.

Describe how data (and if applicable, biospecimens) will be handled study wide.

Any records that contain the subject's name and identifier will either be stored in the Kinesiology file storage room in a file cabinet (locked) or protected on a computer via password protection on the individual digital file and password protection on the computer the file(s) are stored on. All other records that contain the subject identifier only will also be kept in either a file cabinet in our locked file storage room or on a password protected computer. Subject names will never be used in any presentation or publication resulting from this study.

Specify the identifiable information that will be included in the data or associated with the biospecimens.

The following identifiable information may be collected and associated with study data and biospecimens:

- Participant name (for scheduling and record-keeping only)
- Date of birth
- Contact information (e.g., phone number, email address)
- Medical and menstrual history details
- Study ID linked to coded biospecimens and data
- Dates of study visits and procedures
- All identifiable information will be stored separately from research data and linked only via coded identifiers. Biospecimens and data used for analysis will be de-identified to maintain participant confidentiality.

Specify where and how data or biospecimens will be stored and for how long.

The records will be maintained until the data are published and up to a maximum of ten years after the completion of the study. Biospecimen will be stored in a –80 freeer in the PAES Laboratory for up to 5 years.

Specify who will have access to the data or biospecimens.

Access to identifiable data and biospecimens will be limited to authorized members of the research team at The Ohio State University, including the principal investigator, co-investigators, and designated study staff involved in data collection and analysis.

Specify who will be responsible for receipt or transmission/transport of the data or biospecimens and how will transmission/transport will occur.

Members of the study team will be responsible for the receipt, transmission, and transport of data and biospecimens.

- Biospecimens (e.g., blood, urine) will be transported by trained study personnel using secure, labeled containers following institutional biosafety and handling protocols. Samples will be stored in a secure, access-controlled laboratory (PAES 035).
- Electronic data will be transmitted via secure, encrypted university-approved systems, and stored on password-protected, access-restricted servers.

All transfers will comply with HIPAA, university policy, and applicable federal regulations to ensure participant confidentiality and data security.

Indicate what will happen to identifiable data at the end of the study (e.g., kept identifiable, coded, deidentified). If identifiers will be maintained, provide the rationale supporting this request. If the data will be deidentified, describe the process.

At the conclusion of the study, all identifiable data will be deidentified. The process will involve permanently separating the participant's name and any other personal identifiers from their corresponding data. The linking file that contains both the participant's name and Study ID (e.g., RENEW #01) will be destroyed following publication of the study results or no later than ten years after study completion. All remaining research data will be retained in a deidentified format, labeled only with the Study ID. The consent forms, which are the only documents containing personal identifiers, will be securely shredded if in paper format or permanently deleted if stored digitally, after the data retention period. Once the data have been deidentified, there will be no means to re-identify individual participants, ensuring participant privacy and compliance with data protection standards.

If data or biospecimens will be shared broadly with outside groups (i.e. dbGaP), specify what will be shared, with whom, in what form (e.g., identifiable, coded, deidentified/anonymized).

N/A

If data or biospecimens will be shared broadly with outside groups or databases (i.e. dbGaP), specify whether participants will have the ability to opt-in or remove the data/biospecimens from these outside groups later if they choose. Generally, if the materials are identifiable, a participant should be able to withdraw them unless retention is required under federal regulation (e.g., FDA).

N/A

12. HIPAA Research Authorization

PHI is health information that is individually identifiable and created or held by a covered entity. Health information is considered individually identifiable when it contains one or more HIPAA Identifiers or when there is a reasonable basis to believe the information can be used to identify an individual.
For more information, see The HIPAA Privacy Rule

1. Is individually identifiable Protected Health Information (PHI) subject to the HIPAA Privacy Rule requirements to be accessed, used, or disclosed in the study?
   - ☒ No
   - ☐ Yes

Note: The PHI obtained as part of this research must not be reused or disclosed to any other person or entity other than those with IRB approval, except as required by law or for authorized oversight of the research project, without additional approval. IRB approval must be obtained for other research involving the use or disclosure of this PHI.

2. If PHI is accessed, used, or disclosed, specify how authorization requirements will be met (check all that apply). For any waivers or alterations, complete the applicable appendix.
   - ☐ Written Authorization
   - ☐ Partial Waiver (for identification and recruitment purposes only)
   - ☐ Full Waiver (authorization will not be obtained)
   - ☐ Alteration (written authorization will not be obtained or all required elements will not be included)

Explain how the requested PHI (i.e., HIPAA identifiers and associated health information) are the minimum necessary information to accomplish the research objectives.

N/A

13. Reasonably Anticipated Benefits

Potential Direct Benefits:

List the potential benefits that participants may expect as a result of this research study. If there are no direct benefits to individual participants, indicate so.

Participants may experience potential benefits from engaging in this study, including:

- Gaining personalized feedback on sleep, activity, and metabolic health data through wearable tracking and daily glucose/ketone monitoring.
- Receiving access to group-based behavioral support (Group-Mediated Cognitive Behavioral, GMCB) and virtual exercise sessions aimed at improving postpartum wellness.
- Access to nutrition education and individualized support from a study dietitian.
- Possible improvements in mood, energy levels, sleep quality, and emotional regulation, particularly in relation to postpartum depressive symptoms.
- Receiving ongoing social connection and support from other postpartum women in a structured, professional setting.

However, these benefits are not guaranteed, and some participants may not experience direct personal improvement. The primary benefit of participation is contributing to research that may improve understanding and future interventions for postpartum depression and maternal mental health.

Potential Societal Benefits:

List the potential benefits that society and/or others may expect as a result of this study.

This study may contribute to important scientific and public health knowledge by:

- Advancing understanding of how exogenous ketone supplementation and behavioral counseling influence mood, metabolism, and recovery in women with postpartum depression.
- Informing the development of non-pharmacologic, nutrition-based strategies to support maternal mental health and reduce reliance on medications with adverse effects during breastfeeding.
- Enhancing awareness of postpartum mental health and encouraging more integrative, holistic care models that address both physiological and psychological well-being.
- Providing early data to inform future clinical trials and evidence-based guidelines for nutrition and behavioral support in women experiencing postpartum mood disorders.

14. Risks, Harms, & Discomforts

Potential Risks, Harms, and/or Discomforts

Describe all reasonably expected risks, harms, and/or discomforts that may apply to the research. At a minimum, include the risk of breach of data confidentiality. Discuss severity and likelihood of occurrence. As applicable, include potential risks to an embryo or fetus if a woman is or may become pregnant. Consider the range of risks, including physical, psychological, social, legal, economic, and any other potential risk to the study population.

Risks and Discomforts

Participation in this study is expected to involve greater than minimal risk, comparable to those encountered in daily life or during standard wellness activities. The following potential risks and discomforts may occur:

1. Physical Risks
-Exercise-related risks: Participants may experience mild to moderate muscle soreness, fatigue, or strain during the supervised exercise sessions. The risk of injury (e.g., muscle or joint strain) is low due to the light-to-moderate intensity design and professional supervision.
-Fingerstick blood sampling: Minor discomfort, bruising, or bleeding may occur with daily glucose and ketone measurements. These risks are brief and localized.
-Venipuncture for blood draws: Blood collection may cause mild discomfort, bruising, fainting, or infection at the needle site; all procedures will be performed by trained personnel following aseptic technique.
-Ketone supplement (Qitone™): Possible side effects include mild gastrointestinal discomfort (nausea, bloating, or diarrhea). These effects are typically transient and resolve with continued use or dose adjustment. Participants will be advised to take the supplement with food or fluids to minimize symptoms.

2. Psychological Risks
-Mood fluctuations: Discussing depressive symptoms or participating in behavioral sessions may trigger emotional distress or temporary discomfort. A licensed study clinician or PI will be available to address acute concerns, and participants will be referred to their healthcare provider or mental health services if needed.
-Postpartum sensitivity: Some participants may experience frustration or emotional vulnerability when discussing postpartum challenges in a group format. Facilitators will maintain a supportive environment and provide individual follow-up if necessary.

3. Data Confidentiality Risks
-There is a small risk of breach of confidentiality due to the collection of identifiable data (e.g., name, contact information). This risk will be minimized through use of coded study IDs, password-protected electronic storage, and restricted data access. No identifiable information will be shared outside the research team.

4. Reproductive and Pregnancy Risk

-Although unlikely, if a participant becomes pregnant during the study, the effects of exogenous ketone supplementation on the fetus are not well established. Participants will be asked to notify study staff immediately if pregnancy occurs and may be withdrawn for safety.

5. Other Risks
-Social risks: Disclosure of personal experiences during group sessions may cause minor discomfort. All participants will be reminded to maintain confidentiality within the group.
-Economic risks: None anticipated. Participation will not affect employment or healthcare status.

6. Body Composition-DEXA
This study involves exposure to radiation from a DEXA EXPERT spine, femur or whole-body scan. This radiation exposure is used for research purposes only. The total amount of radiation that the participant will receive in this study is around 0.78 mSv or 78 mrem and is approximately equivalent to a uniform whole-body exposure of 47 days of exposure to natural background radiation. This use involves minimal risk and is necessary to obtain the research information desired. DEXA risks include exposure to as much radiation as a flight from New York to Los Angeles which may elevate cancer risk. DEXA risks are minimized as the measures are only performed twice on each participant.

All foreseeable risks are expected to be mild to moderate in severity and transient. Participants will be monitored throughout the study, and any adverse events will be documented and reported per IRB guidelines.

Risk Mitigation

Describe how risks, harms, and/or discomforts will be minimized. Address all risks described in the section above.

All anticipated risks, harms, and discomforts described above will be minimized through established safety protocols and continuous monitoring by trained research personnel.

Exercise Safety: All virtual exercise sessions will be led by qualified exercise professionals with experience in postpartum populations. Participants will be screened for exercise readiness using a standard health questionnaire and will require written clearance from their healthcare provider. Exercise prescriptions will follow national guidelines for postpartum activity and will emphasize gradual progression, symptom awareness, and low-to-moderate intensity. Participants will be instructed to stop immediately if they experience pain, dizziness, or other adverse symptoms.

Blood Collection Procedures: All blood draws will be performed by trained personnel using sterile technique to minimize risk of bruising, fainting, or infection. Capillary fingersticks will use single-use, sterile lancets. Participants will be seated during sample collection to prevent falls due to dizziness.

Supplement Administration: Participants will receive detailed written instructions on supplement dosing and potential side effects (e.g., mild gastrointestinal discomfort). Any adverse symptoms will be recorded and reviewed by the study team. Participants experiencing ongoing discomfort will be advised to discontinue the supplement and consult their healthcare provider.

Behavioral and Emotional Support: Group-mediated cognitive behavioral (GMCB) sessions will be led by trained facilitators who are sensitive to postpartum emotional needs. If a participant demonstrates worsening depressive symptoms or distress, the session leader will immediately notify the principal investigator and provide a referral to their healthcare provider or OSU Counseling and Consultation Services.

Confidentiality Protections: Participant data will be coded, de-identified, and stored securely on password-protected devices or in locked storage rooms as described previously. Only approved research staff will have access to identifiable information.

If testing will be performed to identify individuals who may be at increased risk (e.g., pregnant women, individuals with HIV/AIDS, depressive disorders), address the timing and method of testing; include how positive test results will be handled.

Pregnancy testing will be conducted prior to enrollment using a urine-based test. Participants with a positive result will be excluded from the study. Ongoing monitoring for pregnancy may occur during the study, and any participant who becomes pregnant will be withdrawn immediately to prevent potential risk to the fetus. All results will be kept confidential and communicated privately by trained study staff.

15. Monitoring

	Y	N	Comments
1. Does the research involve greater than minimal risk (i.e., the harms or discomforts described are beyond those ordinarily encountered in daily life or during the performance of routine physical or psychological tests)?	☒	☐	If yes, describe a data and safety monitoring plan below.

Describe the plan to oversee and monitor data collected to ensure participant safety and data integrity. If the plan is outlined in a separate document, upload it to the documents page of the application SmartForm. If not, describe it below and include the following:

- The information that will be evaluated (e.g., incidence and severity of actual harm compared to that expected)
- Who will perform the monitoring (e.g., investigator, sponsor, or independent monitoring committee/board)
- Timing of monitoring (e.g., at specific points in time, after a specific number of participants have been enrolled/treated) and
- Decisions to be made as a result of the monitoring process (e.g., provisions to stop the study early for unanticipated problems)

Participant safety and data integrity will be overseen by the Principal Investigator (PI) and trained study team members. Data will be reviewed on an ongoing basis throughout the 12-week intervention to monitor for adverse events and protocol compliance.

1. What will be monitored: Incidence and severity of side effects (e.g., from diet or supplements), and participant-reported symptoms.
2. Who monitors: The PI and designated study staff will conduct monitoring. No independent board is required for this minimal-risk study.
3. When: Data will be reviewed at each study visit, and adverse events will be evaluated as they occur.
4. Decisions: Participants may be withdrawn for safety concerns (e.g., pregnancy). All findings will be documented and reported to the IRB as required.

16. Data Analysis

Internal/External Validity

Describe measures that have been taken to avoid study bias (consider the threats to internal/external validity).

1. **Randomization:** Participants will be randomly assigned (1:1) to one of two study arms — *Qitone™ + GMCB (Exercise + Nutrition)* or *Placebo + GMCB* — using a computer-generated allocation schedule to minimize selection bias.
2. **Standardized Protocols:** All procedures (e.g., blood draws, DEXA scans, exercise sessions, behavioral sessions) will follow standardized operating protocols to ensure methodological consistency.
3. **Blinded Data Analysis:** While the study is single-blind (participants blinded to supplement assignment), data will be coded and analyzed by team members unaware of group allocation to reduce analytical bias.
4. **Validated Tools:** Measurement tools (e.g., EPDS, PROMIS, DEXA, KetoMojo) are validated instruments, ensuring internal consistency and reliability of outcomes.
5. **Frequent Monitoring:** Weekly behavioral check-ins and monthly lab visits will promote adherence and allow early identification of deviations or adverse effects.
6. **Clear Inclusion/Exclusion Criteria:** Restrictive eligibility criteria will reduce heterogeneity and confounding variables that could compromise internal validity.
7. **Device-Based Data Collection:** Continuous glucose, ketone, and sleep tracking via wearable devices provide objective, time-stamped data, minimizing recall bias.
8. **Participant Engagement:** Regular feedback, check-ins, and supportive behavioral counseling sessions improve protocol adherence and data completeness, strengthening external validity.

Data Analysis Techniques

Specify the analytic techniques the researcher will use to answer the study questions. Indicate the statistical procedures (e.g. specific descriptive or inferential tests) that will be used and why the procedures are appropriate. Note: The IRB does not need the actual formulas to be used, just a description of them. If applicable, specify the proposed analytic approaches for qualitative data.

1. **Descriptive Statistics:** Used to summarize baseline characteristics (e.g., age, BMI, postpartum duration, depression severity) and adherence measures (e.g., session attendance, supplement compliance).
2. **Primary Outcome Analysis:** Changes in *Edinburgh Postnatal Depression Scale (EPDS)* scores from baseline to Week 16 will be analyzed using a **repeated-measures ANOVA** or **mixed-effects model**, controlling for baseline scores and relevant covariates (e.g., parity, breastfeeding status).
3. **Secondary Outcomes:**
    - **Physiological Measures:** Two-way mixed ANOVA or paired *t*-tests will assess changes in glucose, ketone levels, DEXA-derived body composition, and metabolic markers across time and between groups.
    - **Behavioral Measures:** Independent *t*-tests or nonparametric alternatives (Mann–Whitney U) will compare group differences in self-efficacy (ESES), self-regulation (PASR-12), perceived competence (PCS-D; PCS-E) and maternal functioning (BIMF).
    - **Categorical Data:** Chi-square tests will be used for variables such as retention and adherence category.
4. **Qualitative Data:** Responses from post-intervention feedback and GMCB session transcripts will be analyzed using **thematic content analysis** to identify key patterns in participants' perceived changes in mood, motivation, group support and well-being, and to identify the intervention component's (supplementation, group sessions, or exercise) impact, feasibility, barriers, enablers, delivery method and overall perception of quality.
5. **Effect Sizes and Significance:** All analyses will use an alpha level of $\mathbf{p < 0.05}$ for statistical significance. Effect sizes (e.g., Cohen's *d*, η^2) will be calculated to assess magnitude of change.
6. **Missing Data:** Intent-to-treat principles will be applied, with multiple imputation used as appropriate for missing values.

These analytic procedures are appropriate for evaluating the **feasibility, preliminary efficacy, and behavioral mechanisms** of the intervention while addressing the study's mixed-methods design and longitudinal outcomes.

17. Bibliography

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