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Eight weeks of lentil consumption attenuates insulin resistance progression without increased gastrointestinal symptom severity: A randomized clinical trial

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ABSTRACT

Lentils lower acute glycemic responses and promote satiety, benefits that may aid in chronic disease prevention. However, perceived gastrointestinal (GI) effects may deter inclusion of dietary pulses in the diet. We hypothesized that 8 weeks of lentil-based vs meat-based meals would improve glycemic control and improve satiety in metabolically at-risk, nondiabetic adults. Because GI symptoms are rarely reported, we also explored the temporal effects of symptom severity. Adults with an increased waist circumference (male > 40 inches, female > 35 inches) participated in an 8-week dietary intervention that included 5 prepared midday meals each week that were isocaloric but varied in cooked green lentil dosage: 0 g (CON), 300 g (MOD), or 600 g (HI). Assessments included glucose and insulin integrated area under the curve measured during a 75-g carbohydrate tolerance test, hepatic Homeostatic Model of Insulin Resistance (HOMA-IR), and peripheral insulin resistance. On 1 randomized day each week, satiety was assessed at 4:00 PM and GI symptoms at 8:00 PM. A linear model assessed changes in glycemic and GI measures by meal group. Thirty adults (mean $\pm$ SD; age, 41.6 $\pm$ 11.7 years, body mass index, 35.1 $\pm$ 6.3) completed the intervention. HOMA-IR increased in CON (+1.2 units) and decreased in a dose-dependent manner in MOD (−0.9 units, $P = .03$) and HI (−1.5 units, $P < .01$) relative to CON. Most participants (87.4%) reported no to mild GI symptoms. Of these, flatulence was mild on average with bloating, abdominal discomfort, and cramping severity 0.3, 0.5, and 0.5 units lower ($P < .001$). We observed a dose-dependent reduction on rising hepatic insulin resistance and low GI symptom severity with long-term lentil consumption in metabolically at-risk adults.

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Abbreviations: BMI, body mass index; CHOL, cholesterol; CON, control; CTT, carbohydrate tolerance test; DHQ III, diet history questionnaire III; GI, gastrointestinal; GLU, glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HEI, healthy eating index; HI, high; HOMA-IR, Homeostatic Model of Insulin Resistance; iAUC, incremental area under the curve; INS, insulin; ISI_{0,120}, insulin sensitivity index 0, 120; LDL, low-density lipoprotein; MOD, moderate; PPGR, postprandial glycemic response; T2DM, type 2 diabetes mellitus; TG, triglyceride.

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1. Introduction

The Centers for Disease Control and Prevention estimates that 13% of US adults have diabetes and that 10.5% of adults have prediabetes based on their fasting glucose (GLU) and glycated hemoglobin levels (HbA1c) [1]. Type 2 diabetes mellitus (T2DM) is a progressive disorder characterized by chronic elevated blood GLU and altered GLU, lipid, and protein metabolism from impaired insulin (INS) delivery and action [2]. There are genetic, behavioral, and metabolic risk factors associated with greater risk of T2DM development that in part include excessive body fat, particularly around the abdomen, and increased INS resistance in the early phase of T2DM progression [3]. Lifestyle interventions such as healthy dietary changes can be used to prevent T2DM [4], with whole grains, fruits, vegetables, nuts, and legumes shown to reduce T2DM risk by 20% [5].

Reduction of the postprandial glycemic response (PPGR) plays a vital role in the prevention and management of metabolic syndrome and diabetes [6,7]. Regular incorporation of pulses offers a practical dietary means to improve glycemic control, blood lipids, body weight, and reduce disease risk in metabolically at-risk populations [8,9]. Pulses are considered legumes and include chickpeas, lentils, and dry peas, which are nutritionally dense, offering bioactive compounds and fiber but are relatively low in fat and sodium. The high fiber content in pulses promotes a delay in gastric emptying and slow absorption, which contributes to a low glycemic index score [10,11], offering acute benefits to fasting blood GLU and INS. It also offers a reduction of PPGR to the subsequent meal; this has been coined as “the second-meal effect” [10,12,13]. Individuals who regularly consume foods lower in the glycemic index scale and higher in fiber may accumulate the benefit of repeated second-meal effects and have improved GLU tolerance and a decreased risk for INS resistance and developing type 2 diabetes [14].

Despite evidence supporting multiple health benefits, legume consumption among US adults is low, with 15% of the total population estimated to eat the amount of legumes (≥ 87.5 g/d) recommended to achieve disease prevention benefits [15]. Consumer incorporation of legumes, particularly pulses, may be difficult because of real and perceived barriers, including abdominal discomfort, long preparation time, lack of knowledge on preparation, and lack of familiarity because of familial and cultural food habits [16]. Consumers commonly report gastrointestinal (GI) symptoms as a barrier [17]; yet, GI symptoms are rarely reported in pulse interventions [9]. Increased transparency of reported gastrointestinal symptoms in pulse interventions and addressing other barriers can help encourage and increase pulse consumption among consumers so that they may secure health benefits.

There are limited randomized clinical trials evaluating long-term pulse consumption on metabolic health, especially trials examining specifically lentil consumption at current US Department of Agriculture (USDA) pulse recommendations, which is approximately 1.5 cups of cooked pulses for adults per week with a caloric need of 2000 calories per day [9,18]. This is of note as glycemic benefits vary by pulse variety, how pulses are added to the diet (i.e., whole vs ground), pulse dose, and duration of pulse inclusion in the diet [10]. The aim of this

study was to examine the impact of 8 weeks of 0, 300 (1.5 cups), or 600 (3 cups) g of lentils per week affect measures of glycemic control (GLU and INS responses, hepatic and peripheral INS resistance), anthropometrics (weight, fat mass, skeletal muscle mass, and waist circumference), and satiety (hunger, fullness, satisfaction, and desire to eat). We also assessed the dietary impact of lentils on fasting blood lipid profiles (cholesterol [CHOL], low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides [TG]) as a secondary measure of interest. We strategically offered midday meals to adults with increased central adiposity to allow the second-meal effect to occur during the evening meal. We hypothesized that regular midday lentil consumption in individuals who are at greater risk of metabolic disease would improve glycemic control and anthropometric and satiety measures, with more pronounced effects at a higher lentil dosage.

2. Methods and materials

2.1. Ethics statement

The protocol was approved by the institutional review board at Montana State University (MM100218). Written informed consent was obtained from all participants before participation. The study was registered at ClinicalTrials.gov (NCT04448067).

2.2. Study population

Potential participants were recruited on a rolling basis in Bozeman, Montana, from January 2019 to October 2019 by advertisement through flyers, email lists, word of mouth, and snowballing recruitment methods. Interested individuals contacted the research team, which sent additional information about the study. Participants were screened over the phone by members of the research team. Eligible individuals were aged 18 to 70 years and had waist circumferences ≥ 35 inches for females and 40 inches for males. Eligible participants exceeded the metabolic syndrome criteria for waist circumference [19], a criterion meant to recruit individuals with greater risk of T2DM development [3]. Exclusion criteria included diabetes, wheat allergies, oral hypoglycemic medications, lipid- or cholesterol-lowering medications, anti-inflammatory medications, and pregnancy.

2.3. Research design

The study was a single-blind parallel, randomized clinical trial with 0, 300, or 600 g of whole lentils 5 days per week for 8 weeks from January 2019 through December 2019. Randomization was performed by a member of the research team by drawing out of a hat in blocks of 6. Participants were assigned to their dietary intervention, with 13, 12, and 10 participants assigned to 0 g (CON), 300 g (MOD), and 600 g (HI) cooked green lentil dosage, respectively. Participants were asked to come to the Nutrition Research Laboratory at Montana State University on 3 occasions (Fig. 1). Participants were scheduled on a rolling basis after eligibility confirmation for their initial visit with anthropometric measurement collection. Approximately 7 to 14 days after the initial visit, a carbohydrate tolerance

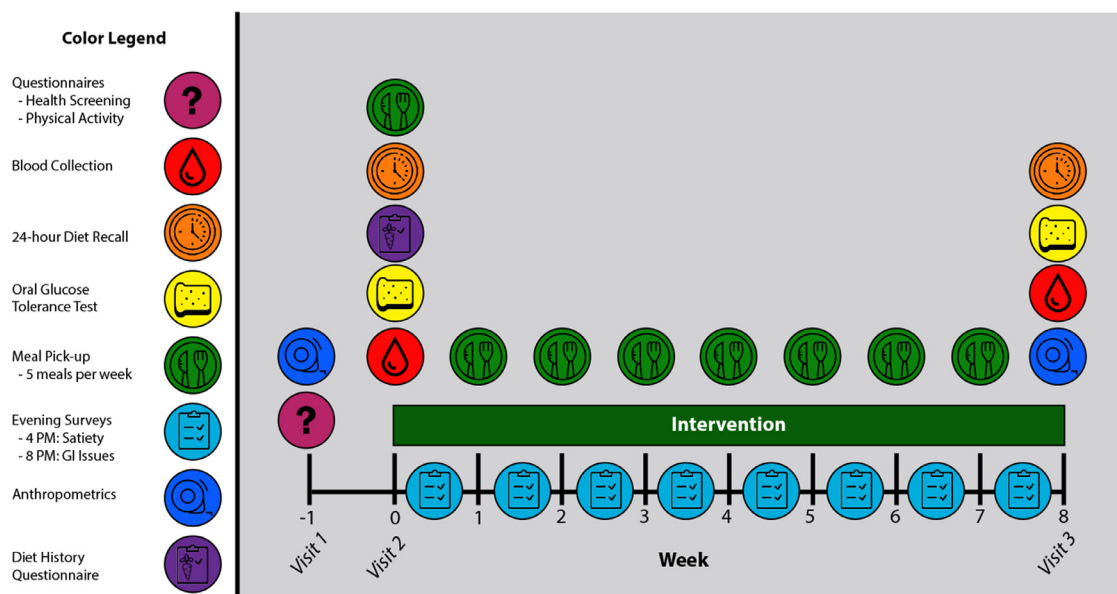


Fig. 1 – Time course of the 8-week dietary intervention. Timeline of study events and how frequently events occurred during the study participation.

test (CTT) was performed in the morning after an overnight fast before and after the 8-week dietary intervention. Weekly online survey questionnaires were delivered during the intervention to assess satiety and GI symptoms. Metabolic health, satiety, and GI symptom measures were primary outcomes of interest.

2.4. Dietary intervention

Participants underwent an 8-week dietary intervention, which included 5 prepared midday meals each week that were isocaloric but varied in dose of cooked whole green lentils (provided by AGT Foods Canada): 0 g, 300 g, and 600 g per week. Throughout the 8 weeks, participants were asked to consume the same 5 provided meals each week but were otherwise asked to maintain their normal dietary and physical activity patterns. Provided meals were prepared by a registered dietitian and trained professional chef on the research team who were not part of the participant recruitment and blood testing process. Meal components were preweighed into a plastic to-go container and frozen with meal-heating instructions included on a printed container label. Participants were asked by the research team to briefly come to the laboratory each week during the intervention and pick up their next week of study meals. Specific study meals included were soup, curry with basmati rice, street tacos, loaf with mashed potatoes and cooked zucchini, and pasta with Bolognese sauce. A detailed weekly diet menu and nutrient profile is listed in Table 1. Control meals were matched in total energy to MOD and HI lentil meals and included ground turkey or chicken instead of green lentils. The intent of this study was to evaluate equivalent meals with meat (CON), a mixture of meat and lentils (MOD), and strictly lentils (HI) as the protein sources in the meals. The strength of this approach is that it maximizes the translational value on the impact of incorporating lentils into the

diet as a protein source. A limitation of this approach is that the macronutrient composition of the meals was not identical.

2.5. Lentil sampling and nutritional analysis

Medium green lentils (CDC Richlea cultivar) used in the diet were sent courtesy of AGT Foods Canada to Medallion Labs (Minneapolis, MN) for analytical testing with the standalone nutrient breakdown and functional properties are provided in Supplementary File 1. Dietary fiber was determined through the analytical method AOAC 991.43.

2.6. Carbohydrate tolerance test

The test meal contained plain, untoasted white bread (Franz Premium White BIG) totaling 75 g carbohydrate intake. The total energy content of the test meal was 400 kcal, with a macronutrient composition of 5 g fat, 75 g carbohydrate, and 10 g protein. Meals were provided in the study laboratory. Water was provided ad libitum with the meal. Participants were instructed to consume the meal within 10 minutes, with the postprandial period timing based on when the meal began. During the 2 hours of the CTT, participants were asked to remain seated and complete a written 24-hour dietary recall and an online survey on their habitual diet.

2.7. Blood sampling

Participants were instructed to avoid alcohol consumption and strenuous physical activity in the 24 hours before their visit and to complete an overnight fast (≥ 10 hours) before blood collection. Fasting blood samples were collected by a trained phlebotomist via venipuncture of the antecubital vein in the morning before ingestion of CTT. Venous blood at fasting was collected into 8.5-mL endotoxin-free serum separating and 4.0-mL heparinized vacutainer tubes (BD Vacutainer,

Table 1 – Sample weekly menu from the 8-week dietary intervention and daily average nutrient profile

	CON – 0 g	MOD – 300 g	HI – 600 g
Bolognese	Turkey Bolognese + ½ cup cooked rotini pasta	Lentil and turkey Bolognese + ½ cup cooked rotini pasta	Lentil Bolognese + ½ cup cooked rotini pasta
Curry	Chicken curry + 1/3 cup cooked basmati rice	Lentil and chicken curry + 1/3 cup cooked basmati rice	Lentil curry + 1/3 cup cooked basmati rice
Loaf	Turkey loaf + ¼ cup mashed potatoes + ½ cup cooked zucchini	Lentil and turkey loaf + ¼ cup mashed potatoes + ½ cup cooked zucchini	Lentil loaf + ¼ cup mashed potatoes + ½ cup cooked zucchini
Taco	Turkey taco filling + ½ oz shredded cheddar cheese + 1 Tbsp salsa + 1 Tbsp sour cream + 2 street flour tortillas	Lentil and turkey taco filling + ½ oz shredded cheddar cheese + 1 Tbsp salsa + 1 Tbsp sour cream + 2 street flour tortillas	Lentil taco filling + ½ oz shredded cheddar cheese + 1 Tbsp salsa + 1 Tbsp sour cream + 2 street flour tortillas
Soup	Chicken soup	Lentil + chicken soup	Lentil soup
Nutrient	332 kcal, 23 g PRO, 29 g CHO, 3 g dietary fiber, 14 g total fat, 5 g saturated fat	343 kcal, 20 g PRO, 42 g CHO, 10 g dietary fiber, 11 g total fat, 4 g saturated fat	355 kcal, 18 g PRO, 54 g CHO, 16 g dietary fiber, 8 g total fat, 4 g saturated fat

Nutrient totals were rounded to nearest whole number.

Abbreviations: CHO, carbohydrate; CON, control; MOD, moderate lentil; HI, high lentil; PRO, protein.

Franklin Lakes, NJ, USA). Blood was obtained by fingerstick at 30, 60, 90, and 120 minutes in the 2-hour postprandial period and collected with microcapillary serum separating 200- μ L tubes (RAM Scientific Inc., Nashville, TN, USA). Blood samples were allowed to clot for 15 minutes before centrifugation at 1200 RPM for 15 minutes with resulting serum aliquoted and stored at -80°C until analysis.

2.8. Biochemical analysis

Fasting blood lipid profiles were determined from whole blood run on Piccolo Xpress Chemistry Analyzer lipid panels (Abaxis, Union City, USA). Components derived from lipid panels include CHOL, HDL, LDL, and TG. HbA1c was determined using the DCA Vantage Analyzer (Siemens Medical Solutions Diagnostics, Cergy-Pontoise, France) performed according to the manufacturer's instructions. For blood GLU determination, whole blood was collected into a microcuvette and run immediately on the HemoCue Hb 201+ System (HemoCue AB, Angelholm, Sweden). For INS determination, fingerstick blood samples were collected and centrifuged at 1200 RPM for 15 minutes, with the resulting serum aliquoted and stored at -80°C . INS concentrations from fasting and postprandial samples were determined through a high-sensitivity INS enzyme-linked immunosorbent assay kit according to manufacturer instructions (ALPCO, Salem, NH, USA) with a mean inter-assay coefficient of variation of 5.2%. Blood GLU and INS responses to the CTT were each summarized as incremental area under the curve method (iAUC) in an effort to normalize high inter-personal variability in PPGRs to the same meal [20,21].

2.9. Insulin resistance

Fasting blood GLU and INS were used to determine the Homeostatic Model of Insulin Resistance (HOMA-IR), a measure of hepatic INS resistance at fasting calculated with the original HOMA-IR formula [22]. Body weight and GLU and INS concentrations at 0 and 120 minutes of the CTT were used to calculate the INS sensitivity index ($\text{ISI}_{0,120}$), a validated measure of peripheral INS resistance [23].

2.10. Habitual dietary habit survey

A validated diet history questionnaire (DHQ III) was self-assessed through a web-based survey offered by the National Cancer Institute. Participants were provided a laptop and asked to complete the survey at the baseline blood collection visit. The DHQ III consists of 135 food and beverage and 26 supplement questions to assess dietary frequency and portion sizes over the past 12 months. Through built-in programming of DHQ III surveys, we obtained a calculated Healthy Eating Index (HEI, 2015) score, which is a measure of diet quality in compliance with the 2015 through 2020 US Dietary Guidelines for Americans. Total HEI score is the sum of 9 components based on adequacy (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids) and 4 components based on moderation (refined grains, sodium, added sugars, saturated fats) [24,25].

2.11. Anthropometrics

Measurements were collected from participants using the validated segmental multifrequency bioelectrical impedance analysis (SECA mBCA 515, Hamburg, Germany) [26]. Participants were instructed to refrain from eating, drinking, or exercising in the 3 hours before testing. Fat mass (%), estimated visceral adipose (liters), and skeletal muscle mass (%) were used for analysis.

2.12. Satiety and Gastrointestinal Surveys

Two brief surveys addressing participant hedonic response, satiety, and GI symptoms were delivered through email using the online platform Qualtrics on the same day, once a week, sequentially delivered on rotation for each weekday, for each week of the 8-week dietary intervention. At 4:00 PM, participants were asked how much they enjoyed their midday meal, followed by their levels of hunger, fullness, satisfaction, and desire to eat in relation to the study meal they consumed mid-day. At 8:00 PM, participants were asked how they felt overall

Table 2 – Participant characteristics at baseline, grouped by assigned dietary intervention (n = 30)

	CON (n = 10)	MOD (n = 11)	HI (n = 9)	P value
Males/females	1/9	3/8	1/8	<.01
Age (y)	38.8 ± 10.9	43.1 ± 12.5	43.0 ± 12.3	.66
BMI (kg/m ²)	35.5 ± 5.2	34.2 ± 6.8	35.9 ± 7.3	.82
FM (%)	45.3 ± 5.4	41.7 ± 8.4	47.0 ± 7.1	.25
WC (cm)	109.7 ± 13.9	108.0 ± 12.1	107.1 ± 11.2	.90
VAT (L)	3.5 ± 1.8	3.5 ± 1.6	3.3 ± 1.3	.94
GLU (mmol/L)	4.9 ± 0.7	5.2 ± 0.6	5.2 ± 0.4	.21
TG (mmol/L)	1.4 ± 0.7	1.3 ± 0.5	1.5 ± 0.5	.70
CHOL (mmol/L)	4.9 ± 1.0	4.6 ± 0.9	4.8 ± 0.7	.76
HDL (mmol/L)	1.4 ± 0.4	1.3 ± 0.3	1.5 ± 0.6	.39
HbA1c (%)	5.2 ± 0.3	5.2 ± 0.3	5.4 ± 0.3	.10

Blood profile determined from venous blood sample at fasting. Participants were metabolically at-risk adults based on their elevated waist circumference. Data represent mean and SD. Sex P value determined through 3-sample test for given proportions; all other P values determined by analysis of variance.

Abbreviations: BMI; body mass index; CON, control; CHOL, cholesterol; FM, fat mass; GLU, glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HI, high lentil; MOD, moderate lentil; TG, triglycerides; VAT, visceral adipose tissue; WC, waist circumference.

that day regarding common GI symptoms. The latter included 4 subquestions asking them to rank the severity (none, mild, moderate, severe) of their flatulence, bloating, cramping, and abdominal discomfort. Participants were able to view definitions of each GI issue during completion of each survey. Survey questions and response scales are outlined in Supplementary File 2.

2.13. Statistical analyses

Analysis and visualizations were conducted in RStudio (1.4.1106) running R 4.0.5, with data visualized using *ggplot2* [27] and *effects* [28] packages. Power was calculated a posteriori from the HOMA-IR regression model using powerSim in the *simr* package [29]. Computed power to detect a meal effect was 94% at a type I probability of 0.05 based on 100 Monte Carlo simulations.

Descriptive summary statistics were performed for participant physical and biological characteristics with general linear models used to determine if participants on average differed between meal groups before the intervention began. Habitual dietary patterns, determined through HEI scores, at baseline were also analyzed through general linear models with 3 fewer individuals included in the analysis because of survey incompleteness. Variables that demonstrated group differences were further analyzed using post hoc tests.

General linear models were used to assess the impact of the dietary intervention on the following categories of variables: anthropometric measures (weight, fat mass, skeletal muscle mass, and waist circumference); blood lipid measures (CHOL, LDL, HDL, TG); and glycemic measures (GLU iAUC, INS iAUC, HOMA-IR, and ISI_{0,120}). Dependent variables were calculated as the change in values from baseline (postintervention – preintervention). Predictor variables were shared within each category of variables and are as follows: anthropometric measures – meal group; blood lipid measures – meal group, visceral adipose tissue; glycemic measures – meal group, change in body mass index (BMI), and HbA1c. Predictor variables for

glycemic measures were chosen based on previous findings by Zeevi and colleagues [21]. Validity conditions were confirmed through visualizations of the response and model residuals.

Linear mixed effects models were used to assess the impact of a week and meal interaction on satiety measures, accounting for meal enjoyment. GI symptom severity was analyzed through a nonlinear mixed effects model with the predictors as a week and meal interaction and symptom type, with week on a quadratic polynomial. Subject was the random effect for models assessing satiety and GI symptom severity.

3. Results

3.1. General characteristics of participants

Two participants were lost to follow-up and 3 participants withdrew from the study for nonintervention-related reasons, leaving 30 healthy overweight and obese adults (mean ± SD; age, 41.6 ± 11.7 years; BMI, 35.1 ± 6.3) who completed the 8-week intervention (Fig. 2). No adverse events were reported.

The proportion of males to females was different between meal groups with the greatest proportion of males observed in MOD, χ^2 ((3, n = 30) = 14.1, $P < .01$). Between meal groups at baseline, participants had similar anthropometric and metabolic characteristics (Table 2). Participants classified as obese according to BMI. Among metabolic characteristics, fasting TG, CHOL, HDL, and GLU were normal on average across meal groups at baseline. One-third of participants (2 CON, 5 MOD, 3 HI) were considered prediabetic based on American Diabetes Association 2021 classification guidelines [30].

3.2. Dietary habits at baseline

Self-reported habitual dietary patterns assessed through the online DHQ III were scored to US 2015 dietary recommendations through built-in HEI scoring. Three participants, 1 from each meal group, did not complete the survey, were unable to be scored, and were not included in dietary pattern analyses.

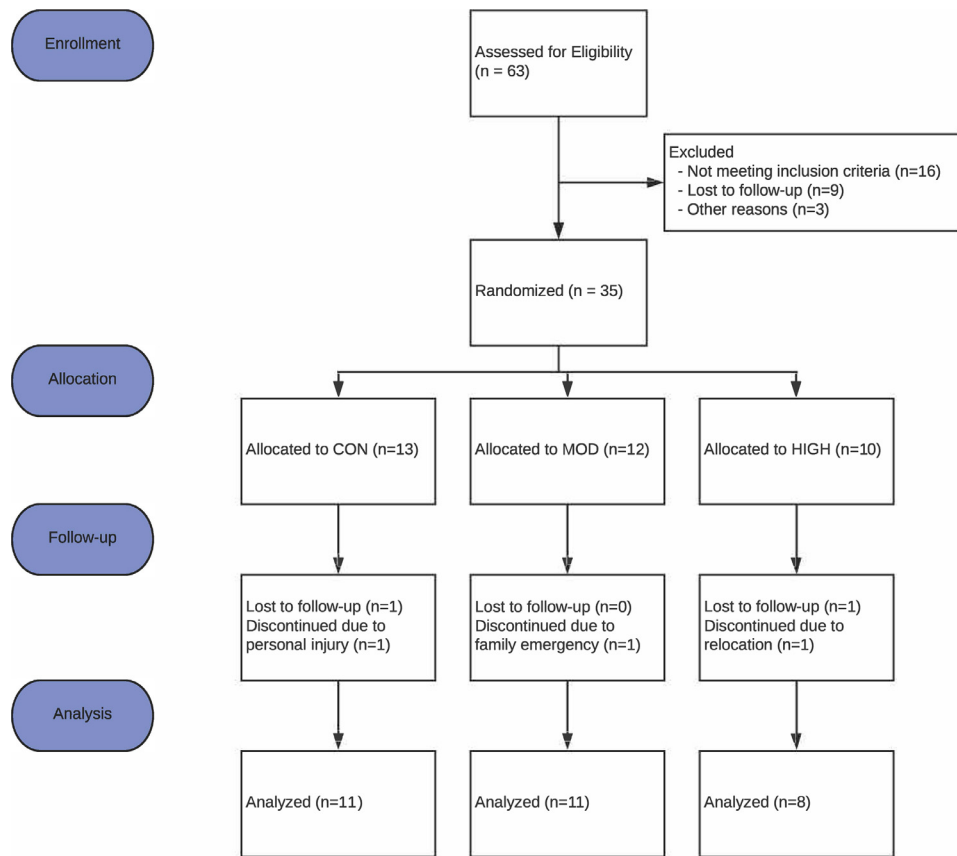


Fig. 2 – A CONSORT flowchart of the study design and enrollment. Flyers and emails were used to recruit interested individuals. Interested individuals contacted the research team, who sent additional information about the study. Sixty-three individuals completed a phone screening with the research team with those individuals who met eligibility requirements enrolled to participate. Participants were randomly allocated to 1 of 3 experimental groups with varying weekly doses of lentils: CON, control (0 g/wk); MOD, moderate (300 g/wk); HI, high (600 g/wk).

Total HEI scores, which indicate overall dietary quality, were not different between meal groups at baseline (Table 3). Sixty-two percent of participants were above the average national HEI score (58.3) for adults, with a group average score of 62.3. With regard to foods to consume in adequacy, self-reported intake of total vegetables and greens and beans did vary between groups. Total vegetable intake in MOD was 0.97 points greater than CON ($t = 2.1, P = .04$) and 1.52 points greater than HI ($t = -3.2, P < .01$). Additionally, intake of greens and beans was 1.50 points greater in MOD than HI than MOD ($t = -2.8, P < .01$). Meal groups were similar at baseline among components to consume in moderation.

3.3. Fasting blood lipids

No meal group differences were detected in the change (post – pre) total CHOL ($F = 1.0, P = .36$), LDL ($F = 0.94, P = .40$), HDL ($F = 0.62, P = .55$), or TG ($F = 0.15, P = .86$) after accounting for change in visceral adipose tissue. However, we did observe a positive relationship ($\beta = 0.29$) of visceral adipose tissue on fasting blood TG ($F = 4.5, P = .04$).

3.4. Anthropometrics

Meal group differences were not detected in the change of body weight ($F = 2.0, P = .15$), fat mass percentage ($F = 0.98, P = .39$), skeletal muscle mass percentage ($F = 0.66, P = .52$), or visceral adipose tissue ($F = 0.35, P = .71$).

3.5. Insulin resistance

After accounting for BMI and HbA1c, MOD and HI had lower hepatic INS resistance than CON as measured through HOMA-IR. One MOD participant was identified as an influential point based on a Cook distance > 1 and removed from HOMA-IR analysis. Participants who consumed meat-based CON meals, on average, increased in HOMA-IR after 8 weeks (Fig. 3). Participants in MOD also had an increase in HOMA-IR, but this increase after 8 weeks was 0.9 units lower than CON ($t = -2.2, P = .03$). Participants in HI had a reduction in HOMA-IR, with the change in HOMA-IR on average 1.5 units lower than CON ($t = -3.5, P = .002$). BMI and HbA1c were both predictors to the change in HOMA-IR. Interestingly, participants who increased in BMI had on average a reduction in HOMA-IR ($t = -4.0$,

Table 3 – Healthy Eating Index (HEI) component scores from metabolically at-risk adult participants at baseline, grouped by assigned meal group (n = 27)

Component	Maximum points	Score			P value
		CON (n = 9)	MOD (n = 10)	HI (n = 8)	
Adequacy					
Total fruits	5	2.6 ± 1.2	3.9 ± 1.5	3.2 ± 1.4	.15
Whole fruits	5	3.6 ± 1.6	4.4 ± 1.5	3.8 ± 1.2	.48
Total vegetables	5	3.7 ± 1.1	4.7 ± 0.5	3.1 ± 1.3	.01
Greens and beans	5	4.4 ± 1.1	4.9 ± 0.2	3.4 ± 1.6	.03
Whole grains	10	2 ± 1.1	2.6 ± 1.6	3.6 ± 2	.13
Dairy	10	8.1 ± 2	6.3 ± 1.8	7.8 ± 1.7	.09
Total protein foods	5	4.8 ± 0.4	4.9 ± 0.3	4.7 ± 0.6	.66
Seafood and plant proteins	5	4.5 ± 0.8	4.3 ± 1	4.4 ± 1.1	.90
Fatty acids	10	2.6 ± 2.1	2.9 ± 3.2	4.8 ± 2.8	.19
Moderation					
Refined grains	10	8.4 ± 1.5	8 ± 3.3	9.4 ± 1	.40
Sodium	10	3 ± 1.8	4.1 ± 3.2	5.5 ± 2.6	.17
Added sugars	10	7.6 ± 1.2	7.8 ± 2.1	6.3 ± 3	.30
Saturated fats	10	2.9 ± 2.2	5.6 ± 2.8	4.1 ± 3.1	.13
Total		58.2 ± 6.7	66.1 ± 10.3	62.3 ± 13.2	.26

HEI component scores were calculated through an online DHQ III in which participants self-reported the types and frequency of foods consumed in the past 12 months. Three participants (1 from each meal group) did not fully complete the DHQ III; thus, HEI scores were not available. Information about the standards for scoring each HEI component can be found in an article by Krebs-Smith and colleagues [25]. Data represent mean and SD. Meal effect P values determined by type II F-test.

Abbreviations: CON, control; DHQ, diet history questionnaire; HI, high; MOD, moderate.

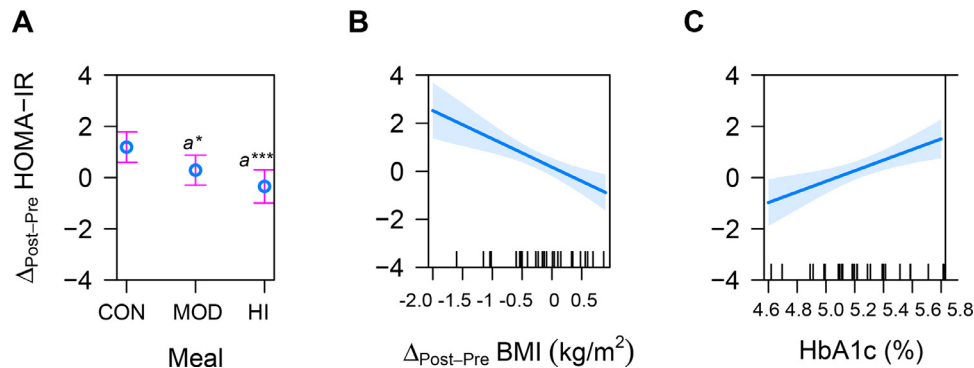


Fig. 3 – Plots for estimated beta coefficients of predictor variables for the change in HOMA-IR. Bands and bars indicate 95% confidence intervals and the ticks on the x-axis in (B) and (C) indicate the observed values. Blue points in (A) and the blue lines in (B) and (C) indicate the average change in HOMA-IR as determined by the general linear model. One MOD participant was identified as an influential point and removed from HOMA-IR analysis. ^aDifference from CON. P values are at a level of *.05, **.01, and *.001. BMI, body mass index; CON, control (0 g/wk); HbA1c, glycated hemoglobin; HI, high (600 g/wk); HOMA-IR, Homeostatic Model of Insulin Resistance; MOD (300 g/wk), moderate.**

$P < .001$). HbA1c was a positive predictor of the change in HOMA-IR, with greater HbA1c related to a rise in HOMA-IR after 8 weeks ($t = 3.4$, $P < .01$). Variance explained by our model was approximately 49.6% according to adjusted R^2 .

Eight weeks of MOD ($t = 1.3$, $P = .21$) or HI ($t = -0.31$, $P = .67$) lentil consumption did not improve peripheral insulin resistance as measured by $ISI_{0,120}$ compared with CON. Further, HbA1c ($t = -0.91$, $P = .37$) and BMI ($t = 1.5$, $P = .15$) were not predictors of $ISI_{0,120}$.

3.6. Postprandial glucose and insulin

The addition of lentils over 8 weeks did not impact GLU iAUC ($F = 0.41$, $P = .67$), accounting for BMI ($F = 1.9$, $P = .18$) and HbA1c ($F < 0.01$, $P = .95$). Similarly, INS iAUC was not affected by the lentil addition for 8 weeks ($F = 0.84$, $P = .44$), accounting for BMI ($F = 0.03$, $P = .86$) and HbA1c ($F = 0.23$, $P = .64$). The same participant in MOD who was removed as an influential point in HOMA-IR analysis was also removed from INS iAUC analysis based on a Cook distance > 1 . Our male participants were

Table 4 – P values of the β -coefficients derived from mixed effects models on reported satiety survey measures from metabolically at-risk adult participants

Question topic	Meal	Week	Meal enjoyment	Meal*Week
Meal enjoyment	0.43	0.05	NA	0.03
Hunger	0.53	0.44	0.02	0.24
Fullness	0.93	0.39	0.07	0.87
Satisfaction	0.83	0.78	<0.001	0.20
Desire to eat	<0.01	0.02	<0.001	0.99
Amount could eat	0.01	0.25	<0.001	0.57

Question language and response levels are provided in Supplementary File 2. Meal*Week indicates an interaction between meal group (CON, MOD, HI) and time (week) in the mixed effect statistical model.
Abbreviations: CON, control; HI, high; MOD, moderate.

not detected as outliers in our modeling of glycemic responses and were consequently included in all analyses. Average GLU and INS concentrations during the CTT before and after the intervention are displayed in Supplementary File 3.

3.7. Satiety during the intervention

The overall response rate to the 4:00 PM survey on satiety was 95.8%. The mean response rates were 95%, 95.5%, and 97.2% for CON, MOD, and HI, respectively. A decline in meal enjoyment was experienced by CON and HI over 8 weeks, whereas meal enjoyment was maintained in MOD over 8 weeks (Supplementary File 4). Satiety measures were not different by meal group over 8 weeks but were largely dependent on meal enjoyment, with the exception of self-reported fullness (Table 4). An inverse relationship was observed between meal enjoyment and self-reported hunger ($\beta = -0.16$), desire to eat ($\beta = -0.51$), and amount that they could eat ($\beta = -0.38$), whereas a positive relationship was observed between meal enjoyment and satisfaction ($\beta = 0.73$). Only in desire to eat was a meal main effect observed.

3.8. Gastrointestinal symptoms during the intervention

The overall mean response rate to the 8:00 PM survey on GI symptoms was 95.4%. Mean response rates for the GI survey were 93.8%, 95.5%, and 97.2%, respectively, for CON, MOD, and HI. Regarding symptom severity responses throughout the entire intervention, 87.4% were none to mild, 11.3% were moderate, and 1.8% were severe.

We observed a main effect for symptom type in our mixed effects modelling, with average reported flatulence as mild throughout the duration of the study, though it was the GI symptom with the highest severity ($P < .001$). Flatulence was followed sequentially in symptom severity by bloating, abdominal discomfort, and cramping (Fig. 4A). The frequency of reported bloating, abdominal discomfort, and cramping fluctuated over 8 weeks, but only in the MOD group did the frequency of average GI symptoms increase then decline after 5 weeks (Fig. 4B, $t = -2.9$, $P < .01$). Mild flatulence was reported by the majority of participants in HI, with an increasing trend seen over time. Weekly fluctuations in symptom severity are visualized in Supplementary File 5.

4. Discussion

The key finding of this study was identification of dose-dependent benefits of dietary lentils for the attenuation of the progression of INS resistance in nondiabetic adults with overweight and obesity, which is line with our hypothesis. To our knowledge, this is the first study that has examined the impact of long-term lentil consumption on glycemic responses in metabolically at-risk, free-living adults. We specifically looked to assess the impact of weekly lentils meeting and surpassing USDA weekly pulse recommendations in a manner that incrementally used lentils instead of meat. In an effort to understand how participants responded to the intervention, we also surveyed participants about their satiety and GI symptoms. Contrary to our hypothesis that satiety would increase in a dose-dependent manner with lentil consumption, we did not observe changes in satiety with lentil consumption compared with meat consumption. Our weekly survey strategy provided novel insights on temporal changes in satiety and GI discomfort with dietary strategies incorporating increased lentil consumption.

Our main finding was that lentil consumption helped to prevent a rise in HOMA-IR with an incremental decrease in HOMA-IR with increasing dietary lentils amounts. HOMA-IR is a measure of fasting INS resistance and is reflective of hepatic INS resistance. In a systematic review of 12 randomized clinical trials in adults without T2DM, only 1 trial found a decrease in HOMA-IR after 16 weeks of pulse consumption [31,32]. The rise of blood GLU and INS after a meal stimulates GLU disposal in the periphery, predominantly into skeletal muscle. Thus, dynamic postprandial conditions are reflective of peripheral INS resistance. Diet-related changes to dynamic postprandial responses such as INS iAUC and GLU iAUC were not observed, which mirrors the lack of change observed in $ISI_{0,120}$, our measure of peripheral INS resistance. Increased INS production during the postprandial phase normally signals the liver to cease glucose production, increase GLU consumption, and store consumed GLU as glycogen or lipids. In INS-resistant individuals, INS is unable to effectively regulate GLU metabolism, resulting in increased GLU production with de novo lipogenesis. The beneficial effect of fiber on fasting glycemic control was previously suggested to be proportionate to the amount of soluble fiber in foods [11], of which the green

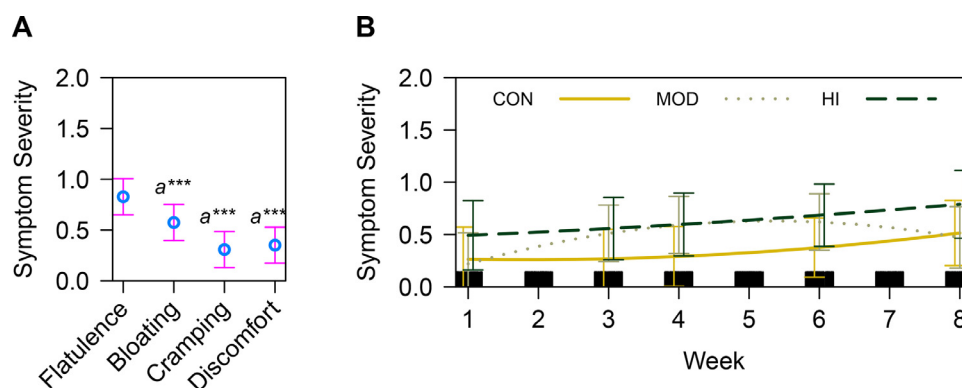


Fig. 4 – Effects plots from the gastrointestinal issue symptom severity mixed effects model with (A) symptom main effect and (B) meal and time interaction. Symptom severity was scored as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Points indicate group means, bars indicate 95% confidence intervals, and ticks on the x-axis indicate observed data frequency. ^aDifference from flatulence. P values are at a level of *.05, **.01, and *.001. CON, control (0 g/wk); HI, high (600 g/wk); MOD (300 g/w), moderate.**

lentils used in the current study contain little. Low soluble fiber content is of note because high-viscosity soluble fibers help slow the passage of the food matrix through the small intestine, which contributes to slowed degradation and absorption of carbohydrate. The whole green lentils in our study meals contained approximately 13 g (per 100 g uncooked) of fiber, with the majority as insoluble fiber. Insoluble fiber may also combat the rise in INS resistance [33] via the potential to disrupt the absorption of protein in the small intestine [34]. Increased plasma amino acid concentrations through amino acid infusions were found to increase INS resistance [35]; thus, it is possible that the consumption of animal-based products contributed to the rise of INS resistance observed in our study.

Hepatic INS resistance is a key contributor to fasting [36] and postprandial lipemia [37]. We did not measure postprandial lipemia in the current study, but with regard to fasting blood lipids, we did not observe changes after 8 weeks of dietary modification. These findings are in contrast to improved serum total and LDL CHOL previously reported in a metaanalysis of 10 clinical trials with at least 3 weeks of legume consumption [38]. Diets high in fiber can contribute to impaired lipid emulsification, decreased chylomicron production, increased clearance of triglyceride-rich lipoproteins, and decreased very-low density lipoprotein production [39]. The cholesterol-lowering impact of lentils may be attributed in part to the ability of bile acids to bind to soluble fiber in the intestinal tract, which helps to prevent reabsorption in the distal ileum and increase its excretion in feces [40]. To maintain the bile acid pool, reduced bile acid absorption triggers increased bile acid production mediated through increased clearance of LDL to uptake CHOL necessary for bile acid synthesis. The green lentils in this study were low in soluble fiber; thus, it is unclear whether bile acid production was affected through incorporation of whole green lentils. Further investigation of acute and long-term effects of pulses on bile acid synthesis and secretion is warranted because bile acid metabolites were also recently shown to predict postprandial GLU and INS responses [41].

A unique finding of the present study with high relevance to dietary strategies for weight management was that meal enjoyment was a key factor in self-reported satiety measures, with higher meal enjoyment related to less hunger and desire to eat in the afternoon. Individuals in MOD maintained their meal enjoyment on average through the study compared with the CON and HI groups, which showed a gradual decline in meal enjoyment. An acute benefit of increased fiber consumption is higher satiety, or a perceived feeling of fullness after a meal [42]. Soluble fiber delays gastric emptying through an increase in digesta viscosity, which helps individuals feel fuller longer after a meal [11]. Individuals who have reduced feelings of hunger may be compelled to eat less at their second meal, promoting a reduction in caloric intake. Satiety in this current study did not vary by meal group during the intervention, and average satiety did not translate to changes in weight, body fat, or skeletal muscle percentage. Obese adults have previously reported greater satiety benefit with fiber compared with studies that examined lower BMI participants [42], an effect that may not have been observed in this study given the low soluble fiber content of our study lentils. However, we note that the dietary intervention was not designed as a weight loss intervention but to simulate a realistic change in dietary behavior in free-living adults. Because increased energy intake has been identified as the key driver of the US obesity epidemic [43], it becomes imperative to regularly incorporate meals that promote satiety and reduce caloric intake to aid weight management.

Another important assessment relevant to dietary strategies to improve metabolic health assessed in the present study was GI symptom frequency and temporal changes in symptoms during the 8-week dietary intervention. GI symptoms are infrequently reported in interventions, with only 3 publications in a recent systematic review of 20 pulse interventions reporting GI symptoms, none of which was exclusively lentils [9]. In our study, participants with moderate lentil consumption reported a decline in frequency of GI symptoms after 5 weeks compared with LO and HI, which experienced a small increase over time. Severe symptoms were reported in-

frequently, with no participants withdrawing from the study because of GI symptom severity. Of specific symptoms, flatulence had the highest severity but was mild on average. GI discomfort largely arises from gas production during bacterial fermentation of increased soluble fiber, some insoluble fibers [44], and resistant starches that cannot be readily digested by intestinal enzymes [45–47]. Intestinal gas production was previously reported to subside in healthy individuals because colonic bacteria adapt to the dietary fiber and resistant starches with long-term consumption of fiber-rich food [48]. HI participants had a steady rise in GI symptom severity in line with increased bacterial fermentation, but it is unclear why the CON group also experienced a steady rise. It is possible that participants in CON may have become more aware and more likely to report GI symptoms over time with repeated surveying, a bias called the memory effect, or their diet was altered outside of the provided study meals. For participants in MOD, who experienced a decline in GI symptom severity, may have had this adaptation occur sooner as participants were already consuming greater vegetables and legumes in their habitual diet than CON and HI as assessed by HEI component scores. Collectively, these findings may aid the effort to counter consumer perception of GI symptom severity as a barrier to lentil inclusion.

We recognize that there are additional factors and limitations that may have influenced changes to INS resistance and PPGR that were not measured in the current study. Although participants were asked to maintain their regular dietary and physical activity patterns, it is possible participants incorporated additional healthy lifestyle patterns that would improve glycemic control and affect GI symptom severity. Assessment of physical activity and background diet during the intervention period could help identify such healthy lifestyle patterns, but also how the dietary intervention may have influenced the background diet, which was not measured in this study. It is possible that antioxidants present in whole lentils may have affected oxidative stress, which is implicated in the development of INS resistance [49]. This study did not assess the impact of the gut microbial community on PPGR. The human gut microbial community is in part influenced by diet [50]. Specific microbial taxa are related to plant-based foods [51] and PPGR [21], which help highlight an ongoing interaction between diet, microbiota, and host responses. Soluble fiber and resistant starch in lentils can undergo bacterial fermentation to produce short-chain fatty acids such as butyrate, which has been shown to have anti-inflammatory and INS-sensitizing effects [52,53]. Because the gut microbiota can metabolize dietary fiber as well as bile acids [54], it is imperative to understand how temporal effects of lentil consumption on the gut microbial community may modulate host postprandial responses as it relates to chronic disease development. In addition, males and females differ in their INS sensitivity [55] and susceptibility to the pathogenesis of T2DM [56]. Though our male participants were not detected as outliers in the modeling of glycemic responses, this analysis was not sufficiently powered for independent analysis of males vs females. Although a lack of evidence exists on sex differences in pulse consumption responses [9], sex differences are an important variable to consider and address in future research, particularly in studies examining glycemic responses.

In conclusion, the findings of the present study provide evidence that long-term lentil consumption above USDA legume recommendations (1.5 cups/wk) in heavier individuals at greater risk of impaired GLU tolerance can reduce an upward drift in hepatic INS resistance, a key target in the early phase in progression of T2DM. Additionally, our findings add to the limited body of research regarding satiety and GI symptoms with legume consumption, with specific findings including the importance of meal enjoyment in satiety and temporal changes in GI symptom severity. Further investigation of the long-term impact of insoluble and fermentable fibers on glycemic control, bile acids, and potential gut-mediated pathways is warranted in at-risk populations.

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Declaration of Competing Interest

The authors declare no conflict of interest. Funding sources were not involved in the design, data collection and analysis, and writing of the manuscript.

CRediT authorship contribution statement

Stephanie M.G. Wilson: Writing – original draft, Writing – review & editing, Investigation, Data curation, Formal analysis, Visualization, Software. **Emily J. Peterson:** Project administration, Writing – review & editing, Investigation, Data curation, Software. **Marcy E. Gaston:** Writing – review & editing, Methodology, Resources. **Wan-Yuan Kuo:** Funding acquisition, Writing – review & editing, Conceptualization. **Mary P. Miles:** Funding acquisition, Supervision, Writing – review & editing, Conceptualization, Methodology, Validation, Resources.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.nutres.2022.08.002](https://doi.org/10.1016/j.nutres.2022.08.002).

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