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Original article

Impact of a 12-month Inflammation Management Intervention on the Dietary Inflammatory Index, inflammation, and lipids

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SUMMARY

Background and aims: The objective of this study was to assess the feasibility (ability to recruit participants and develop the 12-month intervention), acceptability (retention of participants in the intervention), and impact on systemic inflammation and Dietary Inflammatory Index (DII®) scores over a 12-month DII-based intervention.
Methods: Adults were recruited to participate in a self-selection trial (intervention: n = 61, in-person classes; control: n = 34, newsletters). Classes included participatory cooking and dietary recommendations focused on consuming a plant-based diet rich in anti-inflammatory foods (spices, vegetables, etc.). Changes in markers of inflammation, lipids, and DII were analyzed using general linear models with repeated measurements.
Results: At 3 months, intervention participants had significantly lower DII scores (−2.66 ± 2.44) compared to controls (−0.38 ± 2.56) ($p < 0.01$); but not at 12 months ($P = 0.10$). The only biomarker to approach a significant group effect or group-by-time interaction was CRP ($P = 0.11$ for the group-by-time interaction). CRP decreased by −0.65 mg/L (95%CI = 0.10−1.20, $P = 0.02$) at 12 months in the intervention group; no significant decrease was seen for the control group. With both groups combined at 3 months, those with the greatest decrease/improvement in DII score (tertile 1) compared with those whose scores increased (tertile 3) had greater reductions in CRP (−1.09 vs. +0.52 mg/L, $P = 0.04$), total cholesterol (−9.38 vs. +12.02 mg/dL, $P = 0.01$), and LDL cholesterol (−11.99 vs. +7.16 mg/dL, $P = 0.01$).
Conclusions: Although the intervention group had reductions in DII and CRP, main inflammation and lipid outcomes did not differ between groups. Overall, those participants with the largest reduction in DII scores had the largest reductions in CRP and LDL and total cholesterol. Future interventions may need to have more components in place to support maintenance and continued reductions in the DII.
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1. Introduction

Acute inflammation is necessary for mounting inflammatory response necessary to fight infections and to allow the body to heal from an injury [1,2]. Chronic inflammation, however, is associated with increased risks of several chronic diseases, including cardiovascular disease (CVD), cancer, and diabetes [3–5]. In addition,

Abbreviations: PA, physical activity; NSAID, non-steroidal anti-inflammatory drugs; BMI, body mass index; DII, Dietary Inflammatory Index; CRP, c-reactive protein; IL6, interleukin-6; TNF, tumor necrosis factor; HDL, high density lipoprotein; LDL, low density lipoprotein.

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elevated blood lipid levels have been associated with CVD [6]. One of the behavioral factors that plays a role in regulating both chronic inflammation and lipid levels is dietary intake [7–9]. For example, diets rich in fruits and vegetables have been associated with lower levels of inflammation [10], lipids [11], and CVD risk [12,13].

In order to quantify the impact that diet may have on inflammation, the literature-derived Dietary Inflammatory Index (DII®) was developed. This valid instrument can measure the overall effect of an individual's diet on inflammation [14,15]. Higher (i.e., more pro-inflammatory) DII scores have been shown to be associated with the development of cancer [16–18], metabolic syndrome [19], and CVD [20]. In addition, lower (i.e., anti-inflammatory) DII scores have been observed among participants randomized to follow more plant-based diets (vegan, vegetarian, Mediterranean, etc.) as compared to participants assigned to follow more standard low-fat diets [21,22].

Because of the relationship between the DII and chronic disease risk, a behavioral intervention was developed based on the DII to test feasibility, acceptability, and impact on changes in inflammation and DII scores. The **I**nflammation **Ma**na**g**ement **In**t**e**rvention (IMAGINE) was developed to test the feasibility, acceptability, and impact on systemic inflammation among adults who registered to participate in the IMAGINE program as compared to adults who opted for a remotely delivered, information-only control. The objective of this paper was to assess the feasibility (ability to recruit participants and develop the 12-month intervention), acceptability (retaining participants in the intervention), and impact on systemic inflammation and the DII of the IMAGINE intervention. We hypothesized that the IMAGINE intervention condition would demonstrate high feasibility and acceptability and produce larger reductions in markers of inflammation and DII scores than the control condition at both three and 12 months.

2. Material and methods

The IMAGINE study was a 12-month self-selection, inflammation-reduction trial comparing two different conditions: an intensive intervention focused on reducing inflammation via targeting improvements in diet, physical activity, and stress management or a remotely delivered control condition where participants received newsletters on cancer prevention strategies unrelated to diet, exercise, or stress. A self-selection trial was used to reduce concerns that a more traditional randomized controlled trial might introduce bias associated with attrition, poor compliance with dietary modifications, and/or contamination in the control group. For example, participants in a control condition may make dietary changes on their own that mimic those in the intervention group and improve the quality of their diet on their own [23,24]. The IMAGINE intervention required an extensive time commitment, which could impact treatment adherence and there were concerns that treatment preference might influence outcomes [25], because the two conditions were very different in content and time commitment. Therefore, allowing participants to select the condition in which they wanted to participate helped to mitigate the impact of treatment preference [25] and increased the likelihood that those in the intervention condition were willing to fully engage in the intervention. Furthermore, we wanted to assess the type of individual (demographic characteristics, levels of inflammation, etc.) who would potentially enroll in future community-and clinical-based dietary intervention programs. The self-selection process was more conducive to understanding the characteristics of those who would enroll in such a program, the general interest in the program, and the continued level of participation in the program [23].

To participate, individuals needed to have consent from their physician, be $\geq$ 21 years of age, be willing and able to participate fully in the study for a period of one year, and be able to travel to and from the intervention classes. Participants were excluded if they had a severe illness, disability, or chronic condition (e.g., congestive heart failure, cancer treatment within the past 12 months, etc.) that would prevent participation in a dietary intervention; were taking any medications that might influence inflammation; had recent surgery; or were currently pregnant or planned on becoming pregnant in the next year. Participants who were interested in cancer prevention strategies and reducing inflammation were provided with information on both conditions and the requirements for both groups. This allowed participants to select if they wanted to participate in an intensive, in-person lifestyle intervention or receive general cancer prevention information via email.

Both objective and self-reported data (including demographics) were collected at baseline, three months, and 12 months. Fasting blood samples were drawn in the morning for lipids (total cholesterol, HDL, LDL, and triglycerides), as well as inflammatory markers: c-reactive protein (CRP), tumor necrosis factor (TNF-α), and interleukin 6 (IL-6). Inflammatory biomarkers were quantified using quantitative sandwich ELISA kits provided by R&D Systems, Inc. (Minneapolis, MN): IL-6 (Cat. HS600B; sensitivity = 0.11 ρg/mL), CRP (Cat. DCRP00; sensitivity 0.022 ng/mL), and TNF-α (Cat. HSTA00D; sensitivity = 0.19ρg/mL). Height was measured using a stadiometer (INVICTA Plastics Limited, England, Model 2007246) and weight was measured with a digital scale (Tanita, TBF-300WA). Blood pressure was measured with a semiautomatic sphygmomanometer (Prestige Medical, Northridge, CA), with two readings per person, 1-minute apart from each other which were averaged together. Body fat was measured with a DXA scanner (GE Healthcare model 8743, Waukesha, WI).

Sleep efficiency was measured with Sensewear™ armbands, which have been shown to be valid for assessing both physical activity and sleep behaviors [26,27]. With the exception of showering or swimming, participants were asked to wear the armbands continuously for 7–10 days. Participants had to have at least four days with, at least, 20-h per day recorded for their actigraph data to be included in analyses. All armband data were analyzed by computer-based software (SenseWear® Professional software version 7.0; BodyMedia Inc.).

Dietary intake was assessed via three unannounced 24-h dietary recalls (24HR; 2 weekdays and 1 weekend day). The Nutrient Data System for Research software (NDSR, 2015), licensed from the Nutrition Coordinating Center (NCC) at the University of Minnesota, was used to conduct the dietary interviews. Portion estimation was facilitated with the participant using a validated, 2-dimensional, food portion visual that is an integral part of the NDSR software [28]. The quality of the data derived from a 24HR depends on numerous factors, such as the ability of the subject to remember which foods were consumed [29]. The 24HRs were collected by a team of experienced, registered dietitians specifically trained in using the NCC multi-pass protocol. This protocol utilizes prompting to reduce omissions and standardizes the interview methodology across interviewers to ensure that the interviewer elicits complete and accurate information on preparation techniques and recipe ingredients [30].

DII scores were derived from the dietary recalls and utilized 43 food parameters: carbohydrates; protein; fat; alcohol, fiber; cholesterol; saturated, monounsaturated, and polyunsaturated fatty acids; omega 3 and 6 fatty acids; trans-fat; niacin; thiamin; riboflavin; vitamins A, B6, B12, C, D, and E; iron; magnesium; zinc; selenium; folate; beta-carotene; anthocyanidins; flavan-3-ols; flavones; flavonols; flavonones; isoflavones; caffeine; garlic; ginger; onions; saffron; turmeric; pepper; thyme or oregano; rosemary; and tea. The complete details on the derivation of DII scores can be found elsewhere [14]. In short, ‘inflammatory effect scores’ for each food parameter included in the DII were developed based on research from nearly 2,000 peer-reviewed publications, which were based on the effect of a specific food parameter on inflammation. At the same time, DII calculation is standardized to a global database of micro and macronutrient intake; the database contained dietary intake from 11 populations around the world. The global database provided a standard mean and deviation for all DII food parameters. These were then used to create a z-score by subtracting the individual's estimated intake for each food parameter from the standard mean of each food parameter and then dividing by the standard deviation. To account for skewness these z-scores were then centered on 0 with bounds between -1 and $+1$. Next, they were multiplied by the inflammatory effect score for each food parameter. They were then summed across all food parameters to create the overall DII score. DII scores range from about -8 to $+8$ and were calculated for each participant at each time point. Negative or lower scores indicate a more anti-inflammatory diet, and positive or higher scores indicate a more pro-inflammatory diet [14]. DII scores were calculated per 1,000 calories consumed to account for differences in energy intake between people.

2.1. Covariate information

Demographic characteristics, health histories, and lifestyle habits were obtained through self-report questionnaires. We measured stress using the Perceived Stress Scale [31]. Physical activity was measured using Sensewear™ armbands. In addition to this information, several psychosocial metrics were collected. Behavioral self-reports are prone to biases known as response sets, such as social desirability and social approval. Previous research has shown that both social desirability and social approval influence reporting of diet and physical activity [32–34]. The 33-item Marlowe–Crowne Social Desirability Scale (MC–SDS) ascertains an individual's tendency “to avoid criticism” and display oneself in a favorable social image [35]. The 20-item Martin Larsen scale ascertains the tendency to seek approval in a testing situation [36,37]. Both have been shown to have good validity and reliability [35–37]. These two scales were examined as confounders to account for biases typically observed when self-reporting dietary patterns.

2.2. Intervention methods

Participants were recruited from the Columbia, SC metropolitan area on a rolling basis between July 2015 and February 2016 for each of the five study waves (three intervention and two control). Fig. 1 presents the participant flow from recruitment to final enrollment in the intervention. Recruitment methods included flyers, internet and newspaper ads, emails, announcements at medical clinics, and word of mouth. Participants completed an online screener and were then contacted by phone to assess interest and eligibility (e.g., age, medical history, medications). Because IMAGINE was a self-selection trial, all potential participants received information about both the intervention and control conditions and were asked to elect into one of the two conditions. Participants then attended an orientation for condition they selected to learn more about the study, sign consent forms, and sign up for laboratory assessment times. Once all baseline measures were completed, participants began their chosen conditions. The study was approved by the University of South Carolina Institutional Review Board and all participants gave written consent. Participants in the intervention group received $50 for completing three-month assessments and $100 for completing one-year assessments. The control group received $25 for completion of baseline assessments, $50 for three-month assessments and $75 for completing the one-year assessment.

Intervention study participants were provided with 21 classes (one class weekly for 12 weeks and one booster session monthly for the remaining nine months). Class topics focused on inflammation reduction through diet, exercise, and stress reduction. The DII helped to inform the intervention diet, which consisted primarily of plant-based foods, focusing on the consumption of fruits, vegetables, whole-grains, legumes, and spices (garlic, cumin, etc.). Interventionists encouraged participants to avoid refined foods such as sugar, flour, and oils. Nuts, seeds and all high-fat plant foods were treated as condiments, and three optional servings of seafood were permitted a week. All other meat and dairy products were avoided. The interventionist provided dietary guidance in both a group setting and two one-on-one meetings, and participants learned cooking techniques through hands-on cooking in the classes. A private IMAGINE study responsive-design website was created for additional support for intervention participants during monthly booster sessions. Three information blog posts per week were posted on the website for intervention participants.

The IMAGINE study also recommended that intervention participants do moderate-to-vigorous aerobic activities 2–3 days per week for 45–60 min and strength training 2–3 days per week, in line with the physical activity guidelines [38]. For stress reduction, participants were provided materials for managing stress that were available from the Diabetes Prevention Program [39], and practiced the suggested approaches during intervention sessions.

Control participants received weekly (through three months) and then monthly emails or mailed hard copies if they did not have internet access, of readily available cancer prevention educational materials from the American Cancer Society, Centers for Disease Control, American Institute for Cancer, or the National Cancer Institute. Any gender-specific cancer education materials were matched to the gender of the control participant (e.g., ovarian/prostate cancer). Materials focused on cancer prevention-related behaviors unrelated to diet, physical activity, and stress including sun safety and screening recommendations.

2.3. Statistical methods

Analyses were conducted in SAS® version 9.4 (SAS Institute, Cary, NC) [40]. Two series of these analyses were performed: one including only baseline and post-intervention (i.e., 3 months) and the other including post-intervention and post-follow-up (i.e., 12 months). This plan was chosen because baseline to post-intervention focuses on the immediate effect of the intervention; whereas, post-intervention to post-follow-up focuses more on maintenance and long-term adherence. It is conceivable that different mechanisms or influences between these time periods differentially affect the results. Power calculations for this intervention were based on studies that indicate a lower CRP level among those in DII quartile 1 (most anti-inflammatory) compared to DII quartile 4 (most pro-inflammatory). In previous work, the difference in CRP between DII quartile 1 and 4 has typically fallen somewhere between 0.5 mg/L and 3.0 mg/L [41]. Prior to the development of this intervention study, to determine the necessary sample size, a two-sample means approach, assuming normal distributions, was used. The mean difference was set to 1.5 mg/L with a standard deviation of 1.5. Alpha was set to 0.05 and power at 0.80. A total of 29 participants per group were needed to provide sufficient power.

For everyone attending baseline data collection, sample characteristics were described by intervention condition using frequencies and means. Differences between groups at baseline were derived using chi-square or Fisher's exact test for categorical

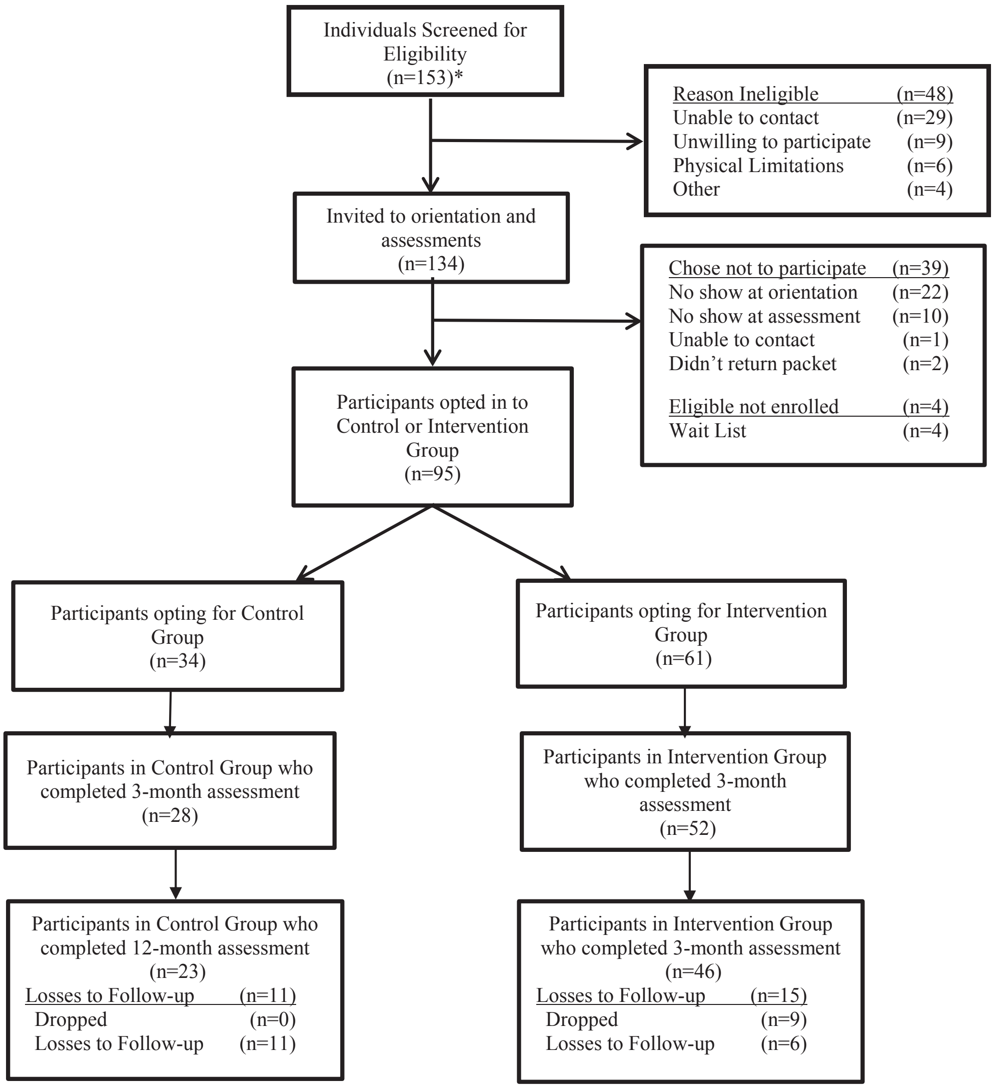

Fig. 1. IMAGINE consort diagram: Flow of participants through the 12-month IMAGINE self-selection trial.

covariates. For continuous covariates, t-tests or Wilcoxon rank sums test, depending on normality, were used. For the main analyses the primary exposure of interest was study status and the outcomes included CRP, IL-6, TNF-alpha, total cholesterol, HDL, LDL, and triglycerides. Elevated inflammatory levels due to acute infection was addressed by removing those with a CRP value greater than 10 mg/L which included 7, 5, and 5 observations at baseline, 3 months, and 12 months, respectively. For the main analyses examining the intervention effect, variable selection started as a series of preliminary analyses (e.g., CRP = intervention status + covariate). Any covariate with a p-value of <0.20 in these analyses were added to a full model. From here, a backward selection process was used to select the final model which included all covariates that lead to a 10% change in the beta coefficient of intervention status when removed; or were, themselves, statistically significant. It was determined that age and BMI would be adjusted for *a priori*. This process was performed for each inflammatory and lipid outcome (see Tables 2 and 4 for list of outcome measures) using baseline and post-intervention only and then repeated when using post-intervention and post follow-up.

Main analyses were conducted using general linear models with repeated measurements. All repeated-measure analyses utilized a compound symmetry covariance structure. Using least-square means, mean outcome levels by intervention status were obtained. Next, an interaction term was added to investigate the intervention-by-time effect. This process was conducted for each outcome.

In randomized controlled trials, some individuals in the intervention arm do not adhere to the intervention; whereas, some in the control arm make changes on their own [42]. This, in turn, makes both groups comparable, thus obscuring an intervention effect. One way to address this methodological issue is to investigate adherence or some aspect of change in the behavior of focus. The IMAGINE program was designed to lower inflammation by reducing dietary-related inflammatory potential which is measurable by the DII. Theoretically, those in the intervention arm should have lower DII scores at the end of the trial, while those in the control arm should stay roughly the same. Although this was a self-selection design, adherence to the intervention assignment was examined. As described in the Results, some intervention participants had a worsening in their DII score after three months (i.e., diet became more pro-inflammatory) and some control participants improved their DII score (i.e., diet became more anti-inflammatory). This *post-hoc* analysis, as opposed to addressing

Table 1
IMAGINE population characteristics for all participants and stratified by intervention status.

	All (n = 95)	Intervention (n = 61)	Control (n = 34)	p-value
Sex				
Male	18 (19%)	10 (17%)	8 (24%)	0.39
Female	77 (81%)	51 (84%)	26 (76%)	
Race				
White	59 (62%)	39 (64%)	20 (59%)	0.62
Black or Other	36 (38%)	22 (36%)	14 (41%)	
Education				
At least some college	25 (26%)	17 (28%)	8 (24%)	0.11
College graduate	38 (40%)	28 (46%)	10 (29%)	
Graduate degree or equivalent	32 (34%)	16 (26%)	16 (47%)	
Marital Status				
Married or living with partner	55 (58%)	39 (64%)	16 (47%)	0.05
Separated/Widowed/Divorced	18 (19%)	13 (21%)	5 (15%)	
Never Married	22 (23%)	9 (15%)	13 (38%)	
Employment				
Full-time	59 (62%)	42 (69%)	17 (50%)	0.10
Part-time	12 (13%)	4 (7%)	8 (24%)	
Retired	14 (15%)	9 (15%)	5 (15%)	
Not employed	10 (11%)	6 (10%)	4 (12%)	
Smoking Status				
Never	66 (69%)	40 (66%)	26 (76%)	0.27
Current or former	29 (31%)	21 (34%)	8 (24%)	
Alcohol last 12 months				
Yes	67 (71%)	47 (77%)	20 (59%)	0.06
No	28 (29%)	14 (23%)	14 (41%)	
Current NSAID Use				
Yes	20 (21%)	13 (21%)	7 (21%)	0.93
No	75 (79%)	48 (79%)	27 (79%)	
	Continuous Measures			
Age (years)	46.9 ± 13.4	51.1 ± 11.0	39.2 ± 14.0	<0.01
BMI (kg/m^2)	31.4 ± 7.1	32.6 ± 7.2	29.2 ± 6.6	0.02
Sleep Efficiency (%)	81.9 ± 7.8	81.9 ± 7.3	81.8 ± 8.7	0.92
Social Approval (Martin-Larsen)	50.6 ± 8.5	51.4 ± 8.8	49.0 ± 7.9	0.18
Social Desirability (Marlowe Crowne)	19.2 ± 5.9	19.0 ± 17.3	19.4 ± 17.3	0.76
Dietary Inflammatory Index	1.36 ± 2.42	1.06 ± 2.31	1.90 ± 2.53	0.11

Stratum totals may not equal column totals due to missing data. For categorical covariates, chi-square test was used to derive p-values except for when cell frequencies were less than 5; in this case, Fisher's Exact test was used. For continuous covariates, t-tests were used to derive p-values except for PA hours per day as this was non-normal; Wilcoxon Rank Sums test was used for this variable. Abbreviations: PA = physical activity; NSAID = non-steroidal anti-inflammatory drugs; BMI = body mass index. The Martin Larsen Approval Motivation score ranges from 0 to 100 and higher scores indicate greater social approval. The Marlowe-Crowne Social Desirability Scale ranges from 0 to 33 with higher scores indicating more social desirability.

whether the intervention led to a reduction in inflammation, examines whether a change to a more anti-inflammatory dietary pattern, in general, led to a change in inflammation. *Post-hoc* analyses were conducted that aimed at addressing changes in DII that occurred in both groups.

Regardless of intervention status, participants were grouped into tertiles based on the change in their DII score over time. These tertiles were based on the distribution of the change in DII score between baseline and three months; the groups were roughly equal in sample size). Those in DII tertile 1 had reductions in their DII scores (i.e., their diets improved and became more anti-inflammatory), those in tertile 3 deteriorated and became more pro-inflammatory, and those in tertile 2 were somewhere in between. Given that change in DII scores between time points was used as the independent variable, multiple regression, as opposed to a repeated measures analysis was utilized. The independent variable was the change in the DII scores analyzed as both continuous and in tertiles. The dependent variables were the change between time points in CRP, IL-6, TNF-alpha, total cholesterol, HDL, LDL, and triglycerides. Variable selection procedures were conducted in a similar manner as described for the main analyses. Multiple least square regression was then performed to obtain least square means of the dependent variables by DII change tertile. Additionally, the change in DII score was examined as a continuous measure where beta coefficients for a one-unit change in the DII score were reported. A one-unit increase in the change in DII score indicates a worsening of the DII score. This set of *post-hoc* analyses was performed using the change in measures between post-intervention (i.e., 3 months) and baseline. They were then repeated for the change between post follow-up (i.e., 12 months) and baseline.

Because of the complex intervention design that included a focus on stress and physical activity, as well as on dietary change, we treated stress (using PSS score) and physical activity as potential confounders; however, they were not selected for inclusion in final models because they failed to meet the criterion of producing a 10% change in the beta coefficient of intervention status. In addition, we also computed the difference in moderate and vigorous physical activity (MVPA) and the PSS score between month 3 and baseline and then conducted a t-test comparing the

Table 2
Mean and standard deviation of biomarker endpoints by time point.

Characteristic	Baseline	Three Months	Twelve Months
CRP (mg/L)	5.37 ± 6.25	4.05 ± 5.26	3.60 ± 3.76
IL6 (pg/mL)	2.23 ± 3.12	1.61 ± 1.36	1.51 ± 0.98
TNF-alpha (pg/mL)	0.60 ± 0.52	0.61 ± 0.48	0.61 ± 0.49
Cholesterol (mg/dL)	190.60 ± 41.19	187.86 ± 44.65	187.54 ± 37.66
HDL (mg/dL)	56.39 ± 13.10	55.40 ± 14.45	56.96 ± 13.51
LDL (mg/dL)	109.48 ± 32.11	106.41 ± 37.86	105.86 ± 33.54
Triglycerides (mg/dL)	134.67 ± 214.85	114.00 ± 64.47	120.39 ± 67.50

Table 3
Baseline characteristics by tertiles of dietary inflammatory index change.

Characteristic	Change in DII between Baseline and Three Months			
	Tertile 1	Tertile 2	Tertile 3	p-value
Age (mean ± STD)	49.8 ± 11.6	51.2 ± 9.9	44.2 ± 15.6	0.13
Sex (n (%))				
Males	5 (21%)	2 (8%)	8 (31%)	0.13
Females	19 (79%)	23 (92%)	18 (69%)	
Race (n (%))				
White	17 (71%)	13 (52%)	19 (73%)	0.23
Blacks or Other	7 (29%)	12 (48%)	7 (27%)	
Body Mass Index (kg/M^2, mean + STD)	31.5 ± 6.2	32.6 ± 9.0	28.2 ± 5.3	0.10
	Change in DII between Baseline and Twelve Months			
Age (mean ± STD)	50.3 ± 13.2	48.2 ± 11.8	46.6 ± 12.8	0.36
Sex (n (%))				
Males	6 (30%)	0 (0%)	2 (10%)	0.02
Females	14 (70%)	19 (100%)	18 (90%)	
Race (n (%))				
White	15 (75%)	15 (79%)	11 (55%)	0.22
Blacks or Other	5 (25%)	4 (21%)	9 (45%)	
Body Mass Index (kg/M^2, mean + STD)	31.4 ± 4.8	30.6 ± 8.9	30.7 ± 8.5	0.81

P-values for age and race were derived using a trend test to examine dose–response across tertiles of the change in DII scores. For sex and race, p-values were based on Fisher's exact test.

mean difference between intervention and control for both MVPA and PSS.

3. Results

A total of 153 individuals were screened for inclusion in the study by phone. Ten individuals were excluded because they had a physical limitation (n = 6) or were participating in another study (n = 4) (Fig. 1). Another nine chose not to participate. Among the remaining 134 eligible participants who were invited to attend orientation, 39 chose not to enroll in the final study. A total of 61 participants were eligible and elected to enroll into the intervention condition and 34 were enrolled into the control condition. Table 1 provides the demographic details of intervention and control participants. Participants were mostly female (81%), White (62%), college-educated (74%), employed full time or part time (75%), and never smoked (69%). Despite a non-randomized design, the only significant differences in baseline demographics between the groups were on age, BMI, and marital status. Participants in the control group were younger, had a lower BMI, and were more likely to have never been married. There were no differences detected in attrition between groups at either three (16% attrition overall, $P = 0.34$ between groups) or 12 months (27% attrition overall, $P = 0.93$ between groups). Table 2 provides the means (±SD) of each assessed biomarker at each time point for all participants combined.

Feasibility for the study was assessed by ability to recruit participants for a 12-month intervention and to design and deliver the intervention. Overall, the study was highly feasible. Participants were recruited over five waves with minimal funds spent on recruitment

Table 4
Adjusted Mean Changes in Inflammation and Lipid Biomarkers by Change in Dietary Inflammatory Index Scores from Baseline at Three and 12 months.

Outcome	DII Change Tertile 1	DII Change Tertile 2	DII Change Tertile 3	P: 1 vs. 3	β Cont	P: Cont
Change in outcomes at 3 months compared to baseline						
CRP (mg/L)	−1.09 (−2.21–0.04)	−1.44 (−2.48–−0.41)	0.52 (−0.52–1.55)	0.04	0.27	0.02
IL6 (pg/mL)	−0.29 (−0.72–0.13)	−0.32 (−0.72–0.08)	0.01 (−0.38–0.40)	0.30	0.06	0.16
TNF-alpha (pg/mL)	−0.02 (−0.19–0.15)	−0.02 (−0.18–0.13)	0.00 (−0.16–0.16)	0.85	0.02	0.32
Cholesterol (mg/dL)	−9.38 (−21.24–2.48)	10.65 (−2.48–23.75)	12.02 (−0.25–24.30)	0.01	2.79	0.03
HDL (mg/dL)	−1.13 (−4.24–1.99)	2.81 (−0.63–6.25)	0.27 (−2.95–3.50)	0.52	0.26	0.42
LDL (mg/dL)	−11.99 (−22.37–−1.61)	7.71 (−4.22–19.64)	7.16 (−3.61–17.94)	0.01	2.30	0.04
Triglycerides (mg/dL)	−3.37 (−27.52–20.77)	−9.08 (−30.71–12.55)	−0.91 (−23.40–21.59)	0.88	0.27	0.91
Change in outcomes at 12 months compared to baseline						
CRP (mg/L)	−1.59 (−2.72–−0.47)	−1.27 (−2.51–−0.02)	−0.04 (−1.21–1.12)	0.05	0.27	0.02
IL6 (pg/mL)	−0.18 (−0.52–0.16)	0.01 (−0.28–0.47)	0.11 (−0.25–0.46)	0.12	0.05	0.23
TNF-alpha (pg/mL)	−0.02 (−0.19–0.15)	0.02 (−0.16–0.20)	−0.06 (−0.24–0.11)	0.72	−0.01	0.45
Cholesterol (mg/dL)	−6.84 (−21.10–7.42)	9.17 (−6.16–24.50)	0.42 (−14.02–14.86)	0.42	1.17	0.42
HDL (mg/dL)	−0.22 (−3.97–3.52)	1.79 (−2.24–5.82)	0.90 (−2.89–4.69)	0.64	0.21	0.58
LDL (mg/dL)	−8.89 (−23.02–5.25)	0.59 (−14.65–15.83)	−3.97 (−17.79–9.86)	0.57	0.67	0.61
Triglycerides (mg/dL)	−4.62 (−22.66–13.42)	4.57 (−18.87–28.00)	7.32 (−11.56–26.20)	0.36	2.11	0.30

Results at three months refer to modeling three-month outcomes while adjusting for baseline. DII Change Tertile 1 indicates more anti-inflammatory changes. DII Change Tertile 3 indicates a more pro-inflammatory change. Ranges of DII change tertiles for changes between baseline and 3 months were as follows: 1 = −8.33 to −3.76, 2 = −3.75 to −0.52, and 3 = −0.51 to 4.25. Ranges of DII change tertiles for changes between baseline and 12 months were as follows: 1 = −7.76 to −3.02, 2 = −3.01 to −0.52, and 3 = −0.51 to 3.74. P: 1 vs. 3 is the p-value for the differences in least square means between tertiles 1 and 3. Β Cont refers to the beta coefficient for the continuous form of the change in the DII and indicates the change in the outcomes per 1-unit increase in the change of the DII. Increasing values of the change in the DII are worse than decreasing values. P: Cont is the p-value for the beta coefficient. CRP, IL-6, and TNF-alpha adjusted for age, NSAID use, BMI, social approval, change in perceived stress, change in moderate to vigorous physical activity, and sleep efficiency. Total cholesterol, HDL, and LDL adjusted for age, race, change in perceived stress, change in moderate to vigorous physical activity, and smoking status. Triglycerides adjusted for age, change in perceived stress, change in moderate to vigorous physical activity, and alcohol consumption. Abbreviations: DII = Dietary Inflammatory Index; CRP = c-reactive protein; IL6 = interleukin-6; TNF = tumor necrosis factor; HDL = high density lipoprotein; LDL = low density lipoprotein.

efforts. The study mainly relied on partnerships with local health clinics, fliers, and posts to listservs as free or low-cost ways to recruit a diverse sample of participants in a timely manner. Intervention materials were developed and delivered on-time. Acceptability for the study was assessed by the ability to retain participants in the intervention condition over a one-year period.

Main analyses examined group and group-by-time effects for each outcome (i.e., CRP, IL-6, TNFα, cholesterol, LDL, HDL, and triglycerides). Models involving only post-intervention and baseline were reduced to be adjusted for NSAIDs, social desirability, sleep efficiency, age, BMI, perceived stress, moderate-to-vigorous physical activity, and time point. Models involving post follow-up and post intervention were adjusted for sleep latency, age, BMI, perceived stress, moderate-to-vigorous physical activity, and time point. For all biomarkers, except CRP, there were no significant group-by-time interactions at baseline and three-months. For CRP, although the group-by-time interaction did not reach significance ($P = 0.11$), trends were in the anticipated directions. For example, a within-group difference was observed for the intervention group. CRP decreased by 0.65 mg/L (95%CI = 0.10–1.20, $P = 0.02$) at month three compared to baseline. Little to no change in CRP was observed among the control group. There were no group-by-time effects when considering three-month and 12-month values for any biomarker (data not shown).

Greater adherence to the IMAGINE protocol should lead to reductions in DII scores. Intervention participants, on average, reduced their DII score by 2.66 ± 2.44 points, whereas the controls decreased their score by 0.38 ± 2.56 points when comparing month 3 to baseline. This difference was statistically significant ($P < 0.01$). When comparing month 12 to baseline, the intervention group showed a persistent reduction in DII score of 2.11 ± 2.51; whereas the controls showed a reduction of 0.88 ± 2.77. This difference did not achieve statistical significance ($P = 0.10$). However, upon further review, it was clear that there was considerable overlap in reduction in the DII between the two study arms. The range of DII change between baseline and three-months in the intervention arm ranged from a +2.23 (worst change) to −8.33 (best change). About 29% of this group had a DII change that was above −1.0, indicating a no change or a pro-inflammatory change. Among the controls, the range in change was from +4.25 to −5.48. About 42% had better than a −1.0 change in their score indicating a more anti-inflammatory improvement. Therefore, *post-hoc* analyses were conducted in which both intervention and control groups were combined.

Table 3 presents the baseline characteristics of the full sample by tertiles of DII change and Table 4 presents the adjusted mean changes in inflammation and lipid biomarkers by change in DII scores from baseline at three and 12 months. Those in the lowest DII change tertile (i.e., more anti-inflammatory improvements) had significantly greater reductions in CRP (−1.09 vs. 0.52 mg/L, $P = 0.04$), total cholesterol (−9.38 vs. 12.02, $P = 0.01$), and LDL (−11.99 vs. 7.16, $P = 0.01$), compared to those in the highest tertile, when taking the difference between month 3 and baseline. The p-values for a one-unit change in DII were statistically significant or nearly significant for these same outcomes. The difference in CRP persisted when comparing month 12 to baseline. Those in DII change tertile 1 showed a reduction in CRP of −1.59; whereas, those in DII tertile 3 remained relatively constant at −0.04 ($P = 0.05$, Table 4).

For the *ad hoc* analyses focusing on stress and physical activity, we found that the mean differences in intervention and control for the PSS between 3 months and baseline were 0.15 and −0.17, respectively (p = 0.81). For MVPA, the intervention group increased by 9.8 min/day and the control decreased by 2.3 min/day, p = 0.09, which did not achieve statistical significance.

4. Discussion

The goal of the IMAGINE study was to assess the feasibility (ability to recruit participants and develop the 12-month intervention), acceptability (retaining participants in the intervention), and impact on systemic inflammation and DII of the IMAGINE intervention. We demonstrated feasibility in the ease of recruiting participants and designing and delivering the 12-month intervention. In addition, there was low attrition over the course of the study (<30%) with no differences in attrition between the control condition and the more intensive lifestyle intervention condition. This attrition rate is similar or less than previous behavioral interventions [43] and demonstrates the IMAGINE participants' willingness to engage with the program over a 12-month period.

In addition, we hypothesized that the IMAGINE intervention would produce larger changes in markers of inflammation and DII scores than the control condition at both three- and 12-months. While the intervention group experienced decreases in CRP there were no statistically significant intervention-by-time interactions. Because the goal of the IMAGINE intervention was to improve DII scores and because variation in response was observed, both intervention and control conditions were collapsed in order to examine the impact of DII scores on outcomes. Those in the lowest tertile for change in DII (meaning most anti-inflammatory scores of the study) had a change in CRP that was approximately 1.7 mg/L lower than the highest DII tertile at month three, and approximately 1.5 mg/L lower at 12 months. In addition, at three months, those in the lowest tertile of DII change had lower total cholesterol levels by approximately 20 points, mostly driven by lower LDL cholesterol levels, as compared to the highest DII tertile. These results indicate the importance of targeting reductions in DII to lower chronic inflammation and lipid levels. Because IMAGINE intervention participants decreased their DII scores more so than the control participants, testing the IMAGINE intervention in a larger, randomized trial is warranted in order to more robustly examine the impact of changing DII via a dietary intervention on important inflammatory and cardiovascular disease risk markers.

The IMAGINE study was the first intervention to use the DII, designed as an epidemiological tool to assess the inflammatory potential of the diet, as a framework to design a dietary intervention. This allowed for a comprehensive way to synthesize the wealth of literature around dietary components and inflammation reduction into an actionable, behavioral nutrition program that participants could follow. In addition, while most previous studies examining the DII have been observational or prospective studies [44–49], to date, few studies have examined changes in DII over time as a result of a nutrition intervention [21,22]. For example, in an Australian study examining differences in six-month changes in DII score among participants randomized to follow a Mediterranean diet or low-fat diet, the Mediterranean group significantly reduced DII scores at 6 months (n = 27; −0.40 ± 3.14 to −1.74 ± 2.81, $P = 0.008$) and the low-fat diet group did not change (n = 29; −0.17 ± 2.27 to 0.05 ± 1.89, $P = 0.65$) [22].

Diet can have a significant impact on inflammatory markers [50,51]. The IMAGINE intervention dietary pattern was primarily plant-based, with all animal products excluded except for three optional servings of seafood per week. Previous studies have shown that vegetarians have lower levels of CRP than non-vegetarians [52–54]. It is possible, however, that we needed to follow participants longer to see a more profound effect on inflammation. In a meta-analysis that examined the relationship between consumption of a vegetarian diet and inflammation, a minimum duration of two years of following a vegetarian diet was needed to see lower CRP levels [55]. Other studies also have suggested that low levels of inflammation among vegetarians are mediated by BMI [56] or gut microbiota composition [57]. While most IMAGINE participants were overweight or obese, not all participants had a BMI above 25 kg/m^2. This may have reduced the impact diet would have on inflammation among some participants. In addition, future studies testing the IMAGINE diet approach should assess changes in gut microbiota composition as well. The IMAGINE trial also found significant associations between DII and CRP, but not for TNF-α and IL6. Previous interventions have demonstrated that the various markers of inflammation may not all respond similarly to dietary changes [58–63]. In addition to the inflammatory cascade (e.g., IL6 is a cytokine responsible for inducing CRP), these cytokines may be influenced by factors such as body weight [64] and insulin resistance [64,65].

Similar to a previous nutrition intervention (the six-month New DIETs intervention) that assessed changes in DII [21], the IMAGINE study observed short-term changes in DII, but changes were not maintained over time as contact frequency with participants decreased. This indicates that additional support may be necessary to sustain and continue important changes in DII and health-related outcomes. While face-to-face group meetings were used in both IMAGINE and the New DIETs studies, this type of intensive intervention delivery is hard to sustain due to participant and interventionist burden, as well as costs. Delivering content to participants remotely, via audio podcasts [66], social media [67], e-mail or phone counseling [68], or mobile web or app [69], may help sustain engagement without greatly increasing burden and cost. The intervention also included stress reduction and physical activity components. While there was no significant effect on stress, there was an apparent ($p = 0.09$) increase in MVPA in the intervention group. Neither stress nor physical activity were confounders of the effect of the DII on study outcomes.

4.1. Strengths and limitations

The present study has some limitations that must be considered when interpreting the results. Participants were mostly White females; however, the participant sample was much more diverse than many other previous behavioral nutrition/exercise interventions. In a recent systematic review of 94 weight loss interventions, African Americans comprised just 18% of samples, compared to 34% in the IMAGINE study [70]. In addition, the percentage of men in the IMAGINE study (22%) is similar to what has been found among 244 other previous lifestyle intervention studies (27%) [71]. The IMAGINE study also was a self-selection trial and did not employ a randomized design. While this type of design allows for a more real-world testing of an intervention, which was important for the present study, it also limits the ability to control for any personal factors that may be motivating a participant to engage with the study [42]. In addition, the study may have been under-powered to detect differences in study outcomes. For example, the sample size for the control group at both 3- and 12-month time points was below the sample size calculated as required to be able to demonstrate statistically significant differences between the groups. The study also has several strengths. We used objective measures to assess changes in lipid and inflammatory marker outcomes. Three telephone-administered multiple-pass 24-h dietary recalls were conducted, including two weekdays and one weekend day, which has been shown to help balance known differences in day-to-day variation in dietary intake patterns [72]. In addition, three dietary recalls are preferred over collecting just one or 2 day at each timepoint [73]. Lastly, the IMAGINE study was a year-long intervention with three assessment timepoints, which allowed for the examination of both short- and longer-term outcomes.

5. Conclusions

The results of the IMAGINE trial suggest that targeting dietary changes that lower the DII is a potential strategy for lowering chronic inflammation and, in turn, chronic disease risk [74]. Although the intervention group saw greater improvements in DII score, main inflammation and lipid outcomes did not differ between groups. Overall, those participants with the largest reduction in DII scores had the largest reductions in CRP and LDL and total cholesterol. These findings suggest that lifestyle interventions targeting reductions in the DII may be important for reducing inflammation and chronic disease risk [74]. The results of this study suggest that future interventions may need a more robust emphasis on dietary changes aligned with a lower DII, with more components in place to support, or more intensive sustained intervention to produce, continued reductions in the DII.

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Statement of authorship

JRH, MDW, NS, DSW, and GTM designed the research. MDW, NS, AC, CGD, and GTM conducted the research. MDW, JH, and TH analyzed the data and provided input for interpreting the results. GTM and MDW wrote the paper. GTM had primary responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest statement

J.R.H. owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the Dietary Inflammatory Index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. In addition to their University of South Carolina appointments, M.D.W. and N.S. are employees of CHI. G.T.M.: No conflict of interest. C.D.: No conflict of interest. A.C.: No conflict of interest. T.H.: No conflict of interest. DSW: No conflict of interest. J.H.: No conflict of interest.

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