

# Impact of a 3-Month Anti-inflammatory Dietary Intervention Focusing on Watermelon on Body Habitus, Inflammation, and Metabolic Markers: A Pilot Study

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**ABSTRACT:** An anti-inflammatory dietary intervention called the Inflammation Management Intervention (IMAGINE) was adapted to emphasize watermelon due to its anti-inflammatory properties. This pilot study (n=23) tested the effect of a watermelon-enhanced IMAGINE intervention (n=15) on body habitus and markers of inflammation and metabolism. This 3-month self-selection trial, consisting of weekly in-person classes and online education for 12 weeks, focused on incorporating watermelon into an already anti-inflammatory diet. Controls (n=8) received basic health education via email and blogs. Measurements, including diet, anthropometrics, actigraphy, and a blood draw, were made at baseline and immediately postintervention. Linear regression analyses were conducted using intervention status as the main exposure. Post hoc analyses then ignored intervention assignment and grouped participants based on their change in their energy-adjusted Dietary Inflammatory Index (E-DII™) score. There were no group-by-time interactions for any of the studied outcomes. However, some intervention participants' diets became more proinflammatory, and several control participants' diets became more anti-inflammatory. Those participants below the median of E-DII change (ie, more anti-inflammatory changes) showed reductions in body fat percent (−1.27% vs +0.90%, respectively, P = .01), body mass index (−0.66 vs +0.38 kg/m<sup>2</sup>, respectively, P = .06) and body weight (−0.99 vs +0.54 kg, respectively, P = .08) compared to those above the median of E-DII change. This study demonstrates that individuals who adopt a more anti-inflammatory diet containing watermelon will have improvements in body anthropometrics. Future studies should focus on increasing adherence and compliance to intervention prescriptions, exploring options to extend interventions to evaluate long-term changes, and further examining changes in inflammatory biomarkers.

**KEYWORDS:** Diet, inflammation, body weight, Dietary Inflammatory Index

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invention of the Dietary Inflammatory Index (DII®) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. M.D.W., N.S., S.V., L.B., and J.S. are or were employees of CHI at the time this work was conducted.

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## Introduction

A properly functioning immune system is vital for activating an acute inflammatory response during times of acute infection and injury.<sup>1,2</sup> This acute inflammatory response helps to attract leukocytes and other immune mediators to the site of infection or injury.<sup>3,4</sup> However, when the inflammatory stimulus is chronic in nature (eg, from long-term physical inactivity, poor-quality diet, obesity, and stress), the individual enters a state of chronic inflammation. Chronic inflammation is associated with increased risks of many chronic diseases, including cancer, cardiovascular disease (CVD), and diabetes.<sup>5-7</sup> Diet quality is one of the strongest environmental influencers of chronic systemic inflammation.<sup>8</sup> Diet patterns characterized by high consumption of fruits and vegetables, spices, herbs, whole grains, and fish (eg, Mediterranean and South Asian) are associated with lower levels of systemic inflammation. On the contrary, diets characterized by high consumption of simple carbohydrates, total and saturated fats, processed and fried

foods, and meats (eg, Western diet) are associated with a pro-inflammatory profile.<sup>8</sup>

The Dietary Inflammatory Index (DII®) was developed to measure the inflammatory potential of one's diet.<sup>9</sup> The use of dietary indices, such as the DII, is important because the conventional alternative line of dietary research, which focuses on single nutrients, does not consider the fact that foods are eaten in combination. In addition, separating the effects of individual nutrients may be difficult, effects of a single nutrient may be too small to detect, or their effect may be confounded by the overall dietary pattern.<sup>10,11</sup> The DII has been construct validated in numerous studies against inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6).<sup>12-15</sup> In addition, the DII has been associated with other inflammation-related conditions including, but not limited to, cancer, CVD, obesity, depression, telomere length, asthma, and mortality.<sup>15-21</sup>

Given the relationship between the DII and chronic disease risk, the Inflammation Management Intervention (IMAGINE),



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a behavioral intervention based on the DII, was developed. The purpose of IMAGINE is to lower one's dietary inflammatory potential; thereby, lowering chronic systemic inflammation. The IMAGINE consists of a baseline clinic assessment, followed by 12 weeks of hands-on cooking classes and online components and, for this study, a postintervention clinic. Previously, IMAGINE was used in a population of overweight or obese, but otherwise healthy, adults. At postintervention (ie, 3 months), compared to baseline, intervention participants showed a significant reduction in DII scores (ie, scores became more anti-inflammatory compared to controls;  $-2.66$  vs  $-0.38$ ,  $P < .01$ ). When using baseline and post-follow-up (ie, 12 months) time points, there was a nearly significant group-by-time interaction for CRP ( $P = .11$ ). Specifically, CRP decreased by  $0.65$  mg/L (95% confidence interval [CI] =  $[0.10-1.20]$ ,  $P = .02$ ) in the intervention group; whereas, no such change was observed in the control group.<sup>22</sup>

In the process of developing IMAGINE, questions arose about the adaptability of the dietary prescriptions to include or focus on specific foods, while yet maintaining its original purpose, that is, to lower dietary inflammatory potential. Previous studies have shown that watermelon or components that are abundant in watermelon (eg, citrulline) have anti-inflammatory effects.<sup>23-25</sup> With support from the National Watermelon Promotion Board in the United States, a small pilot study was undertaken to examine the impact of an IMAGINE intervention with heavy focus on watermelon (IMAGINE-Watermelon) on inflammatory markers and body habitus compared to a remotely delivered, information-only control. It should be noted that the intent of this study was to test the effect of an anti-inflammatory dietary prescription with heavy incorporation of watermelon recipes on inflammation, not the sole effect of watermelon on inflammation, for reasons described above. We hypothesized that the IMAGINE-watermelon intervention condition would produce larger reductions in markers of inflammation and metabolism, as well as measures of body habitus than the control condition at postintervention (ie, 3 months) compared to baseline.

## Methods

The IMAGINE-Watermelon study was a 12-week self-selection trial to examine the effectiveness of the IMAGINE protocol, modified by emphasizing watermelon-based recipes which scored low on DII (ie, more anti-inflammatory), on reductions in markers of body habitus, inflammation, and metabolism. The intervention group was compared to controls given general health information. A self-selection trial was chosen because of concerns of more traditional randomized controlled trials (RCTs) for behavioral interventions.<sup>26</sup> Further explanation and rationale for this strategy can be found in the section "Discussion."

To be eligible to participate, individuals from the greater Columbia, South Carolina area had to be  $\geq 18$  years of age; have no serious, unstable comorbidity that would make

participation in a diet and physical activity (PA) intervention difficult or risky; be willing and able to participate fully in the study for a period of 3 months; have access to the Internet; not be currently enrolled in a weight-loss program or actively taking weight-loss medications; and have a body mass index (BMI,  $\text{kg}/\text{m}^2$ ) of 25.0 to 49.9.

## Intervention design and methods

The Columbia, South Carolina metropolitan area served as the area for recruitment, which occurred between May, 2017 and July, 2017. Recruitment methods included websites, fliers, newspaper ads, Craigslist, and listserv messages. Participants completed phone screeners to assess their interest and eligibility. During an orientation, participants learned more about the study, signed consent forms, and signed up for times to conduct the baseline clinic measurements. Baseline measurements included questionnaires obtaining information on demographics, diet, health histories, and psychosocial factors including social desirability, social approval, depressive symptoms, and stress; blood draws for characterization of inflammation and metabolic markers; anthropometric measurements; and actigraphy. After the baseline clinic, all participants underwent 12 weeks of the intervention, followed by a postintervention clinic obtaining the same set of measures. The study was approved by the University of South Carolina Institutional Review Board, and all participants gave written informed consent. Participants received \$40 for their participation in this study.

The IMAGINE-Watermelon group met once a week for 12 weeks to cook and to engage in exercise and stress-reduction activities meant to increase compliance with the diet intervention.<sup>27,28</sup> The nutritional components of this intervention were based on the DII and focused on anti-inflammatory foods and components. Emphasis was put on watermelon, which is abundant in certain key elements that have been shown to have anti-inflammatory properties.<sup>23-25</sup> Weekly meal plans were designed to provide participants with 2 meals per day that incorporate watermelon. In each weekly class session, recipes containing watermelon were demonstrated and prepared. Most of the recipes involving watermelon used fresh watermelon, as the cooking process may impact nutrient levels. Other foods used during class sessions were those familiar to South Carolinians and are available in local markets. Preparation techniques focused on different methods of cooking that incorporate spices from other parts of the world. At the end of each session, participants received one whole watermelon and 1-gallon bag of precut watermelon per week during class. In addition, participants were provided "homework" to further enhance what was learned in class that week. In each class, participants also discussed the problems faced in adhering to the teachings from previous classes. For continued reinforcement, participants in the IMAGINE-Watermelon group had access to an online portal, which provided weekly blog posts, a recipe database of 84 recipes

that incorporated watermelon into their meal plans, interactive modules, and short vignettes of cooking tutorials.

The PA targets for this intervention were consistent with PA recommendations for adults.<sup>29,30</sup> Participants were encouraged to obtain at least 150 minutes of moderate-intensity PA (equivalent to brisk walking) per week and to engage in at least 2 sessions of strength training each week. For stress reduction, several techniques were employed including breathing exercises and mindfulness-based stress reduction (MBSR)-like activities. However, it should be stressed that the primary focus on the intervention was on dietary changes.

The standard-of-care arm received general health information (eg, general guidelines of healthy eating and PA, stress management, and cancer screening). This information was provided through email, which included a weekly newsletter, healthy recipes that were not focused on reducing DII scores, links to online content, and health-related event announcements in and around Columbia, South Carolina.

#### *Dietary assessment and the DII/E-DII*

Dietary intake was assessed using a modified validated version of the National Cancer Institute's food frequency questionnaire (FFQ), which included about 180 items.<sup>31</sup> Micro and macronutrients were derived using the Nutrient Data System for Research software (NDSR, 2015). Portion estimation was enhanced by use of a validated, 2-dimensional, food portion visual.<sup>32</sup> The DII is described in detail elsewhere.<sup>9</sup> Nearly 2000 research articles examining the relationship between various food parameters (mostly micro and macronutrients) and inflammation were reviewed to derive "inflammatory effect scores" for the food parameters. At the same time, DII calculation is linked to a regionally representative global database which contains means and standard deviations for the food parameters from 11 populations around the world.<sup>9</sup> A *z*-score is created by subtracting the global mean from the participant's estimated intake, then dividing by the global standard deviation. This is then converted to a proportion (values from 0 to 1) and centered by doubling the value and subtracting 1. The product of the literature-derived inflammatory effect score and the centered percentile for each food parameter is summed across all food parameters to create the overall DII score. A total of 38 of the food parameters out of a possible 45 were available from this FFQ, a number that is higher than most FFQs, which average about 27 parameters.<sup>33</sup> These food parameters included: carbohydrates; protein; fat; alcohol; fiber; cholesterol; saturated, monounsaturated, and polyunsaturated fatty acids; omega 3 and 6 fatty acids; transfat; niacin; thiamin; riboflavin; vitamins A, B6, B12, C, D, and E; iron; magnesium; zinc; selenium; folate; beta-carotene; anthocyanidins; caffeine; garlic; ginger; onions; saffron; turmeric; pepper; thyme or oregano; rosemary; and tea. Higher (ie, more positive) scores indicate more proinflammatory diets and negative values are more anti-inflammatory.<sup>9</sup> To control for the effect of total energy intake, the DII was

calculated per 1000 calories of food consumed, and this required the use of a calorie-adjusted reference database. This energy-adjusted DII (E-DII<sup>TM</sup>) score used a calorie-adjusted version of the 11 country global reference database.<sup>33</sup>

#### *Outcome assessment*

Laboratory-based outcomes of interest included CRP, glycosylated hemoglobin (HbA1c) percent, and glucose. All blood samples were drawn from an antecubital vein or dorsal hand vein by a trained phlebotomist while subjects were in the seated position in the morning after an overnight fast. Whole blood and serum samples were processed and delivered to the LabCorp facility in Columbia, South Carolina, the same day as drawn. C-reactive protein (immunochemiluminometric assay), HbA1c (Roche Tina Quant), and glucose (enzymatic assay) concentrations were determined by LabCorp. LabCorp employs internal and external systems to monitor the accuracy and precision of assays.

#### *Actigraphy*

The GT3x-BT produced by Actigraph is lightweight and is about the size of a wristwatch. It has been validated for the measurement of both PA and sleep.<sup>34,35</sup> Participants were asked to wear the GT3x-BT 24 hours per day on their wrist, except during water-based activities, for 10 days around the clinic dates. Minimum wear time requirements were 7 days (including Saturday and Sunday) with at least 20 hours of wear/day. During periods when the GT3x-BT was not worn, participants reported their activities in a log. Energy expenditure during nonwear time was estimated based on the Compendium of Physical Activities.<sup>36</sup> The following PA parameters were obtained using propriety algorithms by the ActiLife 6 software for PA: activity counts, energy expenditure, metabolic equivalents (METs), steps, PA intensity, activity bouts, and sedentary bouts. Sleep also was characterized by the GT3x-BT and has been shown to be valid for sleep when worn on the wrist.<sup>37</sup> Specifically, sleep duration, efficiency, onset (ie, bedtime), and offset (ie, wake time) were characterized.

#### *Anthropometric measurements*

Anthropometric measurements included height (cm), body weight (kg), and body fat percentage assessed according to standard procedures using a wall-mounted stadiometer (Model S100, Ayerton Corp., Prior lake, MN) and electronic scale (Healthometer® model 500 KL, McCook, IL) in bare feet.<sup>38</sup> Body mass index (kg/m<sup>2</sup>) was calculated from measured weight and height. Waist circumference (cm) and hip circumference (cm) were measured with a calibrated, spring-loaded tape measure by trained technicians. Blood pressure was measured according to standard procedures using a stethoscope and

manual sphygmomanometer after the participant had been sitting for 5 minutes.

### Covariates

Covariates were assessed using questionnaires that obtained information on basic demographics, income, education, smoking, other health behaviors, and current medications. Social desirability and social approval<sup>39,40</sup> were measured using the 33-item Marlowe-Crowne Social Desirability (MCSD) Scale<sup>41</sup> and the 20-item Martin-Larson Approval Motivation (MLAM) scale.<sup>42,43</sup> Self-efficacy (confidence in the ability to change across problem situations) for diet and PA using adaptations of previously validated questionnaires<sup>44,45</sup> was obtained. Depression and stress also were measured using the Center for Epidemiologic Studies Depression (scale) and the Perceived Stress Scale, respectively.<sup>46</sup>

### Statistical analyses

Analyses were conducted in SAS<sup>®</sup>, version 9.4 (SAS Institute, Cary, NC).<sup>47</sup> Sample characteristics were described by intervention condition using frequencies and means. Differences between groups at baseline were derived with Fisher's exact test for categorical covariates, given the small sample sizes. For continuous covariates, *t*-tests or Wilcoxon Rank Sums test, depending on normality, was used. Differences in daily average watermelon consumption were tested using *t*-tests.

Outcomes included CRP, HbA1c percent, glucose, BMI, body fat percent, and body weight. Given the small sample size, it was not possible to conduct a confounder selection process. However, all models were adjusted for age. Using general linear models with repeated measurements with a compound symmetry covariance structure, least-square means of the outcomes 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.

The IMAGINE-Watermelon program was designed to lower dietary inflammatory potential as measured by the E-DII. In theory, the intervention arm should have lowered their E-DII score (ie, become more anti-inflammatory) and the control arm should have stayed roughly the same. Adherence to the intervention assignment was examined based on change in the E-DII score. A post hoc analysis was designed to examine whether a change to a more anti-inflammatory dietary pattern led to a change in inflammation regardless of intervention status. Participants were dichotomized at the median based on the change in their E-DII score from baseline to postintervention. Those below the median had reductions in their E-DII scores (ie, became more anti-inflammatory) and those above the median became more proinflammatory. For this *post hoc* linear regression analysis, the independent variable was the change in the E-DII scores analyzed as both continuous and dichotomized at the median. Multiple least-square regression

was then performed to obtain least-square means of the dependent variables by E-DII change adjusted for age. In addition, the change in E-DII score was examined as a continuous measure, where beta coefficients for a 1-unit change in the E-DII score were reported. A 1-unit increase in the change in E-DII score indicates a worsening of the E-DII score.

### Results

A total of 29 individuals were assessed for eligibility. Of these, 2 did not meet inclusion criteria. Of the remaining 27 who self-selected into either the intervention or control arm, 16 in the intervention and 11 in the control, signed the informed consent and agreed to participate. Fifteen of the intervention and 8 of the controls completed baseline clinic assessments. A total of 11 intervention and 7 control participants completed postintervention clinics. Overall, the population was primarily female (83%) and graduate school-level educated (61%). There were similar proportions of White and Black participants (35% and 48%, respectively). The average age was  $48.2 \pm 16.7$  years, and the average BMI was  $33.5 \pm 6.9$  kg/m<sup>2</sup>. Compared to the control group, the intervention group had a higher percentage of Blacks (73% vs 0%,  $P < .01$ ). The intervention group also was older than the control group (55.9 vs 33.8 years, respectively,  $P = .01$ ). Higher systolic blood pressure and lower social desirability also were observed among the intervention group compared to the control group (Table 1).

Within the intervention group, mean daily intake of watermelon increased from  $19 \pm 35$  to  $112 \pm 95$  g from baseline to follow-up. The control group's mean daily intake was  $49 \pm 57$  g at baseline and  $4 \pm 5$  g at follow-up. The intervention group had a significantly greater increase in daily mean watermelon intake compared to the control group (mean difference:  $94$  vs  $-45$  g,  $P < .01$ ).

For the main intent-to-treat analysis, there was no statistically significant intervention-by-time interaction. As can be seen in Table 2, there were no statistically significant differences in study outcomes between intervention and control groups at baseline or postintervention. There also were no statistically significant differences in study outcomes within either study arm across time points after adjustment for age. Additional adjustment for BMI in models with CRP, HbA1c, and glucose as the outcomes did not change the findings (data not tabulated). Upon further review, it was observed that 4 of the 11 (36%) intervention group participants who completed postintervention assessments had an E-DII change of greater than 0.0 indicating no change or transition to a more proinflammatory diet. This indicates a lack of adherence to the IMAGINE-Watermelon protocol, given that the intervention was designed specifically to lower DII scores. At the same time, 4 of the 7 (57%) control participants had E-DII change scores less than 0.0, potentially indicating a change to a more anti-inflammatory diet. The mean change in E-DII scores among the intervention group was  $-1.28 \pm 1.98$ , which indicates a more anti-inflammatory change. However, even the control

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

	ALL (N=23)	INTERVENTION (N=15)	CONTROL (N=8)	P-VALUE
Sex				.59
Male	4 (17%)	2 (13%)	2 (25%)	
Female	19 (83%)	13 (87%)	6 (75%)	
Race				<.01
White	8 (35%)	2 (13%)	6 (75%)	
Black	11 (48%)	11 (73%)	0 (0%)	
Asian	4 (17%)	2 (13%)	2 (25%)	
Education				.84
At least some college	5 (22%)	3 (20%)	2 (25%)	
College graduate	4 (17%)	2 (13%)	2 (25%)	
Graduate degree or equivalent	14 (61%)	10 (67%)	4 (50%)	
Marital Status				.99
Married or living with partner	10 (43%)	7 (47%)	3 (38%)	
Separated/widowed/divorced	5 (22%)	3 (20%)	2 (25%)	
Never married	8 (35%)	5 (33%)	3 (38%)	
Employment				.06
Full time	11 (48%)	5 (33%)	6 (75%)	
Part time	5 (22%)	3 (20%)	2 (25%)	
Not employed	7 (30%)	7 (47%)	0 (0%)	
Smoking status				.37
Never	17 (74%)	10 (67%)	7 (88%)	
Current or former	6 (26%)	5 (33%)	1 (13%)	
Income				.19
<\$40000	10 (45%)	8 (53%)	2 (29%)	
\$40000-\$59000	6 (27%)	5 (33%)	1 (14%)	
\$60000+	6 (27%)	2 (13%)	4 (57%)	
At least 12 alcoholic drinks per year				.06
Yes	17 (74%)	9 (60%)	8 (100%)	
No	6 (26%)	6 (40%)	0 (100%)	
Current NSAID use				.53
Yes	2 (9%)	2 (13%)	0 (0%)	
No	21 (91%)	13 (87%)	8 (100%)	
Current Aspirin use				.12
Yes	5 (22%)	5 (33%)	0 (0%)	
No	18 (78%)	10 (67%)	8 (100%)	

(Continued)

Table 1. (Continued)

	ALL (N=23)	INTERVENTION (N=15)	CONTROL (N=8)	P-VALUE
Age (years)	48.2 ± 16.7	55.9 ± 15.1	33.8 ± 15.1	<.01
BMI (kg/m <sup>2</sup> )	33.5 ± 6.9	34.5 ± 6.8	31.1 ± 7.1	.29
Systolic blood pressure (mm Hg)	126.2 ± 9.8	128.9 ± 10.3	120.3 ± 5.6	.05
Diastolic blood pressure (mm Hg)	78.9 ± 4.0	78.9 ± 3.7	77.0 ± 4.3	.13
Social approval	56.3 ± 5.5	56.5 ± 5.6	56.0 ± 5.7	.85
Social desirability	24.5 ± 2.9	23.5 ± 2.8	26.5 ± 2.2	.01

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 nonnormal; Wilcoxon Rank Sums test was used for this variable.

Abbreviations: PA, physical activity; NSAID, nonsteroidal 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.

group showed a change in the anti-inflammatory direction, with a mean E-DII change of  $-0.38 \pm 1.48$ . This indicates that some of the controls underwent some sort of healthy diet change on their own. For specific changes in dietary intake for parameters included in the E-DII, see Supplemental Table 1.

Table 3 displays results, ignoring intervention assignment. Essentially, all participants were categorized based on their change in the E-DII score using a median split. Those below the median reported a more anti-inflammatory change in their E-DII score, and those above the median had more proinflammatory changes. Those below the median of E-DII change showed a significant reduction in body fat percent compared to those above the median ( $-1.27$  vs  $0.90$ ,  $P < .01$ ) after adjustment for age. Nearly statistically significant reductions in BMI and body weight in the lower E-DII change group, compared to those above the median were observed as well. Results for CRP, HbA1c, and glucose remained unchanged after additional adjustment for BMI (data not tabulated).

## Discussion

This intervention examined the impact of IMAGINE-Watermelon on anthropometrics and inflammatory and metabolic markers. Overall, there were no significant group-by-time interactions for any of the outcomes examined. However, post hoc analyses categorized participants by their change in E-DII score regardless of intervention status (ie, more of an observational design). Those with more anti-inflammatory E-DII changes showed statistically significant improvements in body fat percent and nearly statistically significant improvements in BMI and body weight even given the small sample size. Changes in CRP and HbA1c percent among those with more anti-inflammatory diets also trended in the healthy direction, although the changes were modest at best.

The initial IMAGINE study experienced a similar phenomenon as in this study. In the IMAGINE study, there was no statistically significant group-by-time interactions using

baseline and 3-month postintervention data for a set of similar outcomes as used in this study. However, when using postintervention (ie, 3 month) and 12-month post-follow-up data, there was a nearly significant group-by-time interaction for CRP ( $P = .09$ ). Specifically, CRP decreased by  $-0.65$  mg/L (95% CI =  $[0.10-1.20]$ ,  $P = .02$ ) at 12 months in the intervention group. A 12-month follow-up visit was not possible in IMAGINE-Watermelon given funding limitations. In IMAGINE, a similar approach was conducted that categorized participants by their change in E-DII score. Those with worsening E-DII scores (Tertile 3) compared with those who improved the most (Tertile 1) had higher CRP ( $4.84$  vs  $3.14$  mg/L,  $P = .02$ ), total cholesterol ( $202$  vs  $183$  mg/dL,  $P = .02$ ), and low-density lipoprotein (LDL) cholesterol ( $117$  vs  $98$  mg/dL,  $P = .02$ ). As noted, CRP results for this study using a similar post hoc approach trended in the same direction as the original IMAGINE study results.<sup>22</sup>

The current IMAGINE-Watermelon study and the first IMAGINE intervention described above show that the IMAGINE program can reduce E-DII scores. In fact, a couple of other healthy diet-interventions show reductions in E-DII scores.<sup>48-50</sup> For example, after a 6-month intervention with random assignment to a Mediterranean diet or low-fat diet, the Mediterranean group significantly reduced E-DII scores at 6 months ( $n = 27$ ;  $-0.40 \pm 3.14$  to  $-1.74 \pm 2.81$ ,  $P = .01$ ); whereas, no such change was observed in the low-fat diet group ( $n = 29$ ;  $-0.17 \pm 2.27$  to  $0.05 \pm 1.89$ ,  $P = .65$ ).<sup>49</sup> In another RCT, more anti-inflammatory E-DII changes were observed among vegan and vegetarian diet-assigned participants compared to participants assigned to semivegetarian or omnivorous diets.<sup>48</sup>

Behavior-based RCTs may be susceptible to attrition, poor compliance with dietary prescriptions, and potential contamination in the control group. Prior research indicates that control participants may make dietary changes on their own, which may approximate the effect of the intervention.<sup>26,51</sup> On the

**Table 2.** Mean Age-Adjusted C-reactive Protein, HbA1c Percent, Glucose, and Anthropometric Values by Intervention Assignment and Time Point.

OUTCOME	INTERVENTION		CONTROL		P-VALUE <sup>2</sup>	P-VALUE <sup>3</sup>	
	BASELINE (N=15)	POSTINTERVENTION (N=11)	P-VALUE <sup>1</sup>	BASELINE (N=8)			POSTINTERVENTION (N=7)
C-reactive protein (mg/L)	3.95 (2.09 to 5.82)	3.91 (2.02 to 5.79)	.90	6.09 (3.27 to 8.92)	5.53 (2.70 to 8.36)	.24	.37
HbA1c percent	5.85 (5.42 to 6.29)	5.85 (5.42 to 6.29)	.97	5.61 (4.95 to 6.29)	5.59 (4.93 to 6.26)	.82	.54
Glucose (mg/dL)	103 (92 to 115)	102 (90 to 114)	.77	97 (80 to 114)	101 (84 to 119)	.25	.93
Body mass index (kg/m <sup>2</sup> )	33.3 (29.2 to 37.4)	33.2 (29.1 to 37.3)	.78	33.2 (27.1 to 39.4)	33.4 (27.2 to 39.5)	.77	.97
Body fat percent	39.8 (34.1 to 45.6)	40.3 (34.5 to 46.0)	.44	41.1 (32.4 to 49.9)	40.4 (31.6 to 49.1)	.29	.98
Body weight (kg)	88.5 (78.9 to 98.0)	88.5 (78.9 to 98.0)	.85	93.4 (78.9 to 107.5)	93.4 (78.9 to 107.5)	.93	.59
E-DII	0.07 (-1.29 to 1.43)	-1.24 (-2.67 to 0.18)	.02	-0.90 (-2.96 to 1.15)	-1.29 (-3.34 to 0.77)	.59	.97

Values presented are means and (95% confidence intervals). All models adjusted for age. All P-values estimated using repeated measures analyses with group-by-time interactions. P-value<sup>1</sup> represents differences within study arm between time points. P-value<sup>2</sup> represents differences within baseline across study arms. P-value<sup>3</sup> represents differences within postintervention across study arms. Abbreviations: E-DII, energy-adjusted Dietary Inflammatory Index.

**Table 3.** Mean Adjusted Difference in C-reactive Protein, HbA1c Percent, Glucose, and Anthropometric and Lipid Biomarkers by Change in Energy-Adjusted Dietary Inflammatory Index Scores from Baseline at 3 and 12 months.

OUTCOME	E-DII CHANGE <MEDIAN	E-DII CHANGE ≥MEDIAN	P: MEDIAN CUT	B CONT	P: CONT
C-reactive protein (mg/L)	−0.53 (−1.48 to 0.41)	−0.01 (−0.82 to 0.79)	.39	0.10	.66
HbA1c percent	−0.05 (−0.17 to 0.07)	0.03 (−0.08 to 0.13)	.32	0.02	.34
Glucose (mg/dL)	3.38 (−4.42 to 11.17)	−1.42 (−7.62 to 4.78)	.32	−2.63	.05
Body mass index (kg/m <sup>2</sup> )	−0.66 (−1.51 to 0.19)	0.38 (−0.30 to 1.07)	.06	0.28	.07
Body fat percent	−1.27 (−2.49 to −0.06)	0.90 (0.14 to 1.93)	.01	0.57	.02
Body weight (kg)	−0.99 (−2.33 to 0.34)	0.54 (−0.60 to 1.68)	.08	1.04	.06

All models adjusted for age. E-DII change median 1 indicates more anti-inflammatory changes. E-DII median Tertile 3 indicates a more proinflammatory change. *P*: 1 vs 2 is the *P*-value for the differences in least-square means between medians 1 and 2.  $\beta$  Cont refers to the beta coefficient for the continuous form of the change in the E-DII and indicates the change in the outcomes per 1-unit increase in the change of the E-DII. Increasing values of the change in the E-DII are worse than decreasing values. *P*: Cont is the *P*-value for the beta coefficient.

contrary, the IMAGINE intervention required an extensive time commitment. This may influence adherence to the intervention arm in an RCT design because those assigned to the treatment may not be able to adhere to something that requires extensive time commitment. It is likely that some participants who were willing to be randomized to control would not be fully compliant with the intervention. Therefore, to increase the likelihood of full engagement in the intervention arm, participants were allowed to select the condition in which they wanted to participate. Therefore, this study was designed as a self-selection trial. However, even in a self-selection trial, which arguably allows participants to better comply with their chosen intervention prescriptions, contamination of the control group (ie, because they know that a low DII score is beneficial) and lack of adherence within the intervention group were still observed. The same phenomenon was observed in the first IMAGINE trial. This further highlights the limitations of intervening on health behaviors, specifically dietary-modification trials. The IMAGINE program benefited from both in-person and online components. However, in-person classes only occurred once a week and usage of online content was not tracked rigorously. It is possible that other modalities, such as audio podcasts,<sup>52</sup> social media,<sup>53</sup> email or phone counseling,<sup>54</sup> or mobile web or app<sup>55</sup> are needed to enhance compliance with the intervention prescription without greatly increasing participant burden, especially for younger age groups.

Although IMAGINE and IMAGINE-Watermelon interventions did not show dramatic impacts on inflammation, potentially in large part due to the lack of participant adherence, the interventions still showed reduction in dietary inflammatory potential. It logically follows that it should lower systemic inflammation over sufficient time. As for the unique component of IMAGINE-Watermelon, the watermelon, studies have linked watermelon to anti-inflammatory/antioxidant properties. Watermelon has high levels of several micronutrients including citrulline.<sup>23–25</sup> Cell line and animal studies have shown decreases in tumor necrosis factor- $\alpha$  and IL-1 beta,

which are proinflammatory; whereas, increases in IL-10, which is anti-inflammatory, has been found with administration of this micronutrient.<sup>56,57</sup> Among critically-ill adults, oral citrulline supplementation was found to lower concentrations of proinflammatory cytokines.<sup>58</sup>

The prescribed recommendations of IMAGINE-Watermelon, although not strictly prohibiting meat consumption, were largely vegetarian. Previous studies have shown that vegetarians have lower levels of CRP than meat eaters.<sup>59–61</sup> However, it is likely that 3 months is not sufficient to see biological changes in CRP, especially given that not all participants adopted the intervention and, even among those who did, they may not have fully adopted the intervention from the beginning of the study. A meta-analysis showed that a minimum duration of 2 years of following a vegetarian diet was needed to see lower CRP levels.<sup>62</sup> This is corroborated by the fact that longitudinal studies indicate that adhering to a lower DII diet over a period of years is associated with lower inflammation levels.<sup>63–65</sup>

While dietary interventions that use caloric restriction (CR) can achieve short-term (<6 month) weight loss, sustaining the weight loss is a challenge because many people will regain weight within a few years of dieting.<sup>66,67</sup> This is partially evidenced by the fact that in the United States, prevalence rates for obesity/overweight remain,<sup>68</sup> despite the fact that one half of all Americans report that they are trying to lose weight.<sup>69</sup> It should be noted that in IMAGINE and IMAGINE-Watermelon, CR was not promoted. These interventions focused on improving quality of diet. Yet, in IMAGINE-Watermelon, with a relatively small sample size, improvements in body habitus were still observed. This is not too surprising, given that the caloric density of the diet is strongly related to the DII score.<sup>33</sup>

This study suffered from several limitations. The most important of these was the sample size. This was a pilot study and, therefore, limited funding precluded recruiting more participants. Although we had a diverse sample made up of Whites,



Blacks, and Asians, the distribution across intervention arms was highly skewed. With respect to sex, men made up 17% of the total population. In the first IMAGINE study, the percentage of men was 22%, which is somewhat similar to what has been found among 244 other previous lifestyle intervention studies (27%).<sup>70</sup> Future work should focus on enrolling more men, as men have been shown to have more proinflammatory diets.<sup>17,71,72</sup> IMAGINE-Watermelon was a self-selection trial. This type of design may allow for a more real-world testing of an intervention. However, one major limitation of this approach, given the small sample size, is that it also limited the ability to control for any factors that differ between groups, as well as personal factors that may be motivating a participant to engage with the study. This is especially true for use of nonsteroidal anti-inflammatory drugs and Aspirin.<sup>33</sup> Another limitation was that the control group was not attentionally equivalent to the intervention group. In addition, the control group, although younger, had higher CRP levels than the intervention group, which may be indicative of the differing health status of these 2 groups. Although the focus on the intervention was on diet, PA and stress-reduction practices were discussed and practiced to a minor degree. Additional post hoc analyses indicated that there were no changes in PA or perceived stress throughout the study. Finally, as presented in the section "Introduction," examining the effect of individual nutrients or foods on health outcomes can be highly nuanced. Hence, it was not possible to truly examine the sole impact of watermelon on inflammation.

Strengths of the study included the use of quantifiable biological endpoints. In addition, this study showed the adaptability of the IMAGINE program to focus heavily on a specific food item. This is important because foods are eaten in combination with other foods. Therefore, simply studying the effect of any single food item is highly nuanced. The ability of this program to be modified may open the door for future studies examining personalized-nutritional medicine approaches.

Although this was a pilot study, it provided insights into the use of self-selection trials and the issues related to participant adherence. The science and evidence indicate that the IMAGINE program or, at least, improving one's DII/E-DII over time is associated with improved health outcomes including inflammatory and body habitus markers. However, the compliance and adherence by participants is a major concern. This is true not only of IMAGINE, but is an issue experienced by many researches in behavioral research. Therefore, more research, specifically related to DII-lowering interventions, is needed to better understand participants' motivation and enhance compliance.

### Author Contribution

MDW, in conjunction with NS, led the project overall. MDW oversaw all analyses and was responsible for drafting a majority of the manuscript. NS, in conjunction with MDW, led the project overall and contributed to writing throughout the manuscript.

SK led data collection efforts and wrote sections of the Methods related to data collection. SV supported other study staff in data collection and administration of the intervention, as well as drafted text on recruitment procedures. LB was the lead interventionist and wrote sections of the Methods related to this. JS helped with data collection and led procedures and writing associated with blood collection. JRH served as the senior researcher and reviewed all protocols and writing, as well as contributed to the design of the study.

### Supplemental material

Supplemental material for this article is available online.

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