An AHEI Dietary Intervention to Reduce Pain in Women with Endometriosis Protocol Version 6.0

Version 6.0 Date 07.30.24

Specific Aims

Endometriosis is a disorder characterized by the presence of endometrial-like tissue outside of the uterine cavity. While it affects approximately 10% of reproductive age women in the U.S.,[1] it is understudied. The etiology of this disorder has not been fully delineated, and few modifiable risk factors have been identified. Endometriosis incurs significant health care costs and high morbidity, and can also have significant social and psychological effects that impact quality of life (QOL).[2,3] Over 80% of women with endometriosis report chronic pelvic pain (CPP).[4] Among women with endometriosis who participated in the U.S. National Health Interview Survey, 50% reported an average of 18 days of bed rest in the previous year,[5] estimated to cost the U.S. economy $14.7 million annually due to lost work productivity.[6] Treatment options currently include hormonal suppression and surgery, but pain continues to persist in many women despite these interventions.[7] The primary **objective** of our study is to investigate whether endometriosis symptomatology, specifically pain, poor QOL, and inflammation, can be reduced or alleviated through alterations in diet.

Our research on diet and subsequent laparoscopic diagnosis of endometriosis in the Nurses' Health Study II (NHSII) suggests that some dietary factors are more strongly associated with endometriosis diagnosed because of pain symptoms, compared to endometriosis diagnosed during an infertility work-up.[8-11] Most recently, we observed that adherence to the Alternate Healthy Eating Index (AHEI-2010)[12] was associated with a decreased risk of laparoscopically-diagnosed endometriosis among women experiencing pain symptoms.[9] These results support the **hypothesis** that diet may impact pelvic pain among women with endometriosis. Prostaglandin metabolism, cytokines and inflammation, and smooth muscle contractility are some of the factors that play a role in pain processes, and each of these can be influenced by diet.[13-17]

Although there are multiple lay publications based primarily on anecdotal evidence about the effectiveness of dietary modifications for the treatment of endometriosis,[18-22] there is no evidence from randomized controlled trials (RCTs) and few observational studies to support these claims. The few RCTs to modify endometriosis symptoms have focused on dietary supplements,[23,24] and to our knowledge, no randomized interventions have assessed the effect of adherence to specific dietary guidelines on endometriosis symptoms. The lack of adequately designed RCTs is a **critical barrier** to our ability to provide evidence-based dietary advice for women with endometriosis-associated pain.

The **overall goal** of this study is to evaluate the effects of a 12-week dietary intervention among premenopausal women aged 18-45 years, with laparoscopically-confirmed endometriosis who had a pain score of at least 6 out of 10 on the Visual Analog Scale (VAS) in the three months prior to study entry. Up to 110 participants will be randomized to a 12-week dietary intervention (n=55) or a control group (n=55). The intervention will consist of a diet based on the AHEI-2010 guidelines. The intervention will be delivered by a behaviorally-trained dietitian including one baseline teaching session followed by weekly telephone-based phone support. The intervention group will receive meals, including preparation instructions, shipped directly to their home during the first 4 weeks of the intervention. For the remaining 8 weeks, meal plans and recipes will be provided. Adherence will be assessed using plasma carotenoid concentrations at baseline, 4 and 12 weeks, and analysis of 4-day food records. The control group will maintain their usual diet for the duration of the study. They will be offered the dietary intervention materials and one individual meeting with a study dietitian after completion of the 12-week study. Pain and quality of life will be assessed at baseline, 4, 8, and 12-weeks using validated questionnaires following the guidelines of the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect).[25] Circulating levels of inflammatory markers will be assessed at baseline, 4, 8, and 12-weeks among a subset of participants. In addition, longer-term effects of the intervention will be assessed by examining pain and QOL outcomes at 6 months and 1 year. The **specific aims** are to test the effect of a dietary intervention based on AHEI-2010 guidelines on:

Aim 1. Pain measures among women with endometriosis. Pain will be measured with components of the EPHect participant questionnaire including the VAS pain score, the pain catastrophizing scale, and the mean number of analgesic and/or opiod pills taken per week.
Aim 2. Physical and mental QOL components measured with the Endometriosis Health Profile Questionnaire and Short Form-12 Survey.
Aim 3. Circulating levels of inflammatory markers (interleukin (IL)-6, IL-1β, high sensitivity-C-reactive protein, soluble tumor necrosis factor (TNF) α-receptor 1, and soluble TNF α-receptor 2).

Impact: Many women with endometriosis experience poor QOL due to chronic pelvic pain and other physical and mental sequelae of endometriosis. As symptoms are often not sufficiently abated with hormonal

suppression or surgery, the identification of other evidenced-based, modifiable factors, that improve pain and QOL are critical to improving the lives of the tens of millions of women with endometriosis.

Research Design and Methods

Design overview

The proposed RCT will test the effects of a diet intervention based on the AHEI-2010 guidelines compared to control (no dietary changes) on pain, QOL, and inflammatory markers in premenopausal individuals with laparoscopically-confirmed endometriosis. Up to 110 individuals will be randomized (55 each to intervention and control groups). Participants will be recruited primarily through Kaiser Permanente Washington, with additional patients recruited from Virginia Mason and Swedish Medical Centers, other clinical and research partners, Facebook, mass media, and community partners (numbers described in more detail under recruitment below). Potential participants will undergo several screening activities so that we select people who will be likely to succeed in the intervention, and for whom the outcome measures will be unbiased. The intervention will be 12-weeks long with pain, QOL, and inflammatory markers assessed at baseline, 4, 8, and 12-weeks. Longer-term effects of the intervention will be assessed by examining pain and QOL outcomes at 6 months and 1 year.

Eligibility

People will be eligible if they report laparoscopically-confirmed endometriosis, are premenopausal (at least one period in the past 6 months), aged 18-45, report a VAS pain score of at least 6 out of 10 in the previous 3 months on the screening assessment, and score below 75 on the AHEI-2010. This age range is appropriate given that the symptoms of endometriosis continue throughout the reproductive years.[26] People will be ineligible for enrollment if they are postmenopausal, pregnant, have had a hysterectomy or oophorectomy, have chronic illnesses that are known to affect gastrointestinal absorption of nutrients (celiac disease, Crohn's disease, ulcerative colitis, or cystic fibrosis), or a history of kidney stones, cancer (except basal cell carcinoma), or diabetes. Those with a history of irritable bowel syndrome (IBS) will not be excluded. As there is no diagnostic test for IBS and as laparoscopy is required to definitively diagnosis endometriosis, the overlapping symptoms [27] often make it difficult to disentangle the two conditions. People with endometriosis may be misdiagnosed with IBS,[28,29] especially prior to laparoscopic surgery to diagnosis endometriosis, and studies suggest a significant comorbidity between the two disorders.[29,30] As the focus of our intervention is to alleviate pain among people with endometriosis, we have chosen not to exclude those who have been diagnosed with IBS.

Participants must be able to come to fill out questionnaires in English or Spanish. Seattle metro area participants must be willing to come to in-person visits at the Fred Hutch Prevention Center at at baseline, 4, 8, and 12-weeks. In addition, all participants must be willing to be randomly assigned to intervention or control. This dietary trial will be testing adjuvant dietary treatment in addition to the participants' current clinical standard of care. Participants will hence be allowed to continue medical treatment of their endometriosis throughout the trial per standard of clinical care, with medications such as combination estrogen and progesterone hormonal preparations, oral and injectable progesterone, intrauterine device, gonadotropin releasing hormone agonist, and pain medications as determined by their primary endometriosis-treating physician. However, participants will be required to discontinue all vitamins and nutritional supplements from the time of enrollment through the final 12-week evaluation. Participation will not begin sooner than 6 weeks following surgery for endometriosis.

Recruitment

Kaiser Permanent Washington

Our primary recruitment strategy will be to approach people who are enrolled at Kaiser Permanente Washington, an integrated healthcare system headquartered in Seattle. Potentially eligible KPW members aged 18-45 years will be initially identified using KPWHRI electronic administrative and clinical data. International classification of Disease, 9th and 10th revisions (ICD-9 and ICD-10) diagnosis codes for endometriosis (ICD-9 codes 617.0-617.5, 617.8, 617.9, excluding 617.0 adenomyosis without endometriosis; ICD-10 codes N80.1-80.4, 80.8, N80.9, excluding N80.0) coupled with same-day Common Procedural Terminology (CPT) and ICD procedure codes for laparoscopy/laparotomy will be used to identify women who have undergone surgery likely for diagnosis of endometriosis. Hysterectomy/oophorectomy status will be ascertained using administrative data (CPT codes) and surgical history information from the Clarity reporting database of KPW's EPIC electronic health record, and women with evidence of these surgeries will be

excluded. Based on preliminary data of KPW women residing in Western Washington, we anticipate 534 people will meet these criteria during the proposed study. We will review the medical records of these potentially eligible individuals to confirm diagnosis of endometriosis from the pathology report associated with the laparoscopy/laparotomy surgery, and to confirm exclusion criteria (see Eligibility section). Individuals meeting these criteria after medical record review will be contacted via a mailed recruitment letter with study details and invited to participate in a 15-minute telephone interview. Consenting individuals who complete the telephone screening to confirm eligibility will be provided instructions to enroll in the study at Fred Hutch. We expect to send recruitment letters to ~500 eligible members of KPW, we expect ~400 to be interested.

Social media recruitment

We will work with Fred Hutch Communications to recruit participants through Facebook advertisements. Targeted Facebook and other social media advertisements have been successfully used for clinical trial recruitment[31] including for studies of reproductive health[32-34] and nutritional interventions,[35,36] often at lower cost than traditional recruitment methods.[32,35,37,38] We are confident this recruitment strategy will be even more effective for our younger target population as many endometriosis support organizations operate group pages through Facebook. In addition, this type of targeted advertising can be used to increase study diversity by offering the possibility of targeted ads by zipcode.[31]

Clinical/Research partner recruitment

We will also recruit women from health care providers (e.g., Virginia Mason, Swedish Medical Center affiliated providers) through fliers and brochures placed at clinics. We will also advertise the study to participants of ongoing endometriosis observational studies such as the Boston Center for Endometriosis Women's Health Study: From Adolescence to Adulthood.

Pilot study participants

In addition, we will contact 114 women from our pilot study who provided contact information in order to be invited to participate in future studies. Fred Hutch Communications can also assist with recruitment by arranging timely news stories on local television channels and web-based news outlets. This strategy has been used successfully with previous studies of Dr. McTiernan.

Racial/ethnic diversity

To ensure adequate recruitment of minority individuals we will use the services of the Fred Hutch minority outreach department if we are not meeting our minority recruitment goals (12% Asian, 10% Hispanic, 8% Black) which have been set to reflect the racial and ethnic distribution of the Seattle area population while taking into account that the rate of surgically-confirmed endometriosis diagnosis observed among women of color is approximately ~2/3 that of non-Hispanic white women.[26,39]

Screening

A rigorous multi-level screening process is proposed to insure a highly motivated, adherent group of participants. The steps include:

1) Phone screening questionnaire/interest survey: age, menopausal status, pain measures, medication use, medical history, current work schedule and other time commitments, and plans to remain in the local area for the ensuing 6 months, participation or planned participation in other dietary programs, and willingness to enter a randomized study. This screening will be conducted by KPW for preliminarily eligible KPW members who will then be connected with Fred Hutch for study enrollment. For participants recruited through all other recruitment methods Fred Hutch staff will conduct the initial screening. If individuals are deemed eligible they will be given instructions on a 3-day food diary to be further used as a screening tool to determine if the woman can self-monitor**.**
2) Consent appointment and FFQ completion for screening prior to randomization: sign informed consent form, review 3-day food diary, and FFQ assessments.
3) If randomized to the intervention they will also have an individual meeting with a dietitian following the baseline visit (described below).

Randomization Procedures

People will be randomized into one of the 2 study arms by permuted blocks randomization (N=55 to each arm) with block randomization by oral combination hormone therapy (CHT) use. Dr. Wang will create a

randomization program that will: 1) assess CHT use (yes/no), 2) within CHT group tables will contain a random sequence of 0 (control), 1 (intervention). The following study personnel will be masked to participant study arm: laboratory staff performing assays, study staff reviewing forms and entering data, and the study investigators. Only the statisticians, study manager, and research dietitian will be fully unblinded. After randomization, the intervention subjects will meet with the dietitian. Up to 110 participants will be randomized into the 2 study arms. Analysis of final outcomes will be determined by statisticans and investigators blinded to treatment groups.

Dietary Intervention

Recognizing the difficulty of achieving dietary change, the intervention is designed to maximize success by behavior modification skills combined with training in diet change; frequent contacts to provide support for behavior change; a dietary intervention that provides meals shipped directly to each participant's home for the first 4 weeks, meal plans and restaurant recommendations for ease of adherence, multi-menu options that allow flexibility, and sensitivity to cultural differences; a combination of a structured protocol (in which all participants receive certain common information) and the flexibility to tailor strategies individually to help a specific participant achieve and maintain the study goals. Dr. Harris, in consultation with Drs. McTiernan and Duggan, will provide ongoing oversight, training, and support for nutrition intervention staff.

AHEI-2010 Intervention

Goals

The AHEI-2010 intervention will be based on our modification of the DPP curriculum.[40] The DPP was developed as a set of 16 sessions aimed at reducing weight and increasing exercise. We will modify the sessions as needed to correspond with our intervention goals by focusing on the diet modification components of the DPP (details below). The DPP Program emphasizes the importance of tailoring the intervention for different clinical populations to allow for flexibility within a common protocol. The overall goals for the intervention group will be:

1) achievement of an AHEI-2010 score of 100 (maximum score=110; 90% score adherence) during the weeks when participants are provided two meals and one snack/day;
2) achievement of an AHEI-2010 score of 90 (82% score adherence) when participants are responsible for preparing their own meals based on provided recipes.

Approximately 80% adherence during weeks 5-12 of the intervention is consistent with adherence rates achieved in our previous studies.[41,42] To our knowledge, no previous intervention studies have been based on the AHEI-2010, however, a dietary intervention among participants with type II diabetes reported a statistically significant change in AHEI score from baseline to 22-weeks among participants assigned to a vegan diet (mean increase in score=22.5),[43] providing evidence that targeted dietary interventions can increase AHEI score. An average AHEI-2010 score of 69 was observed in our pilot study, indicating that among our target population (people suffering from painful endometriosis), ample room for AHEI-2010 score improvement exists.

Behavioral modification

The intervention utilizes strategies that have been shown to be most effective for dietary change. These include a multicomponent approach to intervention (including behavioral techniques and diet modification), and ongoing regular contact throughout the follow-up period. The diet intervention will be conducted by dietitians with training in behavior modification. The dietitian will hold one teaching session (either in-person, telephone, or video based [e.g., Microsoft Teams]) at baseline followed by weekly telephone-based or video based sessions/support and two additional teaching sessions at weeks 4 and 8. From the original DPP diet-focused sessions, we will create sessions with information about the AHEI-2010 diet components, diet and behavior strategies such as self-monitoring, goal setting, stimulus control, problem solving, as well as eating out strategies, managing stress, and motivational techniques. For goal setting we will replace the weight loss and fat intake goals from the original DPP with goals focused on AHEI adherence overall as well as adherence to each of the individual AHEI-2010 components. The AHEI-2010 is based on a 11 components with a 0-10 scoring system for each component which allows for ease of self-monitoring. Specific to this intervention, we will not include brussels sprouts, cauliflower, or cabbage in our meal plans more than once per week per food serving (described below) since we observed an increased risk of laparoscopically-diagnosed endometriosis at levels that exceed 1/week with these individual food items in the NHSII.[10]

In consultation with the study dietitian, participants can target individual AHEI-2010 components for daily/weekly goals. Importantly, as this is not a weight loss trial, the goal of intervention will be to focus on

meeting AHEI-2010 components, not on reducing caloric intake. To facilitate this the AHEI meal plan and meal delivery (described below) will be tailored to provide food and portion size recommendations that meet the estimated energy needs of individual participants. This strategy has been used in previous intervention studies.[44,45] Of note, endometriosis is more common in lean women,[46-48] thus in the event that unintended weight loss as a consequence of AHEI-2010 occurrence occurs, it is unlikely to unduly influence the study results. According to the DPP, self-monitoring is considered one of the most effective approaches to change dietary intake and thus will be a critical component of the intervention. Participants will be asked to record their food intake daily to encourage dietary behavior change and promote AHEI-2010 adherence (detailed below). Participants will be given self-monitoring tools including: list of common foods high in AHEI components (e.g., whole grains, long-chain (n-3) fats [EPA+DHA], PUFA) and low in AHEI components (e.g., *trans* fat, sodium), and a pocket-sized food log or recommended food tracking app if preferred.

Procedures to Enhance Intervention Adherence

One of the greatest challenges with dietary interventions is ensuring adherence to the prescribed intervention in order to enable the most accurate assessment of intervention effectiveness. An innovative aspect of this study is that for the first 4 weeks of the intervention we will provide shipped meals for intervention arm study participants. This will occur in two formats: 1) Seattle metro area based intervention participants will receive complete meals and preparation instructions for 2 meals/day, one snack, and one dessert to the participants shipped directly to their home (total of 56 meals received, 28 snacks, and 28 desserts received over 28 days). 2) Non-Seattle metro area based intervention participants will receive frozen meals and snacks/desserts shipped directly to their home along with instructions of for preparation of additional food items (total of 28 full meals and 28 snacks/desserts received over 28 days). This will strongly support adherence and will provide the participants with examples of AHEI-2010 based meals to use as a framework for future meals they will prepare for themselves during weeks 5-12. This meal delivery service will also substantially reduce participant burden in regards to travel time compared to controlled feeding studies which require participants to pick-up meals or consume meals at the study site. This will also allow for a wider geographic recruitment area. Data from our AHEI pilot study demonstrate that the dietary intervention is effective in improving AHEI score and lowering inflammatory biomarkers in the absence of meal shipment (where participants prepare their own meals the entire 12 weeks) thus both our meal shipment options will strongly support greater adherence to the intervention.

Following the 4 weeks of meal delivery, to further facilitate adherence we will provide participants with a 14-day meal plan (3 meals and 2 snacks) that adheres to the AHEI-2010 maximum score criteria. We will also provide suggestions of meals at local and chain restaurants that are most adherent to the AHEI-2010 and will suggest substitutions for popular consumed foods items that will help promote AHEI-2010 adherence. See an example of the meal plan in Table 2. Culturally appropriate dietary options will be incorporated when appropriate by tailoring teaching and study materials. For example, dietitians will provide examples of food substitutions based on cultural dietary options and patient baseline FFQ responses (e.g. substituting mango for samosa as a snack for Asian Indian participants). As necessary, recipes will be adapted for minority partcipants as was done in the DPP's lifestyle change program.

Table 2. AHEI-2010 4-day meal plan

	Day 1	Day 2	Day 3	Day 4
Breakfast	Oatmeal	All bran cereal	Oatmeal	Sprouted Wheat toast
Suggested	Berries	Apple	Berries	Banana
	Greek yogurt	Greek yogurt	Boiled egg	Nut butter
Lunch	Collard Wrap	Turkey Barley soup	Chicken salad sandwich	Tabouli/hummus
Shipped	Veg/hummus/sunflower seeds	Green salad/HNL vinaigrette	Sprouted wheat bread	Veggie sticks
	Soba noodles (buckwheat)	Parmesean cracker	Cucumber salad	Flax crackers
	Orange	Kiwi	Dried mango	Apple
Dinner	Ginger chicken stir-fry	Cod, seasoned poached	Lentil/veggie marinara	Salmon, poached wine sauce
Shipped	Brown rice	Mexi Bowl/Quinoa pilaf	Whole grain pasta	Barley pilaf
	Broc/Peppers/Carrots	Slaw/edamame/Crema sauce	Green salad/HNL vinaigrette	Green beans/red bell peppers
Dessert	Tropical fruit flan	Lemon chia pudding	Millett & PB buckeyes	Blueberry streusel
Snack	Nut butter	Almonds	Walnuts	Edamame
Shipped	Banana	Red grapes	Dried apricots	Green grapes

Adherence Assessment

Four methods will be used to assess and/or encourage adherence in the intervention group. 1) Daily completion of food logs (on-line or paper based on patient preference) will be encouraged to support

Table 1. The AHEI-2010 components, scoring method, and serving sizes[31]

Component	Minimum score criteria	Maximum score criteria	Serving size
Fruits (servings/day)	0	≥4	1 medium piece of fruit or 0.5 cup
Vegetables[1] (servings/day)	0	≥5	0.5 cup vegetables or 1 cup of leafy greens
Whole grains (grams/day)	0	75	0.5 cup of 100% whole grain product (≈15-20 g)
Sugar-sweetened beverages or fruit juice (servings/day)	≥1	0	8 oz
Nuts, legumes, and other vegetable protein[2] (servings/day)	0	≥1	1 oz or 1 tablespoon (15mL) of nut butter
Red/processed meat (servings/day)	≥1.5	0	4 oz of unprocessed meat or 1.5 oz of processed meat
Trans fat (% of energy)	≥4	≤1.5	
Long-chain (n-3) fats (EPA+DHA) (mg/day)	0	250	2 ≈4 oz servings of fish/week
PUFA[3] (% of energy)	≤2	≥10	
Sodium[4] (mg/day)	Highest decile	Lowest decile	
Alcohol (drinks/day)[5]	≥2.5	0.5-1.5	4 oz of wine, 12 oz of beer, or 1.5 oz of liquor
Total points	0	110	

[1]Does not include potatoes. [2]Includes tofu. [3]Does not include EPA or DHA intake. [4]Lowest decile ≤1112 mg/day and highest decile ≥3337 mg/day. [5]Non-drinkers receive a score of 2.5

participant adherence.[49] Study dietitians will review participants' food logs on a weekly basis. Ongoing individual contacts by phone and email will be an important mode of counseling in between individual sessions and will be adjusted as needed based on adherence. The dietitian will call or email all participants between the regular sessions with the following objectives: evaluation of success in meeting goals; problem solving of barriers to adherence; the development of specific plans for coping with problems; and the provision of reinforcement and social support. Importantly, we believe that women with endometriosis suffering from chronic pelvic pain are a highly-motivated group for a dietary intervention, and the high-motivation of this group will be a strong asset in regards to participant adherence. The number of daily food logs completed will be expressed as a percentage of expected completions (total number of days of the intervention). This approach has been used successfully in our other studies.[41] 2) To more rigorously assess adherence by calculating the AHEI-2010 score, intervention participants will complete 3-day food records at 3-time points (weeks 3, 7, and 11) during the 12-week study. Three time-points were chosen to balance accurate assessment of dietary intake with the documentation burden on participants.[50] These records will be analyzed with the Nutrition Data System for Research Software. Measures of adherence to the AHEI-2010 will include mean, intervention-group AHEI-2010 score which will be compared to our study goals of the intervention arm (described above under *Goals*). 3) In both groups (intervention and control), plasma carotenoids will be measured at weeks 0, 4, and 12 as an objective measure of intervention adherence.[51] 4) FFQs will also be administered to both groups at baseline, 4, 8, and 12-weeks, 6 months, and 1 year in order to assess change in adherence during the intervention period and at 6 months and 1 year as participants will not be asked to complete food records at the later two timepoints (post-intervention follow-up described below). The 120-item FFQ was developed for the WHI and has been validated against 4-day food records and 24-hour dietary recalls.[52] To calculate the AHEI-2010 score, each of the individual food items will be summed into 11 components, described in Table 1 below.

Controls

During the 12-week study period the controls will not receive any intervention and will be asked to consume their usual diet as is considered appropriate for a trial of this type.[53] After the study period is complete, including visits at baseline, 4, 8, and 12-weeks, the controls will be provided with study materials including the meal plan and suggestions of AHEI-2010 adherent meals at restaurants. In addition, we will offer them one individual meeting with a study dietitian and $100 after completing the study. Since no current dietary treatment standard exists for endometriosis having a 'no active intervention' control group is an appropriate and valid choice.[54]

Baseline and Follow-up Assessments

Outcomes will be measured at screening, baseline, 4, 8, and 12-weeks. In addition, longer-term effects of the intervention will be assessed by examining pain and QOL outcomes at 6 months and 1 year. All of the data will be collected following the guidelines of the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect). Importantly, the EPHect questionnaire development focused on selecting questions and rating scales that were validated in the literature and are recommended for use in women with endometriosis. In addition, EPHect researchers piloted these questions among endometriosis patients before finalizing the questionnaire.[25,39]

Pain (Aim 1)
Pain will be measured with components of the EPHect questionnaire using the Visual Analogue Scale (VAS) pain score, the pain catastrophizing scale, and mean number of analgesic and opiod pills taken per week at baseline, 4, 8, and 12-weeks. The baseline questionnaire will ask about pain in the three months prior to baseline while all other questionnaires will refer to the preceding period (e.g., 4-week questionnaire will ask about pain between baseline and week 4). At baseline and weeks 4, 8, and 12 the questionnaires will be completed at a clinic visit. The 6 month and 1 year assessments will be completed on-line. The VAS pain score is a validated scale that measures pain on a scale of 0-10 with 10 being the greatest amount of pain.[55] As women with endometriosis experience a variety of pain symptoms, including pain during their period (dysmenorrhea), noncyclical pelvic pain, and pain during vaginal intercourse/penetration (dyspareunia), we will assess a participant's VAS pain score for both dysmenorrhea, pelvic pain not related to a participant's period, and dyspareunia. Questions related to dysuria (painful urination) and dyschezia (painful defecation) are embedded in the questions for each of the pain types mentioned above. Pain catastrophizing, defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience"[56] will be assessed with the Pain Catastrophizing Scale, a validated measure of pain sensitivity.[57] It will be evaluated on a scale of 0-52, with higher scores indicating a greater amount of catastrophizing (e.g., "I think that the pain will never improve"). As suggested by the EPHect guidelines we will place the pain catastrophizing questions before other pain related questions.[25] Frequency of pain medication usage in the preceding period will be assessed including type of medication, days/week, tablets/week, and what type of pain this medication was used for (pelvic pain, other pain, or both).

Quality of Life (Aim 2)
Physical and mental QOL will be measured in participants at baseline and follow-up using the Endometriosis Health Profile (EHP-30) and Short Form Survey (SF-12). The EHP-30 is a reliable and valid instrument that has been designed specifically for use in women with endometriosis.[58-60] It contains 30 items that we will use to address five domains (emotional well-being, control and powerlessness, social support, self image, and pain). Scores for the EHP-30 range from 0 to 100 with lower scores reflecting fewer symptoms and indicating better health status. The EHP-30 has been demonstrated to be sensitive to changes in health status and is suitable for detecting clinical changes in patients' health status over time.[60] The SF-12 is a validated survey that measures an individual's perception of their general health status during the past four weeks using eight dimensions (physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy and vitality, pain, and general perception of health).[61,62] Two global scores are calculated, a physicial component summary (PCS) and a mental health component summary (MCS). The scores have a range of 0 to 100 with higher scores representing better health. While not created specifically for women with endometriosis the SF-12 is considered appropriate for use in these women according to the WERF EPHect guidelines.[25]

Inflammatory markers (Aim 3)
Among Seattle metro area based participants blood (50 ml) will be collected, labeled with study ID and date. Serum will be centrifuged after clot formation, and aliquoted into 1.8-ml aliquots and stored at -80 degrees C until time for analysis. Samples will be collected at baseline, 4, 8, and 12-weeks and all samples from the same participant will be assayed simultaneously to reduce inter-assay variation. Frozen serum aliquots will be shipped in sealed containers in dry ice to Boston Children's Hospital in the CERLab, Department of Laboratory Medicine, that is certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program (see LOS). An equal number of intervention and control participants' serum will be assayed at one time and all assays will be conducted without knowledge of intervention status. Each batch will include 10% blinded replicate samples for quality control. We will use a tracking system for all blood specimens based on ones developed for our previous studies. We will measure the following inflammatory cytokines: IL-6, IL-1β, CRP, sTNFR-1, and sTNFR-2. The sTNF receptors will be measured instead of TNF-α as they are produced by the proteolytic cleavage of TNF cell surface receptors following induction by TNF or other cytokines. They have a longer half-life than TNF and are detected with a higher sensitivity. Levels of IL-6, IL-1β, sTNFR-1, and sTNFR-2 will be measured by immunoassay (R&D Systems, Minneapolis, MN). hsCRP levels will be measured using a high-sensitivity latex-enhanced immunonephelometric assay on a BNII analyzer (Dade Behring, Newark, DL). In repeated testing across several of our studies, this laboratory has been found to have consistently high precision in all of their assays

(all interassay coefficients of variation (CVs) <15%, <10% for IL-6, TNF-αR1, and TNF-αR2, and <5% for CRP), and this laboratory has previously carried out the assays specific to this proposal with great success. Although most inflammatory markers do not vary largely by menstrual cycle phase[63] we will collect information on cycle day at blood collection, and conduct a sensitivity analyses stratifying by cycle phase.

Carotenoids
Blood collection procedures are described above. Plasma carotenoids will be measured in samples collected at weeks 0, 4, and 12 by the Harvard T. H. Chan School of Public Health Nutritional Biomarker Laboratory. Concentrations of alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein+zeaxanthin, retinol, alpha- and gamma-tocopherol will be measured as described by El-Sohemy et al[64] using high-performance liquid chromatography. Because lutein and zeaxanthin co-elute on the chromatogram, the two are grouped and provided as lutein+zeaxanthin. The between-run CVs for alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein+zeaxanthin, and the tocopherols are generally ~5% in plasma.

Covariates
Participants will complete a questionnaire including epidemiologic variables and clinical information that is consistent with WERF EPHect recommendations.[25]

Post-intervention Follow-up
Participants will complete on-line follow-up questionnaires 6 and 12 months after randomization where the following will be assessed: pain measures (VAS pain score, pain catastrophizing scale, mean number of pain pills taken per week), QOL (EHP-30 and SF-12), and FFQ (to assess AHEI-2010 adherence). They will also complete a follow-up questionnaire that will update information on medical history, medication use, psychosocial variables, and other covariates. The purpose of the post-intervention follow-up is not to compare intervention and control groups but to assess: 1) if intervention participants chose to continue adhering to the AHEI-2010 after the 12-week intervention period is over; 2) assess how pain and QOL are affected by AHEI-2010 adherence in a less supportive, non-intervention setting; 3) assess if the control group, who was provided with study materials and one individual meeting with a study dietitian, was able to improve their AHEI-2010 score in the absence of the intensive intervention and if changes in AHEI-2010 adherence influenced pain and QOL measures at 6-months and 1 year.

Protection of Human Subjects
Risks to Human Subjects
Sources of Material

Study participants will donate blood, stool (optional), and saliva (optional) specimens for biomarker measurement. Participants will also report pain measurements, assess with components of the EPHect participant questionnaire including the VAS pain score, the pain catastrophizing scale, and mean number of analgesic and/or opiod pills taken per week. Physical and mental QOL components measured with the Endometriosis Health Profile Questionnaire and Short Form-12 Survey. They will also complete a self-administered questionnaire including epidemiologic variables and non-surgical clinical information that is consistent with WERF EPHect recommendations. This includes information on endometriosis history including treatment(s), other medical and reproductive history, and psychosocial variables. In an optional sub-study participants will complete the Perceived Stress Scale.

All enrolled participants are assigned a unique study ID. This number will be used on study paperwork rather than personal identifiers. Access to personal identifying information is determined by the principal investigator (and KPWHI site PI for KPW participants) and is limited to research staff responsible for direct patient contact, the study manager, and interviewer. Electronic data is maintained in a password-protected computer database. Hard copy records are stored in locked file cabinets. Blood and tissue specimens are collected and stored at -70 degrees C until time for analysis (in FHCRC CERC freezers). All human material referenced above is used expressly for research purposes. The following people and government agencies may get access to subject identities: (1) Authorized study research staff (2) NIH, and (3) Institutional Review Boards at FHCRC and KPWHRI.

Potential Risks

The potential risks of participation on this protocol involve the process of obtaining blood samples. Participants may experience some discomfort during the blood draw and may also develop a bruise or swelling

at the site of the needle puncture. There may also be an increased risk of light-headedness or fainting as a result of the draw. To minimize risk, a maximum of 50 ml of blood for research purposes will be obtained by a person experienced and certified in phlebotomy (i.e. study research nurse or specimen collection specialist) at each study visit (baseline, 4, 8, and 12-weeks). Individuals with medical conditions that contraindicate phlebotomy will not be included in this study. Risks will be described in detail in the study Consent Form and will be reviewed with the woman by a trained study staff member during the baseline visit prior to giving informed consent. Tubes of blood will be marked with a code identifying the blood by a study ID. There is a small risk to participants' confidentiality. We will take measures described below to avoid this.

Although the AHEI-2010 diet is a healthy diet which is likely to have a positive impact on the participant, unknown food intolerances/allergies are also a potential risks. Participants will be asked to report any potential adverse reactions to particular foods and study nutrionistis will make adjustment to meals/snacks as needed. Participants may feel slightly uncomfortable answering some of the questions about their endometriosis symptoms and treatment or collecting stool or saliva samples (optional).

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Up to 110 people will be recruited and randomized to a 12-week dietary intervention (n=55) or a wait-list control group (n=55), eligibility criteria include premenopausal individuals aged 18-45 years, with laparoscopically-confirmed endometriosis who had a pain score of at least 6 out of 10 on the Visual Analog Scale (VAS) in the three months prior to baseline. We will recuit individuals through a variety of mechanisms. Our primary recruitment strategy will be to approach individuals who are members of Kaiser Permanente Washington. People with laparoscopically-confirmed endometriosis who are potentially eligible first will be identified through the KPWHRI database using ICD and procedure codes followed by chart review to confirm eligibility and exclusion criteria. KPW members meeting eligibility criteria after medical record review will be contacted via a mailed recruitment letter with study details and invited to participate in a 15-minute telephone interview. Consenting individuals who complete the telephone screening to confirm eligibility will be provided instructions to enroll in the study at FHCRC. Secondary recruitment strategies include: 1) potentially eligible individuals from health clinics (e.g., Swedish Medical Center, Virginia Mason) and endometriosis observation studies (e.g., Boston Center for Endometriosis Women's Health Study: From Adolescence to Adulthood). 2) FHCC Communications & Marketing Department will recruit participants through Facebook advertisements. People will be directed to our study website where they will complete a screening questionnaire and, if initially eligible, will be given the option to provide their contact information in order to have our study coordinator conduct a more detailed phone screening interview. The FHCC minority outreach department will also help identify community partners if we are not meeting our recruitment goals.

The study coordinator will conduct the consent at the baseline clinic visit or virtually depending on the current COVID-19 situation and participant location and preference as follows:

In-person consenting procedures

- Provide an overall description of the study
- Review the consent with the patient
- Answer patient questions
- Obtain the patient's signature on the consent form

Remote consenting procedures via phone or via video conference call

The following remote consenting procedures will be offered to participants during the COVID-19 pandemic to reduce in-person time at the Prevention Center as well as to non-local participants. The participant will be notified via email (see separate email script) that we are conducting consenting remotely to reduce time at the Prevention Center. Once the potential participant has confirmed they can receive the consent via email, the study staff will schedule the video/phone consent session. On the scheduled day of the session, the consent form will be emailed to the participants.

- At the beginning of the video/phone conference, the study staffer will verify the identity of the participant by visually checking a driver's license or photo id on video conference or asking for the participant's date of birth via phone.
- After verification, the staffer will prompt the participant to follow along as we review the consent form.

- If the participant has any questions, the staffer will thoroughly answer the question before the consent is signed.
- If the individual agrees to be a part of the study, she will sign the consent form and mail, fax, or scan the signed page(s) of the document to the study staff.
- After the study staff receives the consent form, they will sign the consent document.
- The staffer will then document that the consent was done via video or phone. The consent document will then be placed in the appropriate study file.

If the participant choses to sign the informed consent for the main study they will be asked to donate a blood sample (for local participants only) and complete the baseline study questionnaires virtually or at their first study visit. The study coordinator will review the questionnaire results to confirm response completeness. Following completion of study questionnaires participants will be randomized. Those assigned to randomization group will then have their first individual meeting with a study nutritionist.

Protections Against Risk

Anxiety or Emotional Distress- The study activities will not put study participants at any significant level of risk for distress. Staff who will have direct contact with study participants will be given extensive training to prepare them to assist women with any concerns they may express. Participants may feel slightly uncomfortable answering some of the questions about their endometriosis symptoms and treatment but this is likely to be minimal.

Blood Draw- To minimize this risk, a maximum of 50 ml of blood for research purposes will be obtained by a person experienced and certified in phlebotomy under the supervision of the Prevention Center medical staff. Individuals with medical conditions that contraindicate phlebotomy will not be included in this study. Attention will be taken to apply pressure following the procedure to reduce bleeding. There is little risk of anemia in these subjects due to the volume of blood drawn (50 ml).

Diet- The diet program will be a diet based on the AHEI-2010, which is a healthy diet. Its key features include an emphasis on intake of fruits, vegetables, whole grains, nuts/legumes, long-chain (n-3) fatty acids, and polyunsaturated fats, and avoidance of red/processed meat, sugar-sweetened beverages/fruit drinks, and *trans* fats (see Table 1). The goal of the intervention will be to focus on meeting AHEI-2010 components, not on reducing caloric intake, so it is not a weight loss trial. Dietary intake will be carefully monitored by study nutritionists so little risk from this dietary program is anticipated.

Confidentiality- Names and other personal identifying information about subjects are obtained only for subject contact. Personal identifiers will not appear in any computer files used for data analysis. Only study numbers will be recorded on each subject's completed questionnaire and blood samples. Data presented in reports will be in the form of statistical summaries, and characteristics of individual participants will not be delineated. Only persons directly involved in the study will have access to data identifying individual subjects. All study staff with access to identifying information have signed confidentiality oaths and participate in on-going human subjects training. Records and forms will be kept in locked file cabinets when not in use. Access to information stored in computers will require simultaneous knowledge of data format, file name, and password. All patient identifying information (name, address, phone numbers, etc.) is maintained separately from the interview data. The only link to such identifying information will be the unique study number assigned to each subject, and only the study coordinators have access to this link. We do not share any participant data with other researchers without IRB approval.

Adverse Events- Adverse events are not expected. Serious adverse events (death or injury) that could be related to study participation or to the intervention will be reported to the IRB using an Adverse Events form. The occurrence of serious adverse events more than expected may prompt changes in study protocol. Any such change will be approved by the IRB.

Potential Benefits of the Proposed Research to Human Subjects and Others

To be eligible for the study participants must be people with endometriosis who had a pain score of at least 6 out of 10 on the Visual Analog Scale (VAS) in the three months prior to baseline as assessed on the screening

questionnaire. Participants in the study may may benefit directly from the study if the AHEI-2010 diet reduces pain or improves QOL in the participants. This benefit has the potential to apply to both intervention and control group since the control group will receive the AHEI intervention meal plan information and one individual meeting with a study nutritionist after the initial 12-week study period. However, all participants may not directly benefit from the study but their participation may aid in helping researchers gain knowledge in regards to how diet may influence endometriosis pain, QOL, and inflammatory markers. In our experience, the majority of study participants are happy that they were able to participate in studies such as this, feeling that they have made a contribution to our knowledge of endometriosis. In addition, society as a whole will benefit from any insight gained.

Importance of Knowledge to be Gained

To date, no randomized controlled trials of dietary interventions for endometriosis symptoms have been conducted. As endometriosis symptoms are often not sufficiently abated with hormonal suppression or surgery, the identification of modifiable dietary factors that are evidenced-based that improve pain and QOL are critical to improving the lives of people with endometriosis. Risk/benefit ratio. The risks associated with this study are minimal. All participants will be carefully screened, so that only people without contraindications to a dietary intervention will be enrolled. The risk of minor complications from the blood draw and slight discomfort from completing questionnaires on pain and QOL symptoms are described above. The information obtained from these measures will give unique information about the influence of the AHEI diet on endometriosis symtoms that could have important future impacts on addressing endometriosis related pain.

References

1. Missmer SA, Cramer DW: The epidemiology of endometriosis. Obstet Gynecol Clin North Am 30:1-19, 2003
2. Simoens S, Hummelshoj L, D'Hooghe T: Endometriosis: cost estimates and methodological perspective. Hum Reprod Update 13:395-404, 2007
3. Nnoaham KE, Hummelshoj L, Webster P, et al: Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 96:366-373.e8, 2011
4. Mounsey AL, Wilgus A, Slawson DC: Diagnosis and management of endometriosis. Am Fam Physician 74:594-600, 2006
5. Kjerulff KH, Erickson BA, Langenberg PW: Chronic gynecological conditions reported by US women: findings from the National Health Interview Survey, 1984 to 1992. Am J Public Health 86:195-9, 1996
6. Winkel CA: Modeling of medical and surgical treatment costs of chronic pelvic pain: new paradigms for making clinical decisions. Am J Manag Care 5:S276-90, 1999
7. Giudice LC, Kao LC: Endometriosis. Lancet 364:1789-99, 2004
8. Harris HR, Chavarro JE, Malspeis S, et al: Dairy-Food, Calcium, Magnesium, and Vitamin D Intake and Endometriosis: A Prospective Cohort Study. Am J Epidemiol 177:420-430, 2013
9. Dougan M, Harris H, Farland L, et al: Dietary patterns and incidence of endometriosis, 13th World Congress on Endometriosis. Vancouver, British Columbia, Canada, 2017
10. Harris HR, Eke AC, Chavarro JE, et al: Fruit and vegetable consumption and risk of endometriosis. Hum Reprod, 2018
11. Yamamoto A, Harris H, Vitonis A, et al: A prospective cohort study of meat and fish consumption and endometriosis risk. Under review, 2018
12. Chiuve SE, Fung TT, Rimm EB, et al: Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 142:1009-18, 2012
13. Missmer SA, Chavarro JE, Malspeis S, et al: A prospective study of dietary fat consumption and endometriosis risk. Hum Reprod 25:1528-35, 2010
14. Baer DJ, Judd JT, Clevidence BA, et al: Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr 79:969-73, 2004

15. Bartram HP, Gostner A, Scheppach W, et al: Effects of fish oil on rectal cell proliferation, mucosal fatty acids, and prostaglandin E2 release in healthy subjects. Gastroenterology 105:1317-22, 1993

16. Deutch B: Menstrual pain in Danish women correlated with low n-3 polyunsaturated fatty acid intake. Eur J Clin Nutr 49:508-16, 1995

17. Harel Z, Biro FM, Kottenhahn RK, et al: Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. Am J Obstet Gynecol 174:1335-8, 1996

18. Case HS: The vitamin cure for women's health problems. Laguna Beach, CA, Basic Health Publications, Inc., 2012

19. Goldfarb S, Waddell RW: Relieving pain naturally. Garden City Park, N.Y., Square One Publishers, 2005

20. Mears J: Endometriosis : a natural approach. Berkeley, CA, Ulysses Press, 1998

21. Shepperson Mills D, Vernon M: Endometriosis: A Key to Healing and Fertilty through Nutrition. London, Thorsons, 2002

22. Ballweg ML: Endometriosis: The complete reference for taking charge of your health. New York, McGraw-Hill, 2004

23. Nodler J, Divasta A, Karevicius S, et al: The SAGE Trial: Supplementation in adolescent girls with endometriosis. TBD, 2018

24. Santanam N, Kavtaradze N, Murphy A, et al: Antioxidant supplementation reduces endometriosis-related pelvic pain in humans. Transl Res 161:189-95, 2013

25. Vitonis AF, Vincent K, Rahmioglu N, et al: World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research. Fertil Steril 102:1223-32, 2014

26. Missmer SA, Hankinson SE, Spiegelman D, et al: Incidence of Laparoscopically Confirmed Endometriosis by Demographic, Anthropometric, and Lifestyle Factors. Am J Epidemiol 160:784-796, 2004

27. Ek M, Roth B, Ekstrom P, et al: Gastrointestinal symptoms among endometriosis patients--A case-cohort study. BMC Womens Health 15:59, 2015

28. Soumekh A, Nagler J: Gastrointestinal endometriosis causing subacute intestinal obstruction with gradual development of weight loss and misdiagnosed as irritable bowel syndrome. Case Rep Gastroenterol 8:51-5, 2014

29. Seaman HE, Ballard KD, Wright JT, et al: Endometriosis and its coexistence with irritable bowel syndrome and pelvic inflammatory disease: findings from a national case-control study--Part 2. Bjog 115:1392-6, 2008

30. Issa B, Onon TS, Agrawal A, et al: Visceral hypersensitivity in endometriosis: a new target for treatment? Gut 61:367-72, 2012

31. Carter-Harris L: Facebook targeted advertisement for research recruitment: A primer for nurse researchers. Appl Nurs Res 32:144-147, 2016

32. Adam LM, Manca DP, Bell RC: Can Facebook Be Used for Research? Experiences Using Facebook to Recruit Pregnant Women for a Randomized Controlled Trial. J Med Internet Res 18:e250, 2016

33. Motoki Y, Miyagi E, Taguri M, et al: Comparison of Different Recruitment Methods for Sexual and Reproductive Health Research: Social Media-Based Versus Conventional Methods. J Med Internet Res 19:e73, 2017

34. Subasinghe AK, Nguyen M, Wark JD, et al: Targeted Facebook Advertising is a Novel and Effective Method of Recruiting Participants into a Human Papillomavirus Vaccine Effectiveness Study. JMIR Res Protoc 5:e154, 2016

35. Volkova E, Michie J, Corrigan C, et al: Effectiveness of recruitment to a smartphone-delivered nutrition intervention in New Zealand: analysis of a randomised controlled trial. BMJ Open 7:e016198, 2017

36. Leonard A, Hutchesson M, Patterson A, et al: Recruitment and retention of young women into nutrition research studies: practical considerations. Trials 15:23, 2014

37. Arcia A: Facebook Advertisements for Inexpensive Participant Recruitment Among Women in Early Pregnancy. Health Educ Behav 41:237-41, 2014

38. Carter-Harris L, Bartlett Ellis R, Warrick A, et al: Beyond Traditional Newspaper Advertisement: Leveraging Facebook-Targeted Advertisement to Recruit Long-Term Smokers for Research. J Med Internet Res 18:e117, 2016

39. Fuldeore MJ, Soliman AM: Prevalence and Symptomatic Burden of Diagnosed Endometriosis in the United States: National Estimates from a Cross-Sectional Survey of 59,411 Women. Gynecol Obstet Invest 82:453-461, 2017

40. Knowler WC, Barrett-Connor E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393-403, 2002

41. Abbenhardt C, McTiernan A, Alfano CM, et al: Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. J Intern Med 274:163-75, 2013

42. McTiernan A, Ulrich C, Kumai C, et al: Anthropometric and hormone effects of an eight-week exercise-diet intervention in breast cancer patients: results of a pilot study. Cancer Epidemiol Biomarkers Prev 7:477-81, 1998

43. Turner-McGrievy GM, Barnard ND, Cohen J, et al: Changes in nutrient intake and dietary quality among participants with type 2 diabetes following a low-fat vegan diet or a conventional diabetes diet for 22 weeks. J Am Diet Assoc 108:1636-45, 2008

44. Chang L: The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. Gastroenterology 140:761-5, 2011

45. Kruse HP, Kleessen B, Blaut M: Effects of inulin on faecal bifidobacteria in human subjects. Br J Nutr 82:375-82, 1999

46. Lafay Pillet MC, Schneider A, Borghese B, et al: Deep infiltrating endometriosis is associated with markedly lower body mass index: a 476 case-control study. Hum Reprod 27:265-72, 2012

47. Shah DK, Correia KF, Vitonis AF, et al: Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. Hum Reprod 28:1783-92, 2013

48. Shahbazi S, Shahrabi-Farahani M: Evaluation of the correlation between body mass index and endometriosis among Iranian fertile women. Gynecol Endocrinol 32:157-60, 2016

49. Rebro SM, Patterson RE, Kristal AR, et al: The effect of keeping food records on eating patterns. J Am Diet Assoc 98:1163-5, 1998

50. Willett W: Nutritional Epidemiology (ed 3). Oxford, Oxford University Press, 2013

51. Baldrick FR, Woodside JV, Elborn JS, et al: Biomarkers of fruit and vegetable intake in human intervention studies: a systematic review. Crit Rev Food Sci Nutr 51:795-815, 2011

52. Patterson RE, Kristal AR, Tinker LF, et al: Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 9:178-87, 1999

53. Lewis JD, Albenberg L, Lee D, et al: The Importance and Challenges of Dietary Intervention Trials for Inflammatory Bowel Disease. Inflamm Bowel Dis 23:181-191, 2017

54. Friedman L, Furberg C, DeMets D: Fundamentals of Clinical Trials (ed 3rd). New York, NY, Springer-Verlag, 1998 pp. 2

55. Gallagher EJ, Liebman M, Bijur PE: Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 38:633-8, 2001

56. Sullivan MJ, Thorn B, Haythornthwaite JA, et al: Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 17:52-64, 2001

57. Sullivan M, Bishop S, Pivik J: The Pain Catastrophizing Scale: development and validation. Psychol Assess 7:524–532, 1995

58. Jones G, Kennedy S, Barnard A, et al: Development of an endometriosis quality-of-life instrument: The Endometriosis Health Profile-30. Obstet Gynecol 98:258-64, 2001

59. Jenkinson C, Kennedy S, Jones G: Evaluation of the American version of the 30-item Endometriosis Health Profile (EHP-30). Qual Life Res 17:1147-52, 2008

60. Jones G, Jenkinson C, Kennedy S: Evaluating the responsiveness of the Endometriosis Health Profile Questionnaire: the EHP-30. Qual Life Res 13:705-13, 2004

61. Ware J, Jr., Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34:220-33, 1996

62. Fourquet J, Baez L, Figueroa M, et al: Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. Fertil Steril 96:107-12, 2011

63. Jilma B, Dirnberger E, Loscher I, et al: Menstrual cycle-associated changes in blood levels of interleukin-6, alpha1 acid glycoprotein, and C-reactive protein. J Lab Clin Med 130:69-75, 1997

64. El-Sohemy A, Baylin A, Kabagambe E, et al: Individual carotenoid concentrations in adipose tissue and plasma as biomarkers of dietary intake. Am J Clin Nutr 76:172-9, 2002