Investigation of Medical Management to Prevent Episodes of Diverticulitis (IMPEDE) Trial Protocol

Developed by

David R. Flum, MD MPH and Lisa Strate, MD MPH

Study Funder:

National Institute of Diabetes and Digestive and Kidney Diseases

Version Number and Date:

Version 5: August 7, 2023

Table of Contents

1.0 Key Personnel

Principal Investigators	David R. Flum, MD MPH University of Washington Department of Surgery 1959 NE Pacific Street, Box 356410 Seattle, WA 98195 Phone: 206-616-5440 Email: daveflum@uw.edu Lisa Strate University of Washington Department of Medicine Phone: 206-744-7058 Email: lstrate@uw.edu
Director, Data Coordinating Center	Bryan Comstock, MS University of Washington Department of Biostatistics 4333 Brooklyn Avenue NE, Box 359461 Seattle, WA 98105 Phone: 206-543-1882 Email: bac4@uw.edu
Key Personnel	Adam Drewnowski, MA PhD UW School of Public Health Box 353410 Nutritional Sciences Raitt Hall 305B Seattle, WA 98195 Phone: 206-543-8016 Email: adamdrew@uw.edu Joshua Liao University of Washington Department of Medicine 1959 NE Pacific Street Seattle, WA 98195 Email: joshliao@uw.edu

2.0 Background and Rationale

Diverticulitis is one of the most common gastrointestinal indications for inpatient hospital admission, outpatient clinic and emergency room visits, and colon surgery.[1, 2] At least 20% of individuals with an initial episode of diverticulitis will have one or more painful and unpredictable recurrences.[3] The risk of recurrence increases with each subsequent episode.[3] Unfortunately, there is no proven pharmacologic means to decrease the risk of diverticulitis.[4] Currently, secondary prevention relies on segmental colectomy, which is associated with a ~10% risk of major complications and does not eliminate the possibility of future attacks.[5-8] In the face of the enormous burden of recurrent diverticulitis, secondary prevention is a high priority.

Diet and lifestyle factors are modifiable targets for prevention of diverticulitis. Multiple large, prospective cohort studies, including work from our group, have identified low dietary fiber, high red-meat intake, and a Western dietary pattern as risk factors for incident diverticulitis.[9-13] Physical inactivity, obesity, smoking, and nonsteroidal anti-inflammatory drug use also increase risk.[14-19] An observational study of 51,000 men examining the joint contribution of multiple modifiable risk factors found a linear relationship between number of low-risk factors and diverticulitis incidence. Adherence to a low-risk profile (<51g/day red meat, >23g/day fiber, 2 hours exercise/week, normal BMI and never smoked) decreased the risk of incident diverticulitis by nearly 75% (RR 0.27, 95% CI 0.15-0.48).[20] However, these modifiable risk factors have not been evaluated for secondary prevention. Based on the indirect nature of the evidence, U.S. guidelines conditionally recommend diet and lifestyle changes in individuals with a history of diverticulitis. As part of the Dietary Guidelines for Americans, the USDA developed a Healthy Mediterranean-style Food Pattern[21] that includes the main dietary components associated with primary prevention of diverticulitis and may be effective for secondary prevention. However, barriers to adherence relating to cost, cultural preferences, and food restrictions need to be addressed to consider it a practical intervention in a clinical setting.

Growing evidence suggests an interaction between diet, lifestyle, the gut microbiota, chronic inflammation, and episodes of diverticulitis. Cross-sectional studies indicate that gut microbial composition differs in patients with diverticulitis compared with controls,[22-25] and diet and lifestyle are known to influence the gut microbiome.[26-29] Prediagnostic inflammatory markers (interleukin-6 [IL-6]) and a diet with high inflammatory potential were associated with increased risk of diverticulitis.[30] Thus, serum and stool biomarkers may identify high-risk individuals who are likely to respond to preventative interventions. Greater use of the Mediterranean diet decreases dietary inflammation scores and levels of circulating biomarkers of inflammation[31, 32] and it is effective in the prevention of cardiovascular disease[33, 34] and certain cancers.[35]

2.1 Rationale

As our preliminary data indicate, diets that promote inflammation increase the risk of diverticulitis, and are therefore potential targets for secondary prevention. Dietary patterns account for the combined influence of multiple dietary components on disease risk, more closely resemble real world dietary practices, and are more readily translated into public health interventions.[130] A Mediterranean diet is more strongly associated with reduced CRP and other cardiometabolic risk factors than other diet patterns such as AHEI and DASH,[72] and is inversely associated with inflammatory diet scores. It also shares many features with other diets that are inversely associated with incident diverticulitis, including the AHEI and prudent pattern. A USDA Med-style Food Pattern is prominently featured in the widely disseminated Dietary Guidelines for America 2020-2025 and is well known to health professionals.[131] Therefore, we hypothesize that a USDA Med-style Food Pattern diet will reduce the risk of recurrent diverticulitis and the level of inflammatory markers more than a high- fiber diet or fiber supplementation and will be

feasible to implement in a large-scale RCT, as well as clinical practice and public health interventions.

We will study three biomarkers involved in systemic inflammation and implicated in chronic disease. Our prior work linked diet, CRP and IL-6 (but not TNFR1B) to incident diverticulitis.30 CRP and IL-6 are major inflammatory markers implicated in chronic disease and are associated with the inflammatory potential of diet.[30] In this study, we will measure IL-6, IL-1β and IL-10 primary pro and anti-inflammatory cytokines, respectively.[132-134] We will also collect blood samples for future biomarker studies that are outside the scope of this pilot feasibility study. Future biomarker work could explore additional inflammatory cytokines such as CRP, fat derived hormones such as adiponectin and markers of intestinal permeability such as lipopolysaccharide (LPS), as well as repeat multiplex assays (e.g., of IL-6, IL-1b, IL-10) and blood-based metabolome to examine various pathways that are hypothesized to link diet, chronic inflammation, and diverticulitis.

Fecal calprotectin is a protein found in the cytoplasm of neutrophil granulocytes that is released in the stool when the intestinal tract—the colon in particular—is inflammed.[135] It is resistant to bacterial degradation and is easily measured in stool.[136, 137] It is a more sensitive and specific marker of intestinal inflammation when compared with plasma erythrocyte sedimentation rate (ESR) and CRP,[136, 138] and can detect subclinical inflammation. It is commonly used to diagnose and monitor inflammatory bowel disease.[139, 140] Fecal calprotectin is also elevated in acute diverticulitis,[141] and in a study of 48 patients followed every 2 months after recovery, it was predictive of recurrence.[142] In this study, a semi-quantitative test was used (<15µg/g, ≥15µg/g-60µg/g, >60µg/g). Seventeen (37%) of patients had increased fecal calprotectin (>15µg/g) after a normal test following treatment for acute diverticulitis; 7 of 8 (88%) of patients with recurrence had an elevated fecal calprotectin during follow-up. Studies of healthy controls and patients with inflammatory bowel disease indicate that fiber intake and the Mediterranean diet are associated with decreases in fecal calprotectin.[137, 143] Therefore, we have selected fecal calprotectin as an innovative and plausible biomarker that may predict risk of recurrent diverticulitis and be more sensitive than plasma biomarkers. Collection of samples will provide data on the feasibility of stool collection within a larger diet trial. We also plan to collect and store stool for future work on the gut microbiome and metabolome in diverticulitis that is outside the scope of this pilot study.

3.0 Study Aims and Methods

3.1 Study Aims

Aim 1. Conduct a randomized trial (n=75) of the USDA Healthy Med-style Food Pattern intervention versus standardized guidance on fiber intake for patients with diverticulitis to determine feasibility of a larger-scale effectiveness trial focused on long-term clinical outcomes (recurrence and complications). We will examine willingness to randomize and assess adherence to USDA Healthy Med-style Food Pattern.

Aim 2. Explore plasma inflammatory markers in a subset of participants (n=40) (IL-6, IL-1, IL-1β) and fecal calprotectin as short-term, intermediate inflammatory biomarkers of response to treatment and collect samples for future biomarker study.

The hypotheses underlying the IMPEDE trial include 1) A large-scale trial of the USDA Med-style Food Pattern will be feasible (high rate of patient willingness to be randomized, high rate of adherence to the intervention, improvement in Med-style food pattern scores assessed by a well-characterized food frequency questionnaire (FFQ) [measure of extent of use of the Mediterranean diet], acceptability of study survey burden and follow-up). 2) A USDA Med-style Food Pattern reduces serum and fecal biomarkers of inflammation more than standardized

recommendation to encourage a high-fiber diet. Based on prior studies, we expect reductions in these biomarkers will correlate to lower rates of recurrent diverticulitis.

3.2 Methods

This is a feasibility-focused, patient-level randomized trial of an intervention promoting the USDA Healthy Med-Style food pattern versus standardized guidance on fiber intake (standard educational materials related to a high-fiber diet) in patients with a history of diverticulitis. This trial will assess and address barriers to the eventual large-scale trial and lay groundwork for that trial that will focus on the risk of recurrent diverticulitis and other clinical outcomes. We will also compare changes in serum and stool biomarkers of inflammation that are proximal endpoints in the causal path relating a Mediterranean diet pattern's anti-inflammatory properties and recurrence of diverticulitis.

Research Setting

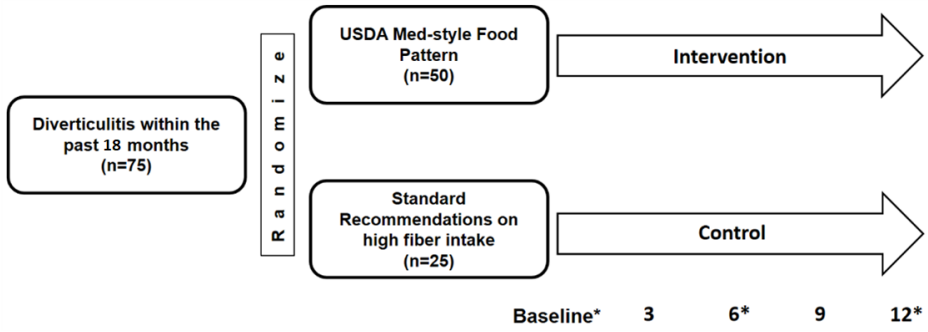
The proposed work will use the infrastructure of the Comparative Effectiveness Research Translation Network (CERTAIN), a collaborative of dozens of health systems across the US with a successful track record of conducting large-scale randomized and observation cohort studies. The CERTAIN diverticulitis research network, described in more detail in the UW Facilities and Resources description, supports our diverticulitis studies (e.g., DEBUT and COSMID) and will provide the setting for the conduct of IMPEDE.

The University of Washington's (UW) Surgical Outcomes Research Center (SORCE) will lead a Clinical Coordinating Center (CCC). The UW Center for Biomedical Statistics (CBS) will serve as the Data Coordinating Center (DCC).

4.0 Study Flow, Participant Screening and Enrollment

4.1 Overview of Study Flow

Figure 1: IMPEDE Trial Design



4.2 Participant Screening

Patients presenting to University of Washington Medicine gastroenterology and surgery clinics at UWMC and Harborview will be screened, remotely and/or in-person, by the research team. Patient-facing flyers will be posted at the clinic locations to allow potential participants to ask their clinician about the study or to access study information via a link/QR code/study contact information. Patients deemed eligible via initial clinician/research team pre-screening will have eligibility confirmed. They will then be given time to ask questions about the study to determine whether they are interested in participating.

Patients will also be able to begin a self-screening process on the Surgical Outcomes Research Center (SORCE) website, guiding them through simple yes/no eligibility questions to determine if the trial might be right for them (study eligibility from screening form). Patients will have the opportunity to review a consent form but will be contacted by a research team member for a consent call before they are able to sign and provide consent to participate. A study investigator will confirm eligibility before randomization, but no clinic visit will be required of those patients interested in enrolling in this manner. To be considered for participation, patients must have had a confirmed diagnosis of diverticulitis by a physician, with medical records to be accessed by study physician(s) to confirm.

The study team will also contact patients previously seen for diverticulitis and screened for other trials. Basic eligibility information will be visible to the research team through medical record screening.

4.3 Inclusion Criteria

1. Adult ≥18 years;
2. Patients presenting (or recently presented) to gastroenterologist or surgeons or accessing study website after recovery from an episode of diverticulitis (within the prior 18 months), either the index episode or recurrent.
3. Ability to provide written informed consent in English.

4.4 Exclusion Criteria

Participants must not have any of the following exclusion criteria:

1. Unable or unwilling to return for specimen collection visits or be contacted for and/or complete research surveys;
2. Currently incarcerated in a detention facility or in police custody (patients wearing a monitoring device can be enrolled) at baseline/screening;
3. Last episode of acute diverticulitis currently unresolved (i.e., on antibiotics for diverticulitis; drain in place)
4. Intolerance/allergy to the main components of the Med-style food pattern;
5. Surgery for diverticulitis within past 6 months without an episode of diverticulitis post-surgery
6. Planned elective surgery in next 6 months

4.5 Consent Process

The research coordinator and a representative from the medical team will confirm the patient's eligibility for the study based on inclusion and exclusion criteria. Patients will be given time to ask questions about the study to determine whether they are interested in participating. Our research team will utilize both in-person recruitment and remote/eConsents as applicable. The research coordinator will review the study and its risks with the patient and those interested in participating will sign informed consent and complete a Health Insurance Portability and Accountability Act (HIPAA) form in accordance with institutional guidelines.

For the remote consent option, access to the consent forms will be available digitally or via paper copies of the consent forms sent through the mail. A member of the study team will contact the patient via phone or over a HIPAA-compliant tele/videoconference line to verbally review the consent process with the patient. The patient will be granted time to consider and discuss the study before deciding to participate. If the patient decides to participate, they can either provide their electronic signature in an electronic consent platform, or they can sign a paper copy of the consent form that has been mailed to them. If the patient chooses to sign a paper copy of the consent, the patient will be mailed two copies of the consent form along with a self-addressed stamped envelope (SASE). One copy of the consent form will be to sign and for the patient to keep for themselves, and the second will be signed and mailed back to the study team.

4.5.1 Randomization Procedures

After consent is obtained, participant information will be entered into an electronic study portal to complete enrollment and perform randomization. Participants will be randomized to either the USDA Mediterranean-style Food Pattern or to standardized guidance on fiber intake in a 2:1 allocation ratio, respectively. Randomization failures, defined as a patient who agreed to randomization but whose treatment was allocated in a non-random fashion or was randomized under inaccurate information and occurring within the first week of randomization will be recorded as protocol violations, described in detail in 11.0.

4.5.2 Those who decline randomization

Participants who decline randomization and participation may be asked to complete a short survey assessing their interest in participating in a future trial of medical management.

4.6 USDA Mediterranean-stye Food Pattern/ Medi for all

Participants randomized to the USDA Mediterranean-style Food Pattern Arm (called Medi for all) will have access to a "toolbox" that includes education materials (e.g., food pattern tables according to daily caloric intake), recipes, grocery lists, group-based online dietary support, feedback, and reminders to encourage dietary change. Recipes and grocery lists can be individualized to a participant's food budget and preferences. Materials will be available in print and Web-based. This state-of-the art intervention will then use electronic feedback in the form of nudge messages designed to motivate participants to sustain or improve adherence to the Med-style Food Pattern. Every two weeks, participants in the intervention arm will be prompted via a

digital online platform[96] (analog also available) to complete the 14-item Mediterranean Diet Assessment Score (an adapted version of the MEDAS Score[145] previously used in the PREDIMED34 study) for the purpose of providing timely, individual feedback on diet adherence (not for assessing adherence to the diet pattern). The MEDAS score will be calculated via the online digital platform and ranked according to 3 cutpoints: ≤7, 8–9, or ≥10.[145] Patients will be encouraged to achieve a score of ≥10 which is considered high adherence. The platform will then offer feedback based on the levels of self-reported adherence to the diet including self vs. peer comparisons and support resources. Nudge messages will utilize information from a baseline assessment of participants' dietary attitudes and beliefs about which food groups within a Med-style food pattern they perceive to be most within their control. Ultimately, this approach will enable us to provide participants with dietary information and services that support adherence by accounting for attitudes, norms, and perceived control.[146-148] The extent of interaction with the online platform will be assessed bi-weekly; degree of adherence to the USDA Med-style food pattern; and engagement in dietician services will be assessed at quarterly intervals.

4.7 High Fiber Diet Arm

Participants randomized to the High Fiber Diet Arm will be given commonly used patient education pamphlet,[149] describing fiber and high-fiber foods, the rationale for increasing fiber intake, and ways patients can promote greater intake. Based on prior observational studies of incident diverticulitis, at least 25 grams/day of fiber will be recommended for participants.

5.0 Study Schedule Overview, Research Assessments, Medical Record Review, Call Triggers, Withdrawal, Compensation, and Retention

5.1 Study Schedule Overview

Consented and randomized participants will be asked to complete research assessments on the topics and at the time points described in Table 1. Research coordinators (RCs) or study team members will offer baseline and follow-up assessments in multiple modalities in order of participant preference (e.g., online, on paper, or over the phone). Participants randomized to the USDA Healthy Med Style food pattern (Medi for All) will receive electronic nudges to support behavior change. Additionally, the study dietitian will provide online group counseling sessions and office hours for participants to schedule individual online follow up counseling sessions which will provide additional content related to wellness, self-efficacy and motivation.

Table 1. Participant Assessment Schedule.

Item	Baseline	Bi-Weekly	Monthly	Follow-Up Time Point			
				Month			
				3	6	9	12
Contact Information	x			x	x	x	x
Food Frequency Questionnaires	x				x		x
Online Diet Program	x	x		x			x
Blood and Stool Sample*	x				x		x
DVQOL	x				x		x

IPAQ	X				x		x
Gastrointestinal Quality of Life (GIQLI)[22]	x				x		x
Mediterranean Diet Assessment Score (MEDAS)		x		x	x	x	x
Adverse Events				x	x	x	x
Self-Reported Weight	x				x		x
Diverticulitis Symptoms & HCU	x			x	x	x	x
Beyond Demographics	x						

*Up to 40 participants will be also invited to submit a stool sample for fecal calprotectin analysis. This will be collected at baseline, 6 months, and 12 months.

To ensure successful retention of participants and completion of research assessments through the follow-up period, detailed contact information including name, address, phone numbers, email addresses, as well as alternate contact persons and phone numbers will be requested from participants at baseline (and updated at subsequent time points). While complete contact information is ideal to optimize future retention, only one means of contacting the participant is required for enrollment. For participants with upcoming travel plans abroad or who may live internationally, it is preferred that they provide phone and email contact information as mailed contact is slow and costly for the short windows around each research assessment.

5.2 Research Assessments

5.2.1 Baseline Assessment (Index Encounter)

The Baseline Assessment as listed in Table 1 should be completed in-person or online and *prior to revealing the participant's random treatment assignment;* however, research coordinators are asked to document when the participant became aware of their assignment, should it be revealed prior to completion of the Baseline Assessment.

- Survey questions will be presented in the order of importance in the event that the participant is unable to complete the full battery of questionnaires.
- Collection and Measurement of Inflammatory Markers: We will collect and store blood samples on all participants. For the exploratory aim of this pilot study, we will measure inflammatory markers in plasma drawn in up to 40 participants. Blood samples will be collected in purple top EDTA tubes (EDTA plasma will be collected and stored for future studies) and immediately processed at room temperature.
- Collection of Stool for Measurement of Fecal Calprotectin and Future Studies: Participants may collect stool samples for future microbiome and metabolome analyses using an easy-to-use kit including catchment materials placed under the toilet lid and a small spatula/spoon. For stool collection, the spatula/spoon will be dipped into the fecal material and 1-5 g (peanut sized sample) will be obtained and placed in a clean, screw-top vial. Another small sample will be obtained and placed in another identical vial containing ethanol with instructions to screw lid tightly and shake. To optimize stability of the specimens, the vials should be refrigerated until shipping or transport.

- Participants randomized to Medi For All will participate in an introductory session regarding a USDA Healthy Med-style Food Pattern. Participants will have access to a "toolbox" that includes education materials (e.g., food pattern tables according to daily caloric intake), recipes, grocery lists, group-based online dietary support, feedback, and reminders to encourage dietary change. Recipes and grocery lists can be individualized to a participant's food budget and preferences. Materials will be available in print and Web-based. This state-of-the art intervention will then use electronic feedback in the form of nudge messages designed to motivate participants to sustain or improve adherence to the intervention. They will also be offered 6L of extra virgin olive oil (EVOO) over the 12-month study period, free of charge, if interested. Participants randomized to the fiber arm will be offered 6L of EVOO at the end of the 12-month study period, free of charge, if interested.

5.2.2 Bi-Weekly Check-in

Participants in the Medi For All intervention will be prompted every other week via a digital online platform (analog also available) to complete the 14-item Mediterranean Diet Assessment Score (MEDAS Score), slightly adapted for a US population, for the purpose of providing timely, individual feedback on diet adherence. The MEDAS Score will be calculated via the online digital platform and ranked according to 3 cutpoints; ≤7, 8–9, or ≥10. Patients will be encouraged to achieve a score of ≥10 which is considered high adherence. The platform will then offer feedback based on the levels of self-reported adherence to the diet including self vs. peer comparisons and support resources (such as group sessions and recipes). Nudge messages will utilize information from a baseline assessment of participants' dietary attitudes and beliefs about which food groups within a Med-style food pattern they perceive to be most within their control.

The extent of interaction with the online platform will be assessed bi-weekly; degree of adherence to the USDA Med-style food pattern; and engagement in dietician services will be assessed at quarterly intervals. Study staff will utilize a multi-modal (email, phone call, text, etc.) outreach for participants who fail to complete the MEDAS Score when prompted.

5.2.3 Follow-up Assessments (3, 6, 9, and 12 months)

In-person follow-up assessments will be prioritized around the participant's clinical appointments. UW study staff will contact the participant to complete assessments prior to their scheduled blood draw/fecal specimen collection. This outreach will include a combination of phone, mail, and email as determined by the contact information provided by the participant. If a participant hasn't completed their scheduled follow up assessment at the time of their visit, the study staff will attempt to complete it in person. The follow-up assessments are listed in detail in Table 1.

In addition to the survey assessments, participants' specimens will be collected at 6 and 12 months following the same guidelines as in the baseline visit. Specimen collection will coordinate with clinical appointments whenever possible.

See section 5.2.1 for specimen collection instructions, which remain the same for follow-up time points. Participants will be reminded that they are welcome to contact their research coordinator at any time if any questions or concerns should arise. UW study staff will communicate with the research coordinator to ensure appropriate reporting is completed should an AE or complication be reported to them.

Self-reported complications or AEs will be recorded. Any serious adverse events (SAEs) will be communicated to the relevant site study team to ensure appropriate reporting is completed.

5.2.7 Participant Burnout and Optimizing Data Collection

Participants may experience research assessment burnout due to the frequency and number of questions asked of them. To optimize complete data collection, research personnel should recognize a participant's reluctance to complete the research assessment and request that the participant instead complete a sub-set of survey responses (minimal research assessment). In the event that a participant prefers to complete a minimal research assessment, research personnel should prioritize asking the research participant questions related to signs and symptoms of diverticulitis and aim to complete the Food Frequency Questionnaires. Study staff will be provided with a prioritization model to clarify what questions are high versus medium priority. Study staff should use their best judgment to determine how many additional survey questions should be asked. It is preferred to miss some responses at one research assessment time point rather than risk the participant withdrawing altogether due to research assessment burnout.

5.3 Medical Record Review

Time points

Participants will have their EMR reviewed at ad-hoc time points if triggered by a survey response or if they have a diverticulitis event. Study staff will conduct an EMR review to assess the following:

1. Complications for patients using the National Surgical Quality Improvement Program (NSQIP) definitions and protocol; and
2. The following information related to diverticular disease:
   a. Indication for healthcare utilization
   b. Length of stay (if hospitalized);
   c. Surgery type, if applicable.

As needed, chart review will be conducted if a patient reports an adverse event and further documentation is needed.

Data Collection

Data will be collected using the following forms:

Form	Description

Form Information	Captures information about when the form was filled out (time point), and by whom
Enrollment Form	Completed at index visit only; captures basic demographics and treatment assignment data; medical history and cohort designation
Healthcare Utilization Form	Captures information about any visit (date, setting, treatments, medications)
Adverse Events Form	Captures information about adverse events at any time point

If a participant seeks care at an outside hospital, the study team will work with the participant to obtain relevant information.

5.4 Adverse Event Reporting

The research coordinator will recommend that the participant contact their clinician for any worrisome concerns or symptoms.

The study team will be responsible for initiating the Serious Adverse Event (SAE) reporting process if the reported patient concern is an SAE. See Section 9.0.

5.5 Reasons for Withdrawal

Participants may be withdrawn from the study for the following reasons:

1. Participant desires withdrawal (reasons for withdrawal will be recorded); and
2. Study investigator(s) deems it in the participant's best interest to be withdrawn (reason for withdrawal recorded).
3. Participant decides to pursue a different dietary plan that conflicts with study

5.5.1 Handling of Withdrawals

If the participant requests to be withdrawn from the study, they will be given appropriate treatment, but will not continue with scheduled study follow-ups. If the participant withdraws from the study and withdraws consent for disclosure of future information, no further evaluations will be performed and additional data will not be collected. The investigators may retain and continue to use data collected before withdrawal of consent.

5.6 Compensation

5.6.1 Participant Compensation

Participants will be paid up to $150 for completing the research assessments described in Table 1 (Section 5.0). Payment will be provided on a pro-rated, weighted fashion: $25 for the Baseline Assessment, up to $20 for Quarterly Assessments through 12 months. Participants will receive $10 for the biospecimen collection at baseline, $15 at 6 months and $20 at 12 months. Compensation will be distributed to participants by UW research staff unless other arrangements have been made.

5.7 Retention Activities

5.7.1 Maintaining Contact

Participants will be asked to confirm their contact information before beginning each research assessment. They will also be asked to confirm the contact information of family members, friends, and employers who may be asked to update the participant's contact information should they be otherwise lost to follow-up.

6.0 Outcome Assessments

6.1 Primary and Secondary Outcomes

Patient Reported Outcomes (PROs) will be assessed for adults using both generic and disease-specific surveys utilizing the QoL instruments in Table 2.

Table 2. Primary and secondary outcomes and intervention related process measures.

Primary or Secondary	Name of Outcome	Specific Measure to Be Used	Time Point
Primary	Willingness to enroll	Enrolled/approached	Baseline
Primary	Adherence to USDA Med-Style Food Pattern	USDA Med-style Pattern score calculated from the NASR FFQ.[161]	Baseline, 6, 12 months
Primary	Participant retention	Proportion enrolled and retained at 3, 6, 9 and 12 months	3, 6, 9 and 12 months
Primary	Interaction with on-line program	Number of times accessed	Bi-weekly
Primary	Engagement with nutrition services	Number of sessions with dietician	Quarterly
Secondary	Plasma, IL-6, IL-10, IL-1β, fecal calprotectin	Concentration	Baseline, 6, 12 months
Secondary	Diverticulitis events	Self-reported (presumed), subset of those resulting in healthcare utilization (e.g., hospitalization, surgery).	Quarterly
Secondary	NSQIP-defined complications, a subset of which are serious adverse events to be reported to ISM	Standardized assessment-serious events defined as death, cardiac arrest, myocardial infarction, pneumonia, progressive renal insufficiency, acute renal failure, pulmonary embolism, deep vein thrombosis, return to operating room, serious site infections	Quarterly
Secondary	DVQOL[65]	A 17-item questionnaire that assesses four domains: symptoms, concerns, emotions, and behavior changes related to diverticulitis.	Baseline, 6, 12 months
Secondary	GIQLI[159]	A 36-item questionnaire that assesses five domains: gastrointestinal symptoms, physical function, emotional well-being, social well-being, and perception of medical treatment measured by a single item question.	Baseline, 6, 12 months

Secondary	IPAQ Short Form[169]	A validated 7-item questionnaire: moderate and vigorous physical activity, walking, and sitting in the past 7 days	Baseline, 6, 12 months
Secondary	Time in healthcare	Days missed from work/school, ED/hospital encounters, diverticulitis-related diagnostic/therapeutic interventions	3, 6, 9 and 12 months
Secondary	Self-reported weight	Self-reported weight	Baseline, 6, 12 months

6.2 Clinical Complications

Death, SAEs, and complications (reported as AEs via EMR review) will be assessed and recorded through the study surveillance period. Complications (reported as AEs) will incorporate NSQIP standards and definitions as well as events related to antibiotic-related complications.

Table 3: Summary of SAE/AEs

Serious Adverse Events	Adverse event
Death	
Life-threatening event	
CVA or stroke	
MI requiring treatment or cardiac arrest	Myocardial infarction Atrial arrhythmia
Unplanned admit to ICU	
Acute Renal Failure (requiring dialysis)	Major UTI (e.g., pyelonephritis) Urinary retention Acute Renal Failure (no dialysis) Progressive renal insufficiency
C. difficile colitis (requiring colon resection)	
Pulmonary embolism requiring therapy	DVT/PE requiring treatment
Coma >24 hours	
Septic shock (requiring pressors)	Sepsis
Bleeding requiring transfusion	
Newly infected prosthetic graft infection	
Mechanical ventilation >48 hours	Tracheal reintubation/tracheostomy
Colostomy or ileostomy	NG tube replacement (non-routine) Bowel obstruction Ileus
	Organ/space infection (including peritonitis) Surgical site infection Intra-ab Abscess Severe dehydration Hernia Malignant hyperthermia Pneumonia Other infection Other post-op occurrence: unspecified Other non-operative intervention: unspecified Unplanned (re)operative intervention during index C. difficile colitis (not requiring colon resect)

Other life threatening event	
Hospitalization*	

*Exception to hospitalizations that do not need to be reported as an SAE:

- Planned, elective surgical procedures
- Labor and delivery
- Psychiatric hospitalizations

7.0 Data Management and Information Security

7.1 Data Management

Data management will be almost exclusively web-based, with paper-based surveys available as needed for mailing. The UW CCC will support an https-secured web page that

provides a centralized location for public information about the project for potential subjects, investigators, and institutional agencies. The web page will contain a link to the project portal (https://uwdcc.org/portal/impede). Study personnel will log on to the private portal on the study web page with individual single sign-on (SSO) authentication usernames and passwords to securely perform study data management activities. An overview of the DCC responsibilities and data management system is presented below.

Study Integration: The UW DCC team has extensive experience developing Application Programming Interfaces (APIs), which allow multiple software programs to seamlessly interact and communicate with one another in a simple and intuitive interface. The web portal API will serve as the wrapper for all data management tools and software utilized in the IMPEDE Trial, including: study ID assignment, screening, centralized image storage (if needed), prospective data collection forms and surveys, and study operations reporting. Screening and eligibility will be determined centrally through the portal and all subjects screened under the trial protocol will be assigned a sequentially generated study participant ID. The DCC will maintain a REDCap database to centrally and securely store patient information, with distinct data access groups for clinical recruitment sites.

Electronic Data Capture: The UW DCC supports its own installation of REDCap, which is software specifically designed for electronic data capture that we have used successfully in several multi-site clinical trials. REDCap features include differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes (http://www.project- redcap.org/software.php). REDCap will serve as the architectural backbone for all data captured prospectively in this study, with all data linked by study subject ID. The web-based data management portal allows for three participant contact methods: research coordinator data entry; electronic survey; or computer-assisted telephone interviewing (CATI). All survey modalities are customized to incorporate project logos and information to increase participant recognition and response rate. Furthermore, surveys may be distributed on any time schedule (e.g., monthly for pain and disability), and in any designated survey format.

All study questionnaires completed on paper will be reviewed by study staff for accuracy and completeness.

7.1.2 Data Quality Monitoring

The CCC and DCC will review participant enrollment, reasons for exclusion, participant demographics, and follow-up rates by site in order to assess proximity to enrollment targets, site performance, and protocol adherence.

The DCC will perform in-line quality assurance checks by using field masking, range checks, and real-time warning messages. Missing data reporting and other customized reports will be developed by the DCC in collaboration with the CCC and recruitment team in order to facilitate efficient work- flow and high-quality data capture. A subset of key personnel from the DCC and CCC will serve as an operations committee and review quality control reports on a weekly or biweekly basis, though quality control reports will be made available on a daily basis. CRF-specific follow-up rates will be tabulated on a nightly basis and reviewed during the weekly check-in meeting with each clinical recruitment site. Nightly, the DCC will generate graphs that monitor CRF-specific follow-up rates over time as well as data quality trigger rates over time to prospectively monitor potential issues that may develop gradually or acutely over time. A data query resolution dashboard will be available to each site on a continuous basis. In similar studies, we have found that establishing a fixed-day for a monthly review of all unresolved queries is an adequate balance of time to resolution and alert fatigue.

On a nightly basis, the DCC will also generate a comprehensive data quality report to flag unusual data and will be made broadly available to the study team. Research staff at the recruitment sites will be asked to review each outstanding query and respond with “confirmed” or “corrected” and may provide a comment beside each query to note relevant details. Each query will be closed by the DCC protocol operations specialist.

7.2 Information Security

All participant data collected on paper will be stored in locked file cabinets located in the site research offices.

All data entered onto UWMC laptop/desktop computers sites will be secured via our Information Security infrastructure. Information Security at UWMC is multi-layered and includes physical security measures, network security measures, managed servers, and desktop/laptop computers with authentication and authorization controls. All systems are designed and implemented to properly secure restricted or confidential information, including PHI, from inadvertent or unauthorized disclosure. All policies and procedures adhere to federal, state, and health system requirements. Servers, desktops, and laptops are under active management by an Integrated Technology Services Group (ITSG) at each participating site. In addition to maintaining anti-virus and firewall installations, the ITSG audits patch status of systems connected to the network and installs any missing updates or patches found. Servers have defined change control periods for operating system maintenance but are patched or updated outside the schedule as necessary to address threats. Anti-virus software is configured to update daily. The host-based firewalls restrict inbound connections to only the subnets where department workforce resides or that are needed for firewall administration. The firewall rule set on the dedicated server is further restricted to the network subnets. A specific Windows domain account is required to access computers. Domain passwords must be at least 8 characters in length, conform to complexity rules, and be changed at least every 120 days. Database systems and security policies are established and overseen by administrative staff members who do not require research funding.

REDCap:

All data, including PHI, names, and contact information will be entered onto a HIPAA and 21 CFR Part 11- compliant database. Participant PHI, including names, contact information, health information, will be entered onto this database. Only study staff will have access to the database and each study staff member will be given separate access only after completing study-required trainings.

8.0 Statistical Analysis Plan and Stopping Rules

The IMPEDE Trial is based on the Practice-Based conceptual model for comparative effectiveness;[162] "there is a comprehensive set of patient, treatment, and outcome variables, and [that by] analyzing them we identify treatments associated with better outcomes for specific types of patients". The strategy for utilizing this model is that a lack of evidence related to the effectiveness of interventions to prevent recurrent diverticulitis is limiting treatment options and leading to excessive use of preventative colon resections. Also, structural barriers (e.g., affordability of Medi For All) may result in differential acceptance of medical management among historically disadvantaged groups.

8.1 Allocation and Randomization

The Data Coordinating Center (DCC) will generate and maintain randomization assignments. Randomization assignments (2:1 randomization; N=50 to USDA Med-style Food Pattern (Medi For All): N=25 to standardized guidance on fiber intake) will be generated separately by site using block randomization randomly permuted block sizes for each site. Research coordinators will randomize eligible patients using a web-based portal that provides the next available assignment once an eligible patient consents for study participation. Study participants will be unblinded to the assigned intervention group (USDA Med-style Food Pattern or standardized guidance on fiber intake), but CERTAIN investigator team and research staff involved in data collection will be blinded to intervention status.

8.2 Study Feasibilities Measures

We will assess willingness to randomize as the number of eligible patients that randomized divided by the number of eligible patients (Aim 1). We will provide descriptive statistical summaries of time to complete survey materials, time interacting with the USDA Med-style Food Pattern platform, and changes in estimated weekly meal expenses. These data will be used to inform the future large-scale trial including the number of study sites, recruitment rate/study duration and amount of coordinator effort. The rate of willingness to randomize is unknown but as long as it is at least 20% our study will be successful. We would also want at least 50% of those willing to randomize to be willing to give a blood sample and at least half of those to give stool.

8.3 Treatment Fidelity and Adherence:

The Fred Hutch FFQ is a standard method of dietary intake assessment that has been used in several large-scale cohort studies including the Women's Health initiative.[153, 154] The degree of adherence with the USDA Healthy Med-style Food Pattern (Aim 1) will be ascertained by assigning point scores based on the estimated daily amounts of the recommended food groups and subgroups habitually consumed. Full points will be awarded to diets that meet all the

recommendations and partial points to diets that do not. Given that the USDA Healthy Med-style Food Pattern provides recommended amounts for relevant food groups, the adherence score will be based on food consumption data normalized per 100 kcal, much along the lines of the Healthy Eating Index (HEI). The HEI is a 100-point score that measures adherence to the DGA and is the standard measure of diet quality in the US. This approach represents an advance over the 14-item food frequency MEDAS score, which ranks adherence to the Med-style diet pattern using 3 cutpoints: ≤7, 8–9, or ≥10 (maximal adherence).[145] The data derived will help us understand the central tendency and variability in Med-style food pattern scores which is critical for determining the sample size of a future trial. Degree of adherence to the different aspects of the medical management regimen will also be used to define per-protocol analysis and be considered as potential mediators and/or effect modifiers in explanatory regression models

8.4 Signal Assessment for Biomarkers:

We will use a linear mixed effects regression model to compare IL-6, IL-10, IL-1β, and fecal calprotectin measures at baseline, 6, and 12 months after randomization between the two groups. We focus our statistical analysis on IL-6 for which there are preliminary data specific to diverticulitis. The linear mixed effects model will be structured as a longitudinal analysis of covariance, allowing for both cross-sectional and longitudinal comparisons of serum biomarkers between intervention groups. From the model, we will estimate the mean difference and 95% confidence interval in time-averaged IL-6 by averaging the time-specific intervention group differences. The longitudinal analysis of covariance model will adjust for intervention (USDA Med-style pattern versus standardized guidance on fiber intake), recruitment site, and baseline IL-6 as fixed effects: $\mathrm{IL6}\,(t) \sim \beta_0 + \beta_1 \cdot Intervention + \beta_2 \cdot Site + \beta_3 \cdot IL6(t=0)$, for t = 6 and 12 months. Follow-up time-point specific differences in mean IL-6 between intervention groups will be estimated by a statistical interaction term between time and intervention status in a second model. Finally, experience in other ongoing trials has shown that serum biomarkers are often positively skewed. We will therefore log-transform IL-6 measurements (and all skewed serum biomarkers) throughout all statistical analyses, and exponentiate model coefficients (as appropriate) for interpretation. Sex and gender (if different from sex assigned at birth) will be considered as exploratory variables in assessing the relationship of the diet-behavioral intervention and the primary and secondary outcomes. Analyses of IL-10, IL-1β, and fecal calprotectin and patient-reported outcomes will mirror the analyses of IL-6, with the primary goal of estimating plausible intervention effect sizes and standard deviations with the goal of informing a larger phase 3 clinical trial. Formal statistical testing will not be conducted and therefore no multiple testing correction will be employed for analyzing multiple serum biomarkers. Sex as a biological variable will be included in an exploratory analysis of all biomarker models. The study of serum and stool biomarkers will also inform the feasibility of performing a biomarker sub-aim within a future phase 3 trial.

8.5 Secondary Statistical Analyses

Binary and categorical endpoints (e.g., adverse events and complications) will be tabulated by intervention group. Time in healthcare will be summarized by group using medians and interquartile ranges, and differences between intervention groups will be summarized using 95% confidence intervals generated from generalized linear regression models appropriate for each type of outcome (e.g., binary, count, continuous, etc.). To examine the sensitivity of adherence to the Med-style Food Pattern on changes in serum biomarkers, we will modify the primary analytic model described for Aim 2 by separately adjusting for a binary indicator of adherence (adherent vs. not) and a graded measure of adherence to intervention. Finally, we will use

mediation analyses to explore the extent to which changes in serum biomarkers over time are mediated through intervention-induced changes in weight and physical activity.

8.6 Missing Data

Participants who do not complete some or all of the baseline and follow-up questions will have missing data points. As summarized in the NEJM guidance,[163] we will employ three primary strategies that are recommended to address missing data. First, the DCC will work in conjunction with the CCC to minimize the amount of missing data since prevention of missing data is preferable to any attempted analysis correction. We will document all reasons for missing data. Second, we will use inverse probability weighting[164] to inflate the weights of cases that are under-represented in the analysis due to selective attrition and/or non-participation. A descriptive analysis that characterizes enrolled participants who do not provide data due to attrition will be conducted, and we will use observed covariates to construct a weighted model using logistic regression. Third, the strategy that we used for two recent primary trial publications[102, 165] and which we will adopt for our primary analysis is the use of 10-fold multiple imputation to assess the robustness of the results when missing data are imputed and allowing all participants to be included in intent-to-treat analysis. Our primary approach is to use multiple imputation since it provides flexibility in inclusion of relevant baseline and follow-up data. We will also impute missing data under both pessimistic and optimistic scenarios to provide bounds on the statistical uncertainty.

8.7 Sample Size and Statistical Power

Using 2:1 randomization, we will enroll 50 patients into a USDA Med-style Food Pattern and 25 patients to receive standardized guidance on fiber intake. The analytic aim of this study is to inform potential effect sizes and variance estimates toward the ultimate goal of conducting a definitive phase 3 randomized trial. While 1:1 randomization is more statistically efficient when group variances in outcome are similar, we plan to enroll more participants into the USDA Med-style food pattern intervention to strengthen the precision of estimates of adherence and patient-reported response. Since statistical testing will not be formally conducted, statistical power was not a primary motivation for sizing for this pilot study.[166] However, enrollment of 50 study participants in the USDA Med-style Food Pattern intervention allows a 95% one-sided confidence interval for the intervention adherence rate to exclude rates less than 0.70 if the observed adherence rate is 0.80 or higher in this pilot study.

8.8 Data and Safety Monitoring Plan (DSMP)

Given the minimal risk nature of this study, monitoring will be conducted by the DCC and an Independent Safety Monitor (ISM). The ISM will review patient-reported outcomes as they accrue over time but will not be responsible for making interim decisions based on observed efficacy (or lack thereof). ISM and the DCC will put together a report according to accrual (at 50%, 75%, and full enrollment). The study team will review and report to the IRB and sponsor as required.

9.0 Study Related SAEs

9.1 Identification of SAEs

Randomized participants will be monitored for SAEs throughout their study surveillance period (enrollment through twelve months). The occurrence of an SAE may come to the attention of study personnel during study follow-up phone interview or by a study participant calling the study team or presenting for medical care. Study staff will use the EMR to fill out the SAE form. The PI will then complete the form and sign the form. The SAE form will then be submitted to the DCC who will provide it to the ISM. The ISM will review the SAE form and ask the study team for additional clarification or specification as he/she sees necessary.

9.2 SAE Reporting

Life-threatening complications or SAEs are a very rare possibility with both intervention arms. SAEs are defined as one of the following conditions (also listed in section 6.2.):

1. Death during the period of protocol-defined surveillance;
2. Life-threatening event related to the treatment or significant disability/incapacity related to the treatment; or
3. Inpatient hospitalization except for:
    - Planned, elective surgical procedures
    - Labor and delivery
    - Psychiatric hospitalizations

All SAEs will be:

1. Recorded on the appropriate SAE case report form;
2. Adjudicated by the ISM;
3. Followed until satisfactory resolution or until the study investigators deem the event to be chronic or the participant to be stable;
4. Reported to the study team and IRBs per their reporting guidelines; and
5. The study investigators will also report SAEs to the funder when appropriate.

9.3 Assignment of SAEs as Treatment Related

The determination of whether an SAE is related to the treatment will be assessed by the ISM and site lead, based on supporting documentation provided by the research coordinators case reports or in consultation with the treating physician, as needed.

10.0 Reporting Procedures

SAEs will be captured on the appropriate source document. Information to be collected includes event description, date event occurred, date study personnel became aware of the event, investigator assessment of event severity, event outcome, and relationship to study treatment. All SAEs will also have information on action taken at time of report, date SAE resolved, outcome at time of SAE report, and, depending on the site, whether the IRB has been notified.

For SAEs, the date of resolution (or when the event is deemed stable/chronic) will be noted on the appropriate case report form.

11.0 Protocol Violations and Deviations

A protocol violation is any non-compliance with the clinical trial protocol or Good Clinical Practices. The noncompliance may be either on the part of the participant, the investigator, or the study site staff and most often is related to study enrollment. Anticipated protocol violations

are 1) Participant enrolled but did not meet inclusion criteria, 2) Participant enrolled but exclusion criteria present or eligibility criteria not met, 3) Consent not obtained in accordance with IRB guidelines, 4) Randomization failure

A protocol deviation is a smaller digression from study protocol. Deviations are monitored with consideration for protocol amendment should it become clear that the original protocol was too inflexible.

It is the responsibility of the research staff to use continuous vigilance to identify and report violations and deviations within 5 working days of identification of the protocol violation/deviation.

All violations and deviations from the protocol will be addressed in study participant source documents. A completed copy of the Protocol Violations and Deviation Form will be maintained in the regulatory file, as well as in the participant's study chart. Protocol violations and deviations will be sent to the local IRB per their guidelines. The study staff will be responsible for knowing and adhering to their IRB requirements.

12.0 Protection of Human Participants

We expect that most patients will have good baseline health but will not exclude patients with most stable and chronic medical conditions, other than those characteristics described in the exclusion criteria.

Patients of childbearing potential will be excluded if they have a positive pregnancy test documented prior to enrollment. Incarcerated patients will be excluded. There is no evidence from prior studies to suggest there will be differences in intervention effect among sex/gender or racial/ethnic subgroups.

The risks and benefits for participants enrolled in this trial are appropriately balanced and minimal. The primary risks of this study are loss of patient privacy, loss of confidentiality, study burden, and risk of bleeding, bruising, or discomfort during the specimen collection.

Loss of confidentiality could occur if the study database were breached. This risk will be low because of numerous steps to protect confidentiality. Approaching patients about enrollment in the clinic poses a risk to privacy. We anticipate this risk to be low. Patients will be approached in a private clinic room. To avoid threats of coercion, providers will be educated but not directly involved with recruitment of patients. We expect the risks of discomfort or anxiety related to study questionnaires to be low. There is a small risk of bleeding, bruising, or discomfort at the site of the blood collection. Attention will be taken to apply pressure following the procedure to reduce bleeding. There is also a small risk of fainting or feeling faint during a blood draw. There is minimal discomfort associated with collection of the fecal (stool) sample. We expect these specimen collection risks to be low.

Study participants could benefit from participation in this study by learning how to increase their dietary fiber intake or how to integrate tools from the Medi For All diet and behavioral intervention, potentially helping their diverticulitis symptoms.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of both interventions will be provided to the participants using standardized materials. Consent forms describing in detail the study procedures and risks will be given to the participant and documentation of informed consent will be required prior to completing study assessments.

Consent forms will be IRB-approved and the participant will be given sufficient time to read and review the document. They will be specifically asked if they have any questions or concerns, which will be addressed, or would like more time to consider their participation, which will also be provided. The study team will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent prior to completing any study related activities. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that they will still be able to receive medical care at the facility if they decline to participate in this study.

Participant confidentiality is strictly held in trust by the participating investigators and their staff.

13.0 References

1. Peery AF, Crockett SD, Barritt AS, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology 2015;149:1731-1741 e3.
2. Peery AF, Dellon ES, Lund J, et al. Burden of Gastrointestinal Disease in the United States: 2012 Update. Gastroenterology 2012;143:1179-1187 e3.
3. Bharucha AE, Parthasarathy G, Ditah I, et al. Temporal Trends in the Incidence and Natural History of Diverticulitis: A Population-Based Study. Am J Gastroenterol 2015;110:1589-96.
4. Stollman N, Smalley W, Hirano I, et al. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology 2015;149:1944-9.
5. Gervaz P, Inan I, Perneger T, et al. A Prospective, Randomized, Single-Blind Comparison of Laparoscopic Versus Open Sigmoid Colectomy for Diverticulitis. Ann Surg 2010;252:3-8.
6. Klarenbeek BR, Veenhof AA, Bergamaschi R, et al. Laparoscopic Sigmoid Resection for Diverticulitis Decreases Major Morbidity Rates: A Randomized Control Trial: Short-Term Results of the Sigma Trial. Ann Surg 2009;249:39-44.
7. Raue W, Langelotz C, Paolucci V, et al. Problems of Randomization to Open or Laparoscopic Sigmoidectomy for Diverticular Disease. Int J Colorectal Dis 2011;26:369-75.
8. Strate LL, Peery AF, Neumann I. American Gastroenterological Association Institute Technical Review on the Management of Acute Diverticulitis. Gastroenterology 2015;149:1950-1976 e12.
9. Aldoori WH, Giovannucci EL, Rockett HR, et al. A Prospective Study of Dietary Fiber Types and Symptomatic Diverticular Disease in Men. J Nutr 1998;128:714-9.
10. Cao Y, Strate LL, Keeley BR, et al. Meat Intake and Risk of Diverticulitis among Men. Gut 2018;67:466-472.
11. Crowe FL, Appleby PN, Allen NE, et al. Diet and Risk of Diverticular Disease in Oxford Cohort of European Prospective Investigation into Cancer and Nutrition (Epic): Prospective Study of British Vegetarians and Non-Vegetarians. BMJ 2011;343:d4131.
12. Ma W, Nguyen LH, Song M, et al. Intake of Dietary Fiber, Fruits, and Vegetables and Risk of Diverticulitis. Am J Gastroenterol 2019;114:1531-1538.
13. Strate LL, Keeley BR, Cao Y, et al. Western Dietary Pattern Increases, and Prudent Dietary Pattern Decreases, Risk of Incident Diverticulitis in a Prospective Cohort Study. Gastroenterology 2017;152:1023-1030 e2.

14. Hjern F, Wolk A, Hakansson N. Smoking and the Risk of Diverticular Disease in Women. Br J Surg 2011;98:997-1002.
15. Hjern F, Wolk A, Hakansson N. Obesity, Physical Inactivity, and Colonic Diverticular Disease Requiring Hospitalization in Women: A Prospective Cohort Study. Am J Gastroenterol 2012;107:296-302.
16. Humes DJ, Ludvigsson JF, Jarvholm B. Smoking and the Risk of Hospitalization for Symptomatic Diverticular Disease: A Population-Based Cohort Study from Sweden. Dis Colon Rectum 2016;59:110-4.
17. Strate LL, Liu YL, Aldoori WH, et al. Physical Activity Decreases Diverticular Complications. Am J Gastroenterol 2009;104:1221-30.
18. Strate LL, Liu YL, Aldoori WH, et al. Obesity Increases the Risks of Diverticulitis and Diverticular Bleeding. Gastroenterology 2009;136:115-122 e1.
19. Strate LL, Liu YL, Huang ES, et al. Use of Aspirin or Nonsteroidal Anti-Inflammatory Drugs Increases Risk for Diverticulitis and Diverticular Bleeding. Gastroenterology 2011;140:1427-33.
20. Liu PH, Cao Y, Keeley BR, et al. Adherence to a Healthy Lifestyle Is Associated with a Lower Risk of Diverticulitis among Men. Am J Gastroenterol 2017;112:1868-1876.
21. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at Https://Health.Gov/Our-Work/Food-Nutrition/Previous-Dietary-Guidelines/2015.
22. Barbara G, Scaioli E, Barbaro MR, et al. Gut Microbiota, Metabolome and Immune Signatures in Patients with Uncomplicated Diverticular Disease. Gut 2017;66:1252-1261.
23. Daniels L, Budding AE, de Korte N, et al. Fecal Microbiome Analysis as a Diagnostic Test for Diverticulitis. Eur J Clin Microbiol Infect Dis 2014;33:1927-36.
24. Hullar MAJ SR, Stamatoyannopoulos JA, Lampe JW, Strate LL. . The Fecal Microbiome in Diverticulitis and Asymptomatic Diverticulosis: A Case-Control Study in the Us. medRxiv 19001404 2019;doi: https://doi.org/10.1101/19001404.
25. Kvasnovsky CL, Leong LEX, Choo JM, et al. Clinical and Symptom Scores Are Significantly Correlated with Fecal Microbiota Features in Patients with Symptomatic Uncomplicated Diverticular Disease: A Pilot Study. Eur J Gastroenterol Hepatol 2018;30:107-112.
26. Claesson MJ, Jeffery IB, Conde S, et al. Gut Microbiota Composition Correlates with Diet and Health in the Elderly. Nature 2012;488:178-84.
27. De Filippis F, Pellegrini N, Vannini L, et al. High-Level Adherence to a Mediterranean Diet Beneficially Impacts the Gut Microbiota and Associated Metabolome. Gut 2016;65:1812-1821.
28. Martinez-Medina M, Denizot J, Dreux N, et al. Western Diet Induces Dysbiosis with Increased E Coli in Ceabac10 Mice, Alters Host Barrier Function Favouring Aiec Colonisation. Gut 2014;63:116-24.
29. Zhang H, DiBaise JK, Zuccolo A, et al. Human Gut Microbiota in Obesity and after Gastric Bypass. Proc Natl Acad Sci U S A 2009;106:2365-70.
30. Ma W, Jovani M, Nguyen LH, et al. Association between Inflammatory Diets, Circulating Markers of Inflammation, and Risk of Diverticulitis. Clin Gastroenterol Hepatol 2020;18:2279-2286 e3.
31. Dai J, Miller AH, Bremner JD, et al. Adherence to the Mediterranean Diet Is Inversely Associated with Circulating Interleukin-6 among Middle-Aged Men: A Twin Study. Circulation 2008;117:169-75.
32. Mayr HL, Thomas CJ, Tierney AC, et al. Randomization to 6-Month Mediterranean Diet Compared with a Low-Fat Diet Leads to Improvement in Dietary Inflammatory Index Scores in Patients with Coronary Heart Disease: The Ausmed Heart Trial. Nutr Res 2018;55:94-107.

33. Estruch R, Ros E, Salas-Salvado J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. N Engl J Med 2013;368:1279-90.
34. Martinez-Gonzalez MA, Corella D, Salas-Salvado J, et al. Cohort Profile: Design and Methods of the Predimed Study. Int J Epidemiol 2012;41:377-85.
35. Mentella MC, Scaldaferri F, Ricci C, et al. Cancer and Mediterranean Diet: A Review. Nutrients 2019;11:2059.
36. Neuhouser ML, Schwarz Y, Wang C, et al. A Low-Glycemic Load Diet Reduces Serum C-Reactive Protein and Modestly Increases Adiponectin in Overweight and Obese Adults. J Nutr 2012;142:369-74.
37. Peery AF, Shaukat A, Strate LL. Aga Clinical Practice Update on Medical Management of Colonic Diverticulitis: Expert Review. Gastroenterol 2021;160:906-911.
38. Simianu VV, Fichera A, Bastawrous AL, et al. Number of Diverticulitis Episodes before Resection and Factors Associated with Earlier Interventions. JAMA Surg 2016;151:604-10.
39. Agrawal N, Duhachek A. Emotional Compatibility and the Effectiveness of Anti-Drinking Messages: A Defensive Processing Perspective on Shame and Guilt. . J Marketing Res 2010;47:263-73.
40. Rosen JE, Agrawal N, Flum DR, et al. Willingness to Undergo Antibiotic Treatment of Acute Appendicitis Based on Risk of Treatment Failure. Br J Surg 2021;108:e361-e363.
41. Darmon N, Drewnowski A. Contribution of Food Prices and Diet Cost to Socioeconomic Disparities in Diet Quality and Health: A Systematic Review and Analysis. Nutr Rev 2015;73:643-60.
42. Drewnowski A. The Cost of Us Foods as Related to Their Nutritive Value. Am J Clin Nutr 2010;92:1181-8.
43. Drewnowski A, Darmon N. Food Choices and Diet Costs: An Economic Analysis. J Nutr 2005;135:900-4.
44. Fulgoni V, 3rd, Drewnowski A. An Economic Gap between the Recommended Healthy Food Patterns and Existing Diets of Minority Groups in the Us National Health and Nutrition Examination Survey 2013-14. Front Nutr 2019;6:37.
45. Gupta S, Hawk T, Aggarwal A, et al. Characterizing Ultra-Processed Foods by Energy Density, Nutrient Density, and Cost. Front Nutr 2019;6:70.
46. Peery AF, Keku TO, Martin CF, et al. Distribution and Characteristics of Colonic Diverticula in a United States Screening Population. Clin Gastroenterol Hepatol 2016;14:980-985 e1.
47. Shahedi K, Fuller G, Bolus R, et al. Long-Term Risk of Acute Diverticulitis among Patients with Incidental Diverticulosis Found During Colonoscopy. Clin Gastroenterol Hepatol 2013;11:1609-13.
48. Anaya DA, Flum DR. Risk of Emergency Colectomy and Colostomy in Patients with Diverticular Disease. Arch Surg 2005;140:681-5.
49. Yen L, Davis K, Hodkins P, et al. Direct Costs of Diverticulitis in a Us Managed Care Population. . Am J Pharm Benefits 2012;4:e118-e129.
50. Etzioni DA, Cannom RR, Ault GT, et al. Diverticulitis in California from 1995 to 2006: Increased Rates of Treatment for Younger Patients. Am Surg 2009;75:981-5.
51. Etzioni DA, Mack TM, Beart RW, Jr., et al. Diverticulitis in the United States: 1998-2005: Changing Patterns of Disease and Treatment. Ann Surg 2009;249:210-7.
52. Reddy VB, Longo WE. The Burden of Diverticular Disease on Patients and Healthcare Systems. Gastroenterol Hepatol (N Y) 2013;9:21-7.
53. Peery AF, Crockett SD, Murphy CC, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology 2019;156:254-272 e11.
54. Parks TG. Natural History of Diverticular Disease of the Colon. A Review of 521 Cases. Br Med J 1969;4:639-42.

55. Nugent KP, Daniels P, Stewart B, et al. Quality of Life in Stoma Patients. Dis Colon Rectum 1999;42:1569-74.
56. Marquis P, Marrel A, Jambon B. Quality of Life in Patients with Stomas: The Montreux Study. Ostomy Wound Manage 2003;49:48-55.
57. Wong WD, Wexner SD, Lowry A, et al. Practice Parameters for the Treatment of Sigmoid Diverticulitis--Supporting Documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum 2000;43:290-7.
58. Gooszen AW, Gooszen HG, Veerman W, et al. Operative Treatment of Acute Complications of Diverticular Disease: Primary or Secondary Anastomosis after Sigmoid Resection. Eur J Surg 2001;167:35-9.
59. Jeyarajah S, Faiz O, Bottle A, et al. Diverticular Disease Hospital Admissions Are Increasing, with Poor Outcomes in the Elderly and Emergency Admissions. Aliment Pharmacol Ther 2009;30:1171-82.
60. Simianu VV, Strate LL, Billingham RP, et al. The Impact of Elective Colon Resection on Rates of Emergency Surgery for Diverticulitis. Ann Surg 2016;263:123-9.
61. Wolff BG, Ready RL, MacCarty RL, et al. Influence of Sigmoid Resection on Progression of Diverticular Disease of the Colon. Dis Colon Rectum 1984;27:645-7.
62. Fozard JB, Armitage NC, Schofield JB, et al. Acpgbi Position Statement on Elective Resection for Diverticulitis. Colorectal Dis 2011;13 Suppl 3:1-11.
63. Thorn M, Graf W, Stefansson T, et al. Clinical and Functional Results after Elective Colonic Resection in 75 Consecutive Patients with Diverticular Disease. Am J Surg 2002;183:7-11.
64. Feingold D, Steele SR, Lee S, et al. Practice Parameters for the Treatment of Sigmoid Diverticulitis. Dis Colon Rectum 2014;57:284-94.
65. Spiegel BM, Reid MW, Bolus R, et al. Development and Validation of a Disease-Targeted Quality of Life Instrument for Chronic Diverticular Disease: The Dv-Qol. Qual Life Res 2015;24:163-79.
66. Dahl C, Crichton M, Jenkins J, et al. Evidence for Dietary Fibre Modification in the Recovery and Prevention of Reoccurrence of Acute, Uncomplicated Diverticulitis: A Systematic Literature Review. Nutrients 2018;10:137.
67. Ridgway PF, Latif A, Shabbir J, et al. Randomized Controlled Trial of Oral Vs Intravenous Therapy for the Clinically Diagnosed Acute Uncomplicated Diverticulitis. Colorectal Dis 2009;11:941-6.
68. Taylor I, Duthie HL. Bran Tablets and Diverticular Disease. Br Med J 1976;1:988-90.
69. Droullard D, Hantouli M, Lois A, et al. S0146 Living with Diverticular Disease: Social Media and Self-Management. AJG 2020;115:S68.
70. Ma W, Jovani M, Liu PH, et al. Association between Obesity and Weight Change and Risk of Diverticulitis in Women. Gastroenterology 2018;155:58-66.
71. Rosemar A, Angeras U, Rosengren A. Body Mass Index and Diverticular Disease: A 28-Year Follow-up Study in Men. Dis Colon Rectum 2008;51:450-5.
72. Mattei J, Sotos-Prieto M, Bigornia SJ, et al. The Mediterranean Diet Score Is More Strongly Associated with Favorable Cardiometabolic Risk Factors over 2 Years Than Other Diet Quality Indexes in Puerto Rican Adults. J Nutr 2017;147:661-669.
73. Pai JK, Pischon T, Ma J, et al. Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women. N Engl J Med 2004;351:2599-610.
74. Pradhan AD, Manson JE, Rifai N, et al. C-Reactive Protein, Interleukin 6, and Risk of Developing Type 2 Diabetes Mellitus. JAMA 2001;286:327-34.
75. Ridker PM, Buring JE, Cook NR, et al. C-Reactive Protein, the Metabolic Syndrome, and Risk of Incident Cardiovascular Events: An 8-Year Follow-up of 14 719 Initially Healthy American Women. Circulation 2003;107:391-7.

76. Kanlioz M, Ekici U, Ayva Y. Analysis of Incidental Gallbladder Cancer in Cholecystectomies. Cureus 2019;11:e5710.
77. Alarcon de la Lastra C, Barranco MD, Motilva V, et al. Mediterranean Diet and Health: Biological Importance of Olive Oil. Curr Pharm Des 2001;7:933-50.
78. Esposito K, Giugliano D. Mediterranean Diet and Type 2 Diabetes. Diabetes Metab Res Rev 2014;30 Suppl 1:34-40.
79. Beunza JJ, Toledo E, Hu FB, et al. Adherence to the Mediterranean Diet, Long-Term Weight Change, and Incident Overweight or Obesity: The Seguimiento Universidad De Navarra (Sun) Cohort. Am J Clin Nutr 2010;92:1484-93.
80. Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effects of a Mediterranean-Style Diet on Cardiovascular Risk Factors: A Randomized Trial. Ann Intern Med 2006;145:1-11.
81. Lassale C, Fezeu L, Andreeva VA, et al. Association between Dietary Scores and 13-Year Weight Change and Obesity Risk in a French Prospective Cohort. Int J Obes (Lond) 2012;36:1455-62.
82. Mendez MA, Popkin BM, Jakszyn P, et al. Adherence to a Mediterranean Diet Is Associated with Reduced 3-Year Incidence of Obesity. J Nutr 2006;136:2934-8.
83. Romaguera D, Norat T, Vergnaud AC, et al. Mediterranean Dietary Patterns and Prospective Weight Change in Participants of the Epic-Panacea Project. Am J Clin Nutr 2010;92:912-21.
84. Rumawas ME, Meigs JB, Dwyer JT, et al. Mediterranean-Style Dietary Pattern, Reduced Risk of Metabolic Syndrome Traits, and Incidence in the Framingham Offspring Cohort. Am J Clin Nutr 2009;90:1608-14.
85. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, et al. Mediterranean Diet Inversely Associated with the Incidence of Metabolic Syndrome: The Sun Prospective Cohort. Diabetes Care 2007;30:2957-9.
86. Woo J, Cheung B, Ho S, et al. Influence of Dietary Pattern on the Development of Overweight in a Chinese Population. Eur J Clin Nutr 2008;62:480-7.
87. Appendix E-3.7.A1. Usda Food Patterns: Healthy Vegetarian Patterns—Recommended Intake Amounts. Available At: Https://Health.Gov/Our-Work/Nutrition-Physical-Activity/Dietary-Guidelines/Previous-Dietary-Guidelines/2015/Advisory-Report/Appendix-E-3/Appendix-E-37a1 , Accessed October 13, 2021
88. Appendix E-3.7.A2. Usda Food Patterns: Healthy Mediterranean-Style Patterns—Recommended Intake Amounts. Available At: Https://Health.Gov/Our-Work/Nutrition-Physical-Activity/Dietary-Guidelines/Previous-Dietary-Guidelines/2015/Advisory-Report/Appendix-E-3/Appendix-E-37a2, Accessed October 13, 2021.
89. Drewnowski A, Eichelsdoerfer P. The Mediterranean Diet: Does It Have to Cost More? Public Health Nutr 2009;12:1621-8.
90. Ajzen I. The Theory of Planned Behavior. Organizational Behavior and Human Decision Processes 1991;50(2):179-211.
91. Deci E, Ryan, RM. Intrinsic Motivation and Self-Determination in Human Behavior. . Springer Science and Business Media, New York 1985.
92. Hibbard JH, Stockard J, Mahoney ER, et al. Development of the Patient Activation Measure (Pam): Conceptualizing and Measuring Activation in Patients and Consumers. Health Serv Res 2004;39:1005-26.
93. Selcuk-Tosun A, Zincir H. The Effect of a Transtheoretical Model-Based Motivational Interview on Self-Efficacy, Metabolic Control, and Health Behaviour in Adults with Type 2 Diabetes Mellitus: A Randomized Controlled Trial. Int J Nurs Pract 2019;25:e12742.
94. Schoeppe S, Alley S, Van Lippevelde W, et al. Efficacy of Interventions That Use Apps to Improve Diet, Physical Activity and Sedentary Behaviour: A Systematic Review. Int J Behav Nutr Phys Act 2016;13:127.

95. Fakih El Khoury C, Karavetian M, Halfens RJG, et al. The Effects of Dietary Mobile Apps on Nutritional Outcomes in Adults with Chronic Diseases: A Systematic Review and Meta-Analysis. J Acad Nutr Diet 2019;119:626-651.
96. Https://Nutr.Uw.Edu/Cphn/About-Cphn/Partners/ Accessed October 13, 2021.
97. Arno A, Thomas, S. The Efficacy of Nudge Theory Strategies in Influencing Adult Dietary Behaviour: A Systematic Review and Meta-Analysis. BMC Public Health. 2016;Jul 30; 16:676. doi: 10.1186/s12889-016-3272-x.
98. Strate LL, Morris AM. Epidemiology, Pathophysiology, and Treatment of Diverticulitis. Gastroenterology 2019;156:1282-1298 e1.
99. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose Expression of Tumor Necrosis Factor-Alpha: Direct Role in Obesity-Linked Insulin Resistance. Science 1993;259:87-91.
100. Ventre J, Doebber T, Wu M, et al. Targeted Disruption of the Tumor Necrosis Factor-Alpha Gene: Metabolic Consequences in Obese and Nonobese Mice. Diabetes 1997;46:1526-31.
101. Li J, Lee DH, Hu J, et al. Dietary Inflammatory Potential and Risk of Cardiovascular Disease among Men and Women in the U.S. J Am Coll Cardiol 2020;76:2181-2193.
102. Collaborative C, Flum DR, Davidson GH, et al. A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis. N Engl J Med 2020;383:1907-1919.
103. Certain: Comparative Effectiveness Research Network. Available At: Https://Www.Becertain.Org, Accessed October 13, 2021.
104. Collaborative C, Davidson GH, Flum DR, et al. Antibiotics Versus Appendectomy for Acute Appendicitis - Longer-Term Outcomes. N Engl J Med 2021.
105. Freedman LS, Midthune D, Arab L, et al. Combining a Food Frequency Questionnaire with 24-Hour Recalls to Increase the Precision of Estimation of Usual Dietary Intakes-Evidence from the Validation Studies Pooling Project. Am J Epidemiol 2018;187:2227-2232.
106. Rosen J, Agrawal N, Flum D, et al. Verbal Descriptions of the Probability of Treatment Complications Lead to High Variability in Risk Perceptions. . Annals of Surgery 2021;October 25, 2021 - Volume - Issue - doi: 10.1097/SLA.0000000000005255
107. Friedly JL, Comstock BA, Turner JA, et al. A Randomized Trial of Epidural Glucocorticoid Injections for Spinal Stenosis. N Engl J Med 2014;371:11-21.
108. Albert CM, Ma J, Rifai N, et al. Prospective Study of C-Reactive Protein, Homocysteine, and Plasma Lipid Levels as Predictors of Sudden Cardiac Death. Circulation 2002;105:2595-9.
109. Ridker PM, Hennekens CH, Buring JE, et al. C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women. N Engl J Med 2000;342:836-43.
110. Tabung FK, Smith-Warner SA, Chavarro JE, et al. Development and Validation of an Empirical Dietary Inflammatory Index. J Nutr 2016;146:1560-70.
111. Liu L, Tabung FK, Zhang X, et al. Diets That Promote Colon Inflammation Associate with Risk of Colorectal Carcinomas That Contain Fusobacterium Nucleatum. Clin Gastroenterol Hepatol 2018;16:1622-1631 e3.
112. Jakszyn P, Cayssials V, Buckland G, et al. Inflammatory Potential of the Diet and Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition Study. Int J Cancer 2020;147:1027-1039.
113. Khor S, Flum DR, Strate LL, et al. Establishing Clinically Significant Patient-Reported Outcomes for Diverticular Disease. J Surg Res 2021;264:20-29.
114. Annibale B, Maconi G, Lahner E, et al. Efficacy of Lactobacillus Paracasei Sub. Paracasei F19 on Abdominal Symptoms in Patients with Symptomatic Uncomplicated Diverticular Disease: A Pilot Study. Minerva Gastroenterol Dietol 2011;57:13-22.

115. Kvasnovsky CL, Bjarnason I, Donaldson AN, et al. A Randomized Double-Blind Placebo-Controlled Trial of a Multi-Strain Probiotic in Treatment of Symptomatic Uncomplicated Diverticular Disease. Inflammopharmacology 2017.
116. Tursi A, Brandimarte G, Giorgetti GM, et al. Balsalazide and/or High-Potency Probiotic Mixture (Vsl#3) in Maintaining Remission after Attack of Acute, Uncomplicated Diverticulitis of the Colon. Int J Colorectal Dis 2007;22:1103-8.
117. Papi C, Ciaco A, Koch M, et al. Efficacy of Rifaximin on Symptoms of Uncomplicated Diverticular Disease of the Colon. A Pilot Multicentre Open Trial. Diverticular Disease Study Group. Ital J Gastroenterol 1992;24:452-6.
118. Papi C, Ciaco A, Koch M, et al. Efficacy of Rifaximin in the Treatment of Symptomatic Diverticular Disease of the Colon. A Multicentre Double-Blind Placebo-Controlled Trial. Aliment Pharmacol Ther 1995;9:33-9.
119. Latella G, Pimpo MT, Sottili S, et al. Rifaximin Improves Symptoms of Acquired Uncomplicated Diverticular Disease of the Colon. Int J Colorectal Dis 2003;18:55-62.
120. Colecchia A, Vestito A, Pasqui F, et al. Efficacy of Long Term Cyclic Administration of the Poorly Absorbed Antibiotic Rifaximin in Symptomatic, Uncomplicated Colonic Diverticular Disease. World J Gastroenterol 2007;13:264-9.
121. Lanas A, Ponce J, Bignamini A, et al. One Year Intermittent Rifaximin Plus Fibre Supplementation Vs. Fibre Supplementation Alone to Prevent Diverticulitis Recurrence: A Proof-of-Concept Study. Dig Liver Dis 2013;45:104-9.
122. Parente F, Bargiggia S, Prada A, et al. Intermittent Treatment with Mesalazine in the Prevention of Diverticulitis Recurrence: A Randomised Multicentre Pilot Double-Blind Placebo-Controlled Study of 24-Month Duration. Int J Colorectal Dis 2013;28:1423-31.
123. Tursi A, Elisei W, Giorgetti GM, et al. Effectiveness of Different Therapeutic Strategies in Preventing Diverticulitis Recurrence. Eur Rev Med Pharmacol Sci 2013;17:342-8.
124. Comparato G, Fanigliulo L, Cavallaro LG, et al. Prevention of Complications and Symptomatic Recurrences in Diverticular Disease with Mesalazine: A 12-Month Follow-Up. Dig Dis Sci 2007;52:2934-41.
125. Raskin JB, Kamm MA, Jamal MM, et al. Mesalamine Did Not Prevent Recurrent Diverticulitis in Phase 3 Controlled Trials. Gastroenterology 2014;147:793-802.
126. Kruis W, Kardalinos V, Eisenbach T, et al. Randomised Clinical Trial: Mesalazine Versus Placebo in the Prevention of Diverticulitis Recurrence. Aliment Pharmacol Ther 2017;46:282-291.
127. Kruis W, Meier E, Schumacher M, et al. Randomised Clinical Trial: Mesalazine (Salofalk Granules) for Uncomplicated Diverticular Disease of the Colon--a Placebo-Controlled Study. Aliment Pharmacol Ther 2013;37:680-90.
128. Smith JK, Humes D, Garsed K, et al. Oc-119 Mechanistic Randomised Control Trial of Diverticular Disease. . 2012;Bapen Symposium Free Papers AUGIS Oesophago-Gastric, n.d., 1–2. .
129. Zhang I, Norwitz D, Drewnowski A, et al. Applying Behavioral Nudges in a Dietary Comparator for Surgical Trials: Developing the Medidiet. . https://t.co/LhLKPX6GPm #medRxiv 2021.
130. Sacks FM, Obarzanek E, Windhauser MM, et al. Rationale and Design of the Dietary Approaches to Stop Hypertension Trial (Dash). A Multicenter Controlled-Feeding Study of Dietary Patterns to Lower Blood Pressure. Ann Epidemiol 1995;5:108-18.
131. McCullough ML. Diet Patterns and Mortality: Common Threads and Consistent Results. J Nutr 2014;144:795-6.
132. Dinarello CA. Interleukin-1, Interleukin-1 Receptors and Interleukin-1 Receptor Antagonist. Int Rev Immunol 1998;16:457-99.
133. Ouyang W, Rutz S, Crellin NK, et al. Regulation and Functions of the Il-10 Family of Cytokines in Inflammation and Disease. Annu Rev Immunol 2011;29:71-109.

134. Paulus WJ. Cytokines and Heart Failure. Heart Fail Monit 2000;1:50-6.
135. Johne B, Fagerhol MK, Lyberg T, et al. Functional and Clinical Aspects of the Myelomonocyte Protein Calprotectin. Mol Pathol 1997;50:113-23.
136. Roseth AG, Fagerhol MK, Aadland E, et al. Assessment of the Neutrophil Dominating Protein Calprotectin in Feces. A Methodologic Study. Scand J Gastroenterol 1992;27:793-8.
137. Poullis A, Foster R, Shetty A, et al. Bowel Inflammation as Measured by Fecal Calprotectin: A Link between Lifestyle Factors and Colorectal Cancer Risk. Cancer Epidemiol Biomarkers Prev 2004;13:279-84.
138. van Rheenen PF, Van de Vijver E, Fidler V. Faecal Calprotectin for Screening of Patients with Suspected Inflammatory Bowel Disease: Diagnostic Meta-Analysis. BMJ 2010;341:c3369.
139. Tibble JA, Sigthorsson G, Bridger S, et al. Surrogate Markers of Intestinal Inflammation Are Predictive of Relapse in Patients with Inflammatory Bowel Disease. Gastroenterology 2000;119:15-22.
140. Tibble JA, Bjarnason I. Non-Invasive Investigation of Inflammatory Bowel Disease. World J Gastroenterol 2001;7:460-5.
141. Tursi A, Brandimarte G, Elisei W, et al. Faecal Calprotectin in Colonic Diverticular Disease: A Case-Control Study. Int J Colorectal Dis 2009;24:49-55.
142. Tursi A, Elisei W, Picchio M, et al. Increased Faecal Calprotectin Predicts Recurrence of Colonic Diverticulitis. Int J Colorectal Dis 2014;29:931-5.
143. Godny L, Reshef L, Pfeffer-Gik T, et al. Adherence to the Mediterranean Diet Is Associated with Decreased Fecal Calprotectin in Patients with Ulcerative Colitis after Pouch Surgery. Eur J Nutr 2020;59:3183-3190.
144. Https://Sites.Google.Com/Site/Theipaq/. Accessed March 31, 2021.
145. Martinez-Gonzalez MA, Garcia-Arellano A, Toledo E, et al. A 14-Item Mediterranean Diet Assessment Tool and Obesity Indexes among High-Risk Subjects: The Predimed Trial. PLoS One 2012;7:e43134.
146. Carey A, Yang Q, DeLuca L, et al. The Relationship between Weight Loss Outcomes and Engagement in a Mobile Behavioral Change Intervention: Retrospective Analysis. JMIR Mhealth Uhealth 2021;9:e30622.
147. May CN, Ho AS, Yang Q, et al. Comparing Outcomes of a Digital Commercial Weight Loss Program in Adult Cancer Survivors and Matched Controls with Overweight or Obesity: Retrospective Analysis. Nutrients 2021;13.
148. Toro-Ramos T, Michaelides A, Anton M, et al. Mobile Delivery of the Diabetes Prevention Program in People with Prediabetes: Randomized Controlled Trial. JMIR Mhealth Uhealth 2020;8:e17842.
149. Https://Newsinhealth.Nih.Gov/Special-Issues/Eating/Rough-up-Your-Diet. Accessed Dec. 1, 2021.
150. Schakel SF. Procedures for Estimating Nutrient Values for Food Composition Databases. J Food Comp and Anal. 1997;10:102-114.
151. Schakel SF. Maintaining a Nutrient Database in a Changing Marketplace: Keeping Pace with Changing Food Products - a Research Perspective. J Food Comp and Anal. 2001;14:315-322.
152. Schakel SF, Sievert YA, Buzzard IM. Sources of Data for Developing and Maintaining a Nutrient Database. J Am Diet Assoc 1988;88:1268-71.
153. Prentice RL, Aragaki AK, Van Horn L, et al. Low-Fat Dietary Pattern and Cardiovascular Disease: Results from the Women's Health Initiative Randomized Controlled Trial. Am J Clin Nutr 2017;106:35-43.

154. Beasley JM, Rillamas-Sun E, Tinker LF, et al. Dietary Intakes of Women's Health Initiative Long Life Study Participants Falls Short of the Dietary Reference Intakes. J Acad Nutr Diet 2020;120:1530-1537.
155. Neuhouser ML, Tinker LF, Thomson C, et al. Development of a Glycemic Index Database for Food Frequency Questionnaires Used in Epidemiologic Studies. J Nutr 2006;136:1604-9.
156. Vogtmann E, Chen J, Amir A, et al. Comparison of Collection Methods for Fecal Samples in Microbiome Studies. Am J Epidemiol 2017;185:115-123.
157. Sinha R, Ahsan H, Blaser M, et al. Next Steps in Studying the Human Microbiome and Health in Prospective Studies, Bethesda, Md, May 16-17, 2017. Microbiome 2018;6:210.
158. Pavlidis P, Chedgy FJ, Tibble JA. Diagnostic Accuracy and Clinical Application of Faecal Calprotectin in Adult Patients Presenting with Gastrointestinal Symptoms in Primary Care. Scand J Gastroenterol 2013;48:1048-54.
159. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: Development, Validation and Application of a New Instrument. Br J Surg 1995;82:216-22.
160. EuroQol G. Euroqol--a New Facility for the Measurement of Health-Related Quality of Life. Health Policy 1990;16:199-208.
161. Sofi F, Macchi C, Abbate R, et al. Mediterranean Diet and Health Status: An Updated Meta-Analysis and a Proposal for a Literature-Based Adherence Score. Public Health Nutr 2014;17:2769-82.
162. Horn SD, Gassaway J. Practice Based Evidence: Incorporating Clinical Heterogeneity and Patient-Reported Outcomes for Comparative Effectiveness Research. Med Care 2010;48:S17-22.
163. Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinical Trials. N Engl J Med 2012;367:1355-60.
164. Moelnberghs G KM. Missing Data in Clinical Studies. Wiley; Chichester: 2007;https://scholar.google.com/scholar_lookup?title=Missing+data+in+Clinical+Studies&author=G+Molenberghs&author=MG+Kenward&publication_year=2007&.
165. Juul SE, Comstock BA, Wadhawan R, et al. A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants. N Engl J Med 2020;382:233-243.
166. Thabane L, Ma J, Chu R, et al. A Tutorial on Pilot Studies: The What, Why and How. BMC Med Res Methodol 2010;10:1.
167. Vogtmann E, Chen J, Kibriya MG, et al. Comparison of Fecal Collection Methods for Microbiota Studies in Bangladesh. Appl Environ Microbiol 2017;83:e00361-17.
168. Loftfield E, Vogtmann E, Sampson JN, et al. Comparison of Collection Methods for Fecal Samples for Discovery Metabolomics in Epidemiologic Studies. Cancer Epidemiol Biomarkers Prev 2016;25:1483-1490.

169. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003 Aug;35(8):1381-95. doi: 10.1249/01.MSS.0000078924.61453.FB. PMID: 12900694.