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A dietary intervention to improve the microbiome composition of pregnant women with Crohn's disease and their offspring: The MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy) trial design

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ABSTRACT

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is a chronic condition of the gastrointestinal tract that is caused by the loss of mucosal tolerance towards the commensal bacteria resulting in inflammatory responses. It has long been postulated that the gut microbiota, a complex and dynamic population of microorganisms, plays a key role in the pathogenesis of IBD. Maternal diagnosis of IBD has been identified as the greatest risk factor for IBD in offspring increasing the odds of developing the disease >4.5-fold. Moreover, babies born to mothers with IBD have demonstrated reduced gut bacterial diversity. There is accumulating evidence that the early life microbiota colonization is informed by maternal diet within the 3rd trimester of pregnancy. While babies born to mothers with IBD would pose an ideal cohort for intervention, no primary prevention measures are currently available. Therefore, we designed the MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy) trial to test whether the IBD-AID™ dietary intervention during the last trimester of pregnancy can beneficially shift the microbiome of CD patients and their babies, thereby promoting a strong, effective immune system during a critical time of the immune system development. We will also test if favorable changes in the microbiome can lead to a reduced risk of postpartum CD relapse and lower mucosal inflammation

Abbreviations: MELODY, Modulating Early Life Microbiome through Dietary Intervention in Pregnancy; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-AID™, IBD Anti-inflammatory Diet.

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in the offspring. This study will help create new opportunities to foster a healthy microbiome in the offspring at high risk of other immune-mediated diseases, potentially reducing their risk later in life.

1. Introduction

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is a chronic condition caused by the loss of mucosal tolerance towards gut bacteria resulting in inflammatory responses. Currently, over a million individuals are affected in the United States alone [1], and the incidence is on the rise [2]. Maternal diagnosis of IBD has been identified as one of the greatest risk factors for IBD in offspring, increasing the odds of developing the disease >4.5-fold [3]. Moreover, studies have suggested a higher transmission rate from mothers with IBD compared to fathers [4–6]. It has been postulated that the gut microbiota, a complex and dynamic population of microorganisms, plays a key role in the pathogenesis of IBD [7]. Early-life events impacting microbiota development, such as maternal diet in-utero, feeding behavior, and antibiotics exposure, have been linked to the risk of developing IBD [8–12].

Babies born to mothers with CD are at a substantially increased risk of developing the disease. Furthermore, they have a higher risk of delivery by Cesarean section (C-section) and are less likely to be exclusively breastfed, exposing them to additional risk factors linked to future IBD [10,13,14]. Our team has previously demonstrated that babies born to mothers with IBD had a higher abundance of pro-inflammatory *Proteobacteria* and depletion of beneficial *Bifidobacteria* compared to babies born to control mothers [15]. When inoculated into germ-free mice, the microbiome of babies born to mothers with CD induced the development of an imbalanced immune system [15]. Recently, altered microbiome in early life has been linked to the risk of developing asthma, eczema, allergy, autism, type 1 diabetes and other immune-mediated diseases [16–20]. These findings suggest that modulating the microbiome in early life could be an efficient approach to promote a stronger immune system and potentially reduce CD risk later in life.

Several studies have shown that maternal diet impacts the offspring's microbiome assemblage and composition and immune system development, with potential consequences on health outcomes [21,22]. In babies, the early life microbiota is reportedly informed by maternal diet within the 3rd trimester of pregnancy [23]. In murine models, pups born from mice exposed to a high-fat diet during pregnancy exhibited altered disease susceptibility and exacerbated colonic inflammation [24]; phenotypes which were correlated to inheritance of an altered microbiota. Maternal diet during pregnancy is key in shaping microbiota to be transmitted to the offspring, which in turn may affect susceptibility to disease later in life. The MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy) trial is designed to test whether the IBD-AID™ dietary intervention during the last trimester of pregnancy can beneficially shift the microbiome of CD patients and their babies, promoting a strong immune system during a critical time of the immune system development. We will also test if favorable changes in the microbiome can lead to a reduced risk of postpartum relapse and lower mucosal inflammation in the offspring. This study will help create new opportunities to foster a healthy microbiome in the offspring at high risk of other immune-mediated diseases, potentially reducing their risk later in life.

2. Study approach and design

2.1. Study objectives

The MELODY Trial is a two-center non-randomized dietary intervention trial aimed to investigate whether or not following an anti-inflammatory diet during the 3rd trimester of pregnancy in women with CD can increase the diversity and restore homeostasis of their gut microbiome and reduce the risk of post-partum flares, as well as lead to the colonization of a healthier microbiome in their babies, compared to pregnant CD patients not following the diet.

2.2. Target population and setting

The MELODY Trial is being conducted at the Icahn School of Medicine at Mount Sinai (ISMMS) in New York, NY and the University of Massachusetts Medical School (UMMS) in Worcester, MA. Both sites are tertiary medical centers with inpatient and outpatient obstetrics/gynecology and gastroenterology (GI) departments and clinics. The study includes three arms: 1. Pregnant CD patients counseled and following the IBD-AID™ (CD IBD-AID™ intervention), 2. Pregnant CD patients following their habitual diet (CD, no intervention), and 3. Pregnant controls (no CD, no intervention). The study is approved by Institutional Review Boards at each institution (IRB docket #H00016462 at the University of Massachusetts and #18–01206 at the Icahn School of Medicine).

2.3. Recruitment strategies

Pregnant women with CD enrolled in other ongoing studies at ISMMS and UMMS are invited to participate. Also, we reach out to clinicians that care for pregnant women and patients with CD to identify eligible study subjects. Specifically, our research team provides educational sessions to the health care providers within our networks to maximize reach for recruitment. Thus, health care providers including IBD patient caregivers, obstetricians and pediatricians can introduce the study to potential participants and provide contact details of women (with and without CD) who are interested in participating to the research team. After a patient referral, the clinical research coordinators contact the potential study participants to explain the study, confirm eligibility, and obtain informed consent over the phone (e-consent is also available).

Additionally, we search electronic medical records at our institutions for an intersection of ICD-9 and ICD-10 (the International Classification of Diseases codes, 9th and 10th revision) for pregnancy and Crohn's disease to identify potential study participants, who then receive a letter of invitation to participate in the study via mail. Letters are sent to women with more than 14 weeks of pregnancy. Interested prospective mothers then contact the clinical research coordinators via e-mail or phone to establish eligibility and consent for participation.

Furthermore, we are advertising through professional foundations (e.g., the Crohn's and Colitis Foundation, the New York Crohn's and Colitis Organization) and using IBD patient advocacy groups on social media to increase our outreach within the patient and physician communities. To reach a larger audience that also includes healthy pregnant women, as well as women with CD, we have also launched social media campaigns through the UMMS Center for Applied Nutrition Facebook, Twitter, and Instagram accounts. Moreover, Google ads have been utilized to increase visibility. Interested patients are redirected to the UMMS Center for Applied Nutrition website where they can solicit additional information about the study. After this initial contact, patients are contacted by clinical research coordinators to establish eligibility and secure study enrollment.

2.4. Inclusion and exclusion criteria

Women are being included if they are willing to participate in the trial, can sign informed consent, carry singleton pregnancy, and have documented CD diagnosis or are willing to serve as healthy controls. The diagnosis of CD is based on patient's history and clinical examination and supported by serologic, radiologic, endoscopic, and histologic

findings by gastroenterologists [25]. For patients recruited within the hospitals affiliated with our institutions, CD diagnosis is confirmed through medical chart reviews. For participants attending non-affiliated hospitals nation-wide, we request that treating gastroenterologists or medical providers confirm the diagnosis. The exclusion criteria are inability to provide informed consent, HIV/AIDS, multi-fetus pregnancy, fetal chromosomal or structural abnormalities, intrauterine growth restriction, active infection (including chorioamnionitis or sepsis), alcohol use disorder, diagnosis of diabetes or renal disease, or dietary regime that conflicts with the IBD-AID™. Also, pregnant CD patients who have active perianal or extra-intestinal disease or are treated with antibiotic therapy or steroids at recruitment, as well as women scheduled for C-section prior to week 37, are being excluded.

2.5. Screening

At screening (week 27–29), eligible patients wishing to participate in the IBD-AID™ intervention are asked to provide a note from a treating physician indicating that a potential study subject does not have any contraindications to participate in the study. In a letter sent to the treating physicians we stress that they have complete freedom to treat pregnant women according to the disease and pregnancy state at any time during or after the trial and to change or add medical therapy as needed. Written or online informed consent is obtained from each study participant.

2.6. The IBD-AID™ diet

Diet may play a role in the pathogenesis and treatment of IBD [26,27]. Exclusive enteral nutrition (EEN) has been shown to induce remission and mucosal healing in children [28–30] and adults with CD [31]. However, EEN can only be used short-term [32,33]. It has been suggested that the primary effect of dietary therapy is exclusion of dietary components that may cause dysbiosis, and increase of beneficial foods that alter innate immunity or affect the barrier function [34,35]. Other diets have gained popularity among IBD patients, namely: Specific Carbohydrate Diet, the Crohn's Disease Exclusion Diet, and FODMAPS [36–38]. However, while those diets have shown evidence of assisting patients during disease flares [37–42], they are focused mainly on *exclusion* of foods, which may be difficult to sustain long-term and can result in nutritional deficiencies. Moreover, these *exclusion* diets do not consider the variation between patients' manifestations of the disease. Thus, the dietary pattern recommendations are universally applied despite differences in patient digestion, absorption, severity of disease, and symptoms.

To prepare clinicians for the complex management of IBD patients, we developed the IBD-Anti-Inflammatory Diet or IBD-AID™ [43–46]. This is a culinary diet that addresses nutrient adequacy and malabsorption issues, promotes symptom relief, and assists with remission. The IBD-AID™ is rooted in substitution of adverse foods and *inclusion* of foods thought to favor bacterial species responsible for modulating the local immune response, while providing needed nutrients to the patient. Building upon that understanding, the IBD-AID™ has been designed to favor short chain fatty acid (SCFAs) bacterial producers [47]. SCFAs are produced in the colon by the gut microbiota and are the end products of anaerobic fermentation of dietary fibers in the small intestine. High levels of SCFAs then promote a hyporesponsive immunological environment to commensal bacteria through the down-regulation of pro-inflammatory cytokines and chemokines (TNF-α, IL-2, IL-6 and IL-10), eicosanoids, and chemokines (*e.g.*, MCP-1 and CINC-2) by acting on macrophages and endothelial cells, aiding homeostasis maintenance [48,49]. Thus, the IBD-AID™ emphasizes foods known to have beneficial *probiotic* (e.g. yogurt, aged cheese, kefir, fermented cabbage, etc.) or *prebiotic* (e.g. legumes, onions, artichokes, leeks, etc.) properties to sustain beneficial bacteria known to maintain gut homeostasis (Table 1).

To support nutrient adequacy, the IBD-AID™ is also based on a balance of nutrients (aligned with the Alternative Healthy Eating Index, or AHEI [50,51]), through *substitution* of avoided foods. IBD-AID™ foods are additionally staged in phases 1–3 (see Table 2), according to the patient's symptomology (bleeding, stool frequency, urgency and consistency), and texturally modified to improve digestive absorption. Improved symptoms indicate the patient is ready to move to the next phase, adding a wider variety of textures and foods. Each phase includes prebiotic foods, probiotic foods, and optimal nutrient and caloric intake. For detailed information on the IBD-AID™ foods, recipes, and phases, please visit: https://www.umassmed.edu/nutrition/ibd/ibdaid/.

We have previously demonstrated that when adopting the IBD-AID™ for four or more weeks, all patients were able to work with their gastroenterologists to downscale their medication regimen, and all of the patients had their IBD symptoms reduced [35]. More recently, we have found that IBD-AID™ is able to reduce CD activity in adults, as assessed by patient-reported symptoms, clinician notes and medical records, validated questionnaires [52,53], and microbiota signatures that have been associated with colonic health (unpublished). Specifically, we observe an increased abundance of SCFAs-producing bacteria after intervention along with declines in putative pathogenic strains [54], such as *Escherichia* sp. Table 1 summarizes the four main principles of the IBD-AID™.

2.7. The intervention

After screening, CD patients at 27–30 weeks of pregnancy are self-selected to 1) a 7 to 10-week IBD-AID™ intervention (CD IBD-AID™ intervention, anticipated N = 66, Fig. 1) or 2) habitual diet with no intervention (CD no intervention, anticipated N = 66). Unaffected controls follow habitual diet and receive no intervention (anticipated N = 66). The diet is adapted to address specific needs of 3rd trimester pregnancy without compromising the IBD-AID™ principles (Table 1). Recipes and dietary support, shopping tips, videos and cooking classes for didactic and experiential learning are provided by trained dietitians.

Patients from all groups receive recommendations regarding adequate nutritional intake according to guidelines for 3rd trimester [55]. Patients may continue all supplements and medications as recommended by their physician or dietitian.

Study registered dietitians are required to attend 2 4-h training sessions on the IBD-AID™ consulting protocol, with required homework, prior to engaging with the patients. Dietitians are provided with scientific background of diet and IBD, trained to use the patient-centered counseling approach, and educated in IBD complications. Case studies are presented, with opportunity to practice counseling objectives. Handouts, resources, and ongoing support from the senior dietitian are available. All calls are recorded for quality assurance and training purposes.

Patients in the CD IBD-AID™ intervention arm receive instructions to adopt the IBD-AID™. There is an initial consult to assess the patient's current diet and lifestyle, and subsequent weekly or bi-monthly calls as

Table 1
Principles of the IBD-AID™.

Component	IBD-AID™
1. Prebiotic Foods	E.g.; Sources of soluble fiber and inulin: including oats, legumes, peas, certain seeds, nuts, asparagus, onions, leeks, spinach and other greens, banana, papaya
2. Probiotic Foods	E.g.; Yogurt, miso, kefir, sauerkraut, kimchi, cultured foods and beverages
3. Foods Emphasized	Beneficial fatty acids such as mono- and omega-3 fatty acids, e.g. avocado, nuts and seeds, safe fish Essential nutrients and other components balanced for participant and baby needs, delivered in phases appropriate to participant's digestive and absorptive ability
4. Foods Avoided	Sucrose, lactose, artificial sweeteners, certain emulsifiers, wheat, corn, white potatoes, many processed foods, *trans*-fatty acids, limit saturated fats (from all animal sources)

Table 2
IBD-AID™ phases according to patient's symptomatology and food tolerance.

Phases		
Phase	Why should I be following this phase?	Examples of Foods
I Soft foods, pureed foods, no seeds	Currently experiencing a flare, any bleeding, urgency, high frequency of bowel movements or pain. This phase emphasizes soft and pureed foods using a blender.	*Smoothies, well-cooked groats or steel cut oats, ground flax, pureed soups, pureed vegetables, yogurt and miso, and ground lean meats.*
II Soft textures, well-cooked, no seeds. May still need to avoid stems, choose floppy greens or other greens depending on individual tolerance.	Symptoms have improved significantly but are not completely alleviated. You may be able to tolerate some fiber but might still have trouble digesting foods high in fiber and fat. More fibrous foods are added in this phase, in the form of soft cooked vegetables and pureed beans/lentils. Increase water and probiotic foods.	*Soft greens, well-cooked lean meats, aged cheeses, nut butters, tomatoes, pureed berries with seeds strained out, and foods baked with IBD-AID™ friendly flours (bean flours, nut flours).*
III If in remission with no strictures, gradually increase intact fiber intake.	Your symptoms are gone. You are feeling stronger and are becoming more comfortable eating a greater variety of foods. Your bowel movements are well controlled and solid.	*Stir-fried vegetables, cruciferous vegetables, lean proteins, citrus fruits, whole beans, and whole nuts. Individualize per tolerance.*

needed until the patient has reached compliance or the extent to which they can change. Our experienced team of dietitians utilizes the Patient-Centered Counseling Model (PCCM), developed at UMMS, to deliver IBD-AID™ dietary instructions [56]. The PCCM is a unique and supportive care structure proven to achieve diet adherence and compliance. The PCCM uses strategies consistent with social cognitive theory to facilitate dietary change (Table 3) [56,57]. With this model, interventions are targeted to create appropriate outcome expectations, build self-efficacy, and encourage self-monitoring, goal-setting and problem-solving skills to manage behaviors related to dietary intake [58,59]. For the MELODY Trial, trained registered dietitians deliver personalized behavioral counseling and coaching to guide participants in making and maintaining a dietary lifestyle change to the IBD-AID™ in the 3rd trimester. The dietitian asks questions, carefully assesses current diet and lifestyle and provides recommendations for adherence to the IBD-AID™. Dietitians provide resources tailored to the unique needs, culture, socioeconomic status, and lifestyle of each family. These include tips on buying and preparing IBD-AID™ healthy foods and meals, provision of menu plans, and training of skills in the kitchen through in-person classes and videos provided on the website [60].

2.8. Tracking and improving adherence to intervention

Promoting a sustainable dietary behavior is challenging. Examples from data about dietary recommendations in Australia [60] demonstrate that it is not enough to suggest that people consume a healthy diet; there is a need to match cuisine elements in the diet with traditional foods and promote preparation methods for healthy foods. Therefore, we created a password-protected portal within the UMMS Center for Applied Nutrition website, where patients in the CD IBD-AID™ intervention arm can find helpful material and tools to increase diet adherence and compliance. These tools include a series of 10 videos featuring a local chef who demonstrates cooking skills necessary to "break into the kitchen." We also provide videos for: 1) "setting up your pantry for IBD-AID™", 2) a tour of a local grocery store, and 3) cooking instructions to specific IBD-AID™ recipes. In this website, we have also posted shopping lists, more than 500 IBD-AID™ approved recipes, appropriate choices from menu options at restaurants, and advice for when eating with family and friends. For local participants we also provide cooking classes

Table 3
Principles of the patient-centered counseling model.

Social Cognitive Theory Construct	Strategies
Knowledge – patient understanding of what constitutes a healthy IBD Diet	Provide information about IBD-AID™ and its components important for mom and baby's health
Outcome expectations – the anticipated benefits of the behavior change	Identify outcomes that will motivate the patient to engage in the behavior change
Behavioral capability – the knowledge and skills to perform a behavior, learned through goal setting, problem solving, self-monitoring and self-reward; includes patient and family ability to set goals, problem solve challenges, track progress, reinforce behavior change	Practical skills training, including goal setting, strategies to engage the patient, identifying barriers/problem solving solutions, cooking and shopping skills, videos, website resources, homework assignments to apply skills learned; provide encouragement for positive changes made
Self-efficacy – the patient's confidence in performing the behaviors, found to predict behaviors including specific dietary changes and exercise	Set specific and attainable goals; track successes [61,62]

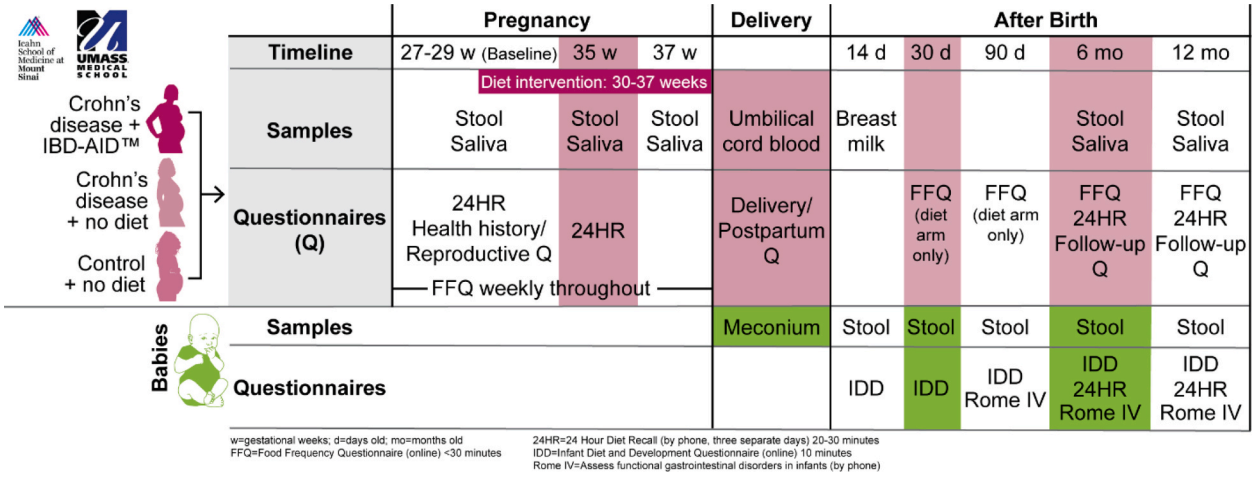

Fig. 1. Study design.

throughout the intervention period.

We also distribute monthly newsletters with useful tips and new ways of adding ingredients to foods; thus, patients are constantly engaged with information regarding IBD-AID™.

We closely monitor patient progress, performing weekly check-ins during the intervention (at 30 through 37 weeks of pregnancy) by experienced dietitians. Web and telephone-based consultations are performed to assess dietary compliance and nutritional state and to adjust the diet as needed. We do not exclude non-adherent patients but try to negotiate the diet with patients willing to continue in the study as partial adherence may be sufficient to beneficially alter the microbiome and achieve the desired outcomes.

2.9. Data collection

At recruitment (27–29 weeks of pregnancy), demographics and health history are collected on all study participants (Fig. 1). Clinical information, including disease severity using the Harvey-Bradshaw Index (HBI) [63] is captured using a set of validated questionnaires and later confirmed using electronic medical records or verified medical records. All current drugs or medications are logged into a case report form. After delivery, mode of delivery (C-section or vaginal), need for antibiotics, maternal *Streptococcus B* carriage, birth weight, Apgar scores and newborn health status are recorded. We also collect information on baby's feeding behavior (exclusive breastfeeding, exclusive formula feeding or mixed), health status, vaccinations, medications, and other exposures throughout the first year of life using established questionnaires [15]. Mothers are asked to record antibiotic use during the first year for both mother and infant and time of introduction of solid foods. Infants' colic and other functional gastrointestinal symptoms will be assessed at 90 days, 6 months, and 12 months using the new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers [64]. A 24-h behavior diary will be used to confirm the total amount of crying and fussing and the regurgitation frequency, defined as the involuntary retrograde passage of gastric contents into the esophagus, two or more times per day for three or more weeks in the absence of retching, hematemesis, aspiration, apnea, failure to thrive, abnormal posturing or feeding or swallowing difficulties [64].

2.10. Dietary assessment

Assessment of diet is challenging due to numerous limitations, including self-report bias and weakness in methodology. Thus, a combination of tools is required to maximize precision and validity of the assessment. We assess dietary compliance by employing a combination of 24-h dietary recalls (24HDRs) and our specially designed *pre*biotic and *pro*biotic food frequency questionnaire (FFQ, or PREPRO FFQ) during intervention and post-partum using the University of Minnesota's Nutrition Coordinating Center's (UM-NCC) Nutrition Data System for Research software (current version: NDS-R, 2019, updated yearly) as previously described [65–68]. Three 24HDRs (2 weekdays and one weekend intake day to capture in-depth dietary quality) are administered by a non-intervention study dietitian and are repeated at baseline and at week 35, and then at 6 and 12 months postpartum to capture the variability of the diet longitudinally (Table 4).

In addition, food intakes are recorded weekly from baseline (27–29 weeks) to 37 weeks of gestation and at 6 and 12 months after delivery using a custom self-administered PREPRO FFQ developed by our team. Participants in the CD IBD-AID™ intervention arm will also complete the PREPRO FFQ at 1 month and 3 months post-partum, to evaluate adherence to the diet after delivery (Table 4). The PREPRO FFQ is unique as it measures *pre*biotic and *pro*biotic foods as well as beneficial and adverse food intake. Using the PREPRO FFQ, the four main principles of the IBD-AID™ are measured, both individually and combined, and used to estimate the IBD-AID™ scores. Pre- and probiotic foods are not captured by NDS-R; thus, the two methods of dietary assessment are complementary.

Infant feeding history with emphasis on duration of exclusive or mixed breast feeding, type of formula, and timing of the first introduction of complementary foods will be recorded from phones call with mothers at 6- and 12-months post-partum (Table 4).

There will be 3564 phone calls conducted to collect 24HDRs over the length of the study. 198 mothers will complete 12 phone calls about their own diet as well as 6 phone calls to report their babies' diet, for a total of 2376 calls regarding maternal diet and 1188 calls regarding infant diet.

2.11. Biospecimen collection

Maternal stool and saliva and babies' diapers are collected at home using a collection kit with detailed instructions and shipped to the lab overnight on ice (Fig. 1). We collect pregnant participants' stool and saliva samples at baseline (27–29 weeks, for CD patients on habitual diet and for controls) or before the initiation of the diet (for the CD IBD-AID™ intervention arm), at week 35 and at 37 weeks, as well as at 6 and 12 months postpartum (Fig. 1). Umbilical cord blood is collected from the umbilical cord vein within 10 min after the placenta is delivered and the umbilical cord is cut (Table 5). Blood is drawn using a butterfly needle and vacutainer into at least one 7.0 mL EDTA whole blood collection tube and one 7.0 mL serum collection tube. EDTA tubes are stored at −20 °C; serum tubes are centrifuged to isolate cord blood serum and stored at −80 °C. Baby's stool samples include the meconium, a first stool discharge, and diapers collected at 14 days, 30 days, 90 days, 6 months, and 1 year as described previously [15]. Breast milk is collected in a 3.0 mL sterile vial via self-sampling by mothers at 14 days after birth, if mothers are breastfeeding their baby.

3. Study outcomes

3.1. Primary outcomes

Maternal:

- Diet-dependent changes of the gut microbiome pre- and post-IBD-AID™ intervention.

Offspring:

- Differences in the relative abundance of *Proteobacteria* and *Bifidobacterium,* and the overall alpha- and beta-diversity at 14 days, 30

Table 4
Timeline of dietary assessment.

Tool	Baseline (27–29 weeks, w)	Intervention								Post-partum			
		30 w	31 w	32 w	33 w	34 w	35 w	36 w	37 w	1 month (m)	3 m	6 m	12 m
PREPRO FFQ	X	X	X	X	X	X	X	X	X	X[a] Mom	X[a] Mom	X Mom	X Mom
24HDRs	3 calls	3 calls at week 35										3 calls for mom 3 calls for baby	3 calls for mom 3 calls for baby

[a] Indicates that assessment only applies to mothers participating in the CD IBD-AID™ intervention arm.

Table 5
Timeline of biospecimen collection.

Time-point	Pregnancy			Delivery	Post-partum				
	27–29 weeks	35 weeks	37 weeks		14 days	30 days	90 days	6 months	12 months
Mother	Stool Saliva	Stool Saliva	Stool Saliva	Umbilical cord blood	Breast milk			Stool Saliva	Stool Saliva
Baby				Meconium	Stool	Stool	Stool	Stool	Stool

days, 90 days, 6 months, and 1 year between babies born to mothers with CD who followed IBD-AID™, babies born to mothers with CD who followed habitual diet, and babies born to control mothers. These bacterial taxa were selected based on our findings that babies born from moms with IBD have a significant enrichment in *Proteobacteria* and depletion in *Bifidobacterium* [15].

3.2. Secondary outcomes

Maternal:

- Differences in the metabolite levels in the umbilical cord blood of CD patients who followed the diet, CD patients on habitual diet, and controls. We will use a metabolomics panel to profile >11,000 biochemicals, with the focus on bacterial and SCFA metabolism.
- 1-year postpartum disease relapse. Maternal CD activity will be assessed at 6 and 12 months postpartum through chart reviews or medical record release forms to evaluate a disease relapse defined as Harvey Bradshaw Index (HBI) > 4 for >1 week [69] and, when available, endoscopy results and biomarkers. The development of a serious disease-related complication, need for surgery or hospitalization due to disease worsening, or for change in therapy or escalation of therapy [69], as determined by a treating gastroenterologist or electronic medical records, will also be recorded.
- Sustained remission is defined as HBI<5[63] since institution of the diet through 6 or 12 months. Time to relapse is defined as the number of weeks until first documented flare.

Offspring:

- Longitudinal changes in the microbiome diversity during the first year of life as a function of maternal CD diagnosis, dietary assignment and other early life events.
- Baby's functional gastrointestinal disorders, defined according to the new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers [64].
- 1-year baby fecal calprotectin, a recognized surrogate marker of intestinal inflammation [70,71]. Of importance, we showed that babies born to mothers with IBD had higher fecal calprotectin levels at 1 year compared to those born to mothers with no IBD [72]. Calprotectin levels have been shown to correlate with relative abundance of *Gammaproteobacteria* [72].

4. Data analysis

Continuous outcomes will be analyzed using multivariate linear regression models for cross-sectional analyses or generalized estimating equations (GEE) and mixed effects models for repeated measurements. Binary outcomes will be analyzed using logistic regression to estimate odds ratios associated with the IBD-AID™ intervention compared to respective control groups. All analyses will be adjusted for maternal medications during pregnancy, gestational age, mode of delivery, and infant early life exposures (breastfeeding, antibiotic use, and timing of solid food introduction). Case-only analyses will be adjusted for maternal disease activity and CD-directed medications.

4.1. 16S rRNA gene sequencing

Total DNA will be isolated from stool samples using a bead beating method and amplified at the phylogenetically informative V3-V4 region of bacterial *16S rRNA* gene. Reads will be quality filtered, demultiplexed, grouped into sequence variants and assigned with taxonomic classification using QIIME2 [73] and DADA2 [74]. We will assess the diversity of the overall microbiota communities within or across each sample, and calculate the core diversity metrics (α- and β-diversity) using Faith's phylogenetic diversity [75] and unweighted UniFrac [76] distances. The PERMANOVA test will be performed to test the overall microbiota differences by intervention group (e.g., CD IBD-AID™ intervention vs. CD no intervention vs. no CD, no intervention). Unweighted distance matrices and sample metadata will be visualized in multidimensional scaling (MDS) plots. A generalized linear model will be used to identify candidate taxa associated with the intervention, taking into account other confounders.

4.2. Metagenomic analysis

We will select the most informative mother-baby pairs (~20 pairs from each group) based on the largest differences in bacterial diversity (presence/absence and abundance by unweighted UniFrac distances) between the groups, as determined by *16S rRNA* gene sequencing. Metagenomic analyses will be performed as described elsewhere [77]. Briefly, following fragmentation and library preparation, sequencing will be performed on the Illumina HiSeq platform on high-throughput mode. Raw sequencing data will be processed and mapped to bacterial genomes to obtain species and strain-level information, as well as to characterize bacterial pathways present in each sample. Species-level identification will be performed using Ensemble, a novel method for accurate bacterial species identification developed at the Clemente lab. Strain-level identification will be performed using ConStrains [78] and LSA [79]. Finally, bacterial gene and pathway information will be annotated using Humann2 [80]. Next, we will use *PICRUSt* [81] to predict bacterial functions based on the operational taxonomic units (OTU) table generated from *16S rRNA* gene sequencing data. Accuracy of *PICRUSt*-predicted data will be estimated by comparing it against the metagenomic-sequenced data on the subset of samples. The resulting metagenomic data will be further analyzed using the HUMAnN (HMP unified metabolic analysis network) pipeline [82] to allow for annotation and testing of metabolic pathway abundance as an alternative to isolated bacterial genes. We will look for enriched or depleted microbial strains associated with maternal CD status and dietary intervention group using a Fisher's exact test. Also, for mother-baby pairs, at 37 weeks of pregnancy and 90 days, respectively, we will determine particular bacterial strains and/or related metabolites transmitted from the mother to the baby that can serve as direct targets for intervention. We will investigate if particular microbiome features identified in the metagenomics analysis remain or disappear from the gut of babies. Then bacterial retention at different time points will be compared between maternal dietary groups using a Chi-square test. Sensitivity analyses will be carried out according to compliance with the study interventions. Primary results presented under the mixed-model analysis will assume that missing data follow a missing-at-random framework.

4.3. Metabolomic analysis

Biochemicals in the umbilical cord blood will be measured using HD4 Global *Metabolomics Profiling* Screens (Metabolon Inc., Morrisville, NC). These data will complement the metagenomics sequencing analysis by allowing to identify not only bacterial strains passed by the mother to the baby, but also detect bacterial *products* (e.g., antibodies, metabolites) transmitted through the cord blood.

4.4. Proteomic analysis

Proteomics data will be generated on breast milk samples using the *Olink* Inflammation Panel, which is a high-throughput, multiplex immunoassay enabling analysis of 92 inflammation-related protein biomarkers using the PEA technology.

4.5. Fecal calprotectin

Levels of fecal calprotectin, a suitable surrogate marker of intestinal inflammation [70,71], will be measured in maternal samples and in baby stool samples collected at up to 1 year using a quantitative enzyme immunoassay (CalproLab™ Calprotectin ELISA, CALPRO AS, Norway).

To identify specific biomarkers associated with dietary intervention, the cord blood metabolites, breast milk inflammatory proteins and fecal calprotectin levels will be compared between the dietary groups using Kruskal Wallis test, followed by pairwise Wilcoxon rank sum test while adjusting for multiple hypothesis testing. The Spearman's correlation analysis will be used to identify correlations of the biomarker levels with bacterial diversity and relative bacterial abundance.

5. Sample size estimation

Recent reports from the Cochrane Nursing care Network [83] and others [84] stated that the lack of studies with large sample size (power) are among the major challenges to determine whether dietary interventions relate to outcomes. For the proposed study, the primary hypothesis is that the IBD-AID™ intervention can increase the diversity and restore homeostasis of the maternal gut microbiome. Therefore, we estimated a sample size needed to determine differences in microbial abundance before and after the dietary intervention. Using a two-sided, paired *t*-test, assuming $p < 0.05$, an effect size of 0.9, and statistical power of 0.8, we need 13–14 individuals. However, to allow for subgroup analysis, we doubled the number of individuals to account for differences in maternal medications ($n = 14x2 = 28$) and doubled again to also account for mode of delivery ($n = 28x2 = 56$). Moreover, we expect ~20% dropout rate and loss to follow up, thus our goal is to recruit 66 CD patients self-selected to IBD-AID™ (CD IBD-AID™ intervention), 66 CD patients self-selected to habitual diet (CD no intervention), and 66 unaffected controls on habitual diet with no intervention (no CD, no intervention).

6. Discussion and summary

Accumulating evidence suggests that maternal health, perinatal environmental exposures and microbial colonization during early life exert marked effects on immune and metabolic programming in the baby with long-term health-related consequences [85], including the predisposition to IBD and other immune-mediated diseases [86,87]. The MELODY trial is aimed to investigate if bacterial manipulation through diet during the 3rd trimester of pregnancy will improve the microbiome composition in the gut of CD patients and lead to the development of a healthier microbiome in the offspring.

We considered a randomized study design for pregnant women with CD, however, this diet requires shopping, cooking, and planning skills in order to reach the dietary objectives. There is a distinct educational component that requires time and attention, even if facilitated by nutritionists. Since diet is both extrinsically and intrinsically motivated [88] and compliance is closely associated with these factors, we agreed on a self-selected intervention design to improve adherence to protocol.

This study will also inform whether a multifaceted dietary intervention may reduce the risk of postpartum flares in the patients and gastrointestinal symptoms and mucosal inflammation in the baby. If successful, the IBD-AID™ could be applicable in clinical practice.

Our study may inform the design of future large-scale intervention studies with the goal of primary risk prevention in high-risk babies born to mothers with immune-mediated diseases. We anticipate that both the expected (and unexpected) data outcomes from this study will stimulate further studies evaluating how the present protocol may be further pursued by the examination of feeding practices in moms, babies and children. We will also generate an extensive collection of serial samples and longitudinal clinical data, including identification of specific dietary components correlated with certain functional and quantitative bacterial patterns for future investigations.

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CRediT author statement

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