
2023 SCSG
GI SYMPOSIUM

Disorders of the Brain Gut Axis: DDW Abstracts 2023

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Disclosures

- Ardelyx Scientific Communications Advisory Board for IBS-C

Objectives

- Highlight notable abstracts from DDW 2023
- Focus on studies of lower disorders of gut-brain interaction (functional bowel disorders)
- Summarize key findings

The Colonic Biological Clock and Predictability of Time of Bowel Movements During Treatment With a Vibrating Capsule (Vibrant®) in Patients With Severe Chronic Idiopathic Constipation

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Background & Aims

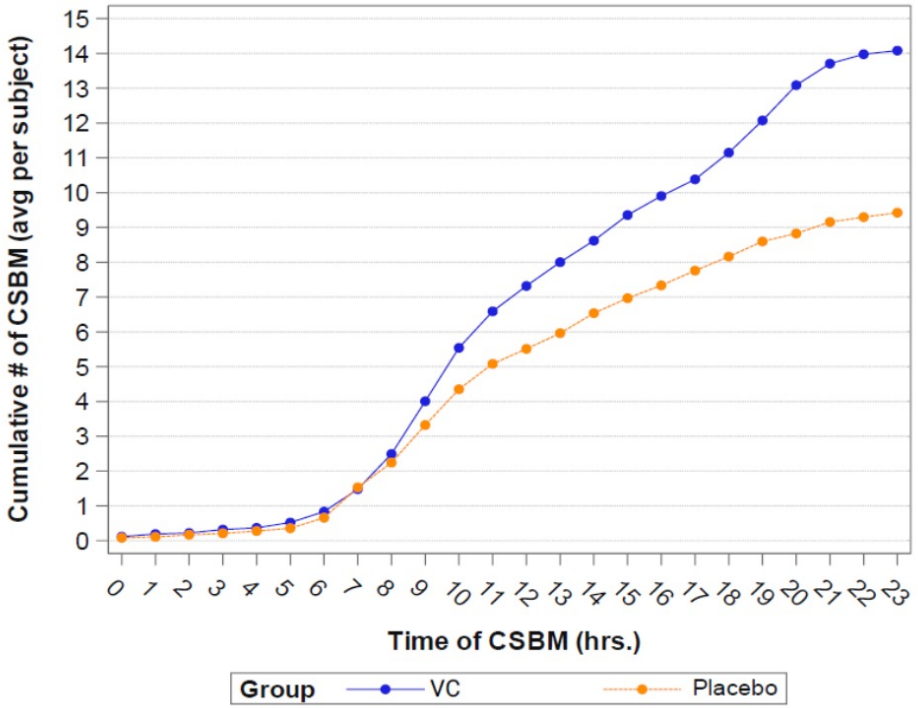
- Healthy subjects defecate after activation of high amplitude propagating contractions (HAPC), mainly after waking and/or after a meal, a pattern attributed to the colonic biological clock regulated by circadian rhythms.
- Circadian rhythm and diurnal distribution of bowel movements have not been investigated in patients with Chronic Idiopathic Constipation (CIC).
- Prior studies demonstrate that a vibrating capsule (VC) significantly increases complete spontaneous bowel movements (CSBMs) compared to placebo in CIC (*FDA marketing authorization 8/30/2022*).
- **Aim: To examine the diurnal distribution of CSBMs in severe CIC patients who were treated with VC or placebo.**

Methods

- **Study Design:** Post-hoc analysis from the phase 3, multicenter, randomized, double-blind, placebo-controlled, 8-week trial of a VC (Vibrant®, Yokneam, Israel) in CIC
- **Participants:** Subgroup with severe CIC defined by 0 CSBMs reported on electronic diaries during 2- to 3-week baseline period
- **Study procedures:** Capsules were taken at 10 pm with activation of the VC programmed to occur 14 hours later
- **Study outcomes:** (1) Time of occurrence of CSBMs and (2) CSBM responder rates (defined as % of subjects with increases of at least 1 or 2 weekly CSBMs over baseline for 75% of treatment weeks)

Results: CSBMs Occur Later the Day

- **Participant characteristics:** CIC subgroup comprised 175 (56%) of 312 enrolled in the Phase III trial
- CSBMs occurred later in the day in both groups
- Cumulative average significantly higher for VC vs. pcbo during hours 18:00 to 22:00



Results: Stratification of Cumulative Number of CSBMs Between 18:00 and 2:00 for 8-week Period

	VC			Placebo			p-value
	N	n	%	N	n	%	
At least 1 C SBM	89	43	48.31%	86	27	31.40%	0.0224
At least 2 C SBM	89	32	35.96%	86	14	16.28%	0.0031
At least 3 C SBM	89	22	24.72%	86	9	10.47%	0.0135
At least 4 C SBM	89	18	20.22%	86	8	9.30%	0.0423
At least 5 C SBM	89	17	19.10%	86	4	4.65%	0.0033
At least 6 C SBM	89	15	16.85%	86	4	4.65%	0.0095
At least 7 C SBM	89	12	13.48%	86	2	2.33%	0.0065
At least 8 C SBM	89	10	11.24%	86	2	2.33%	0.0197
At least 9 C SBM	89	9	10.11%	86	2	2.33%	0.0339
At least 10 C SBM	89	9	10.11%	86	1	1.16%	0.0182

- Stratification revealed significantly more CSBMs for VC vs placebo during this time period (Table).
- Significantly greater number of CSBM responders with severe CIC in the VC group vs. placebo.
- Similar patterns were observed for the entire phase 3 study population.

Conclusion

- Individuals with severe CIC tend to move their bowels later in the day suggesting alterations in their colonic biological clock
- VC improved constipation by significantly increasing the number of CSBMs later in the day
- Optimal treatment of patients with CIC requires awareness of this abnormal colonic diurnal rhythm in these patients

Strengths & Limitations

- **Strengths**
  - Rigorous, multi-center, prospective study design
  - Target subgroup with severe CIC
- **Limitations**
  - Post-hoc analysis
  - Did not assess physiological features (e.g. transit or colonic pressure) that may provide direct insight into circadian rhythm
  - No direct comparison with bowel movement activity in healthy adults

3D Imaging and Computerized Quantitation of Sigmoid Mucosal Biopsies Show Correlations Between the Proximity of Mast Cells to Sensory Nerve Fibers and IBS Symptoms

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Background & Aims

- Colonic mucosa is innervated by extrinsic efferent and afferent nerves and intrinsic enteric neurons that modulate motor, secretory and sensory functions.
- The complex interplay of nerves and immune cells may be altered in IBS.
- **Study Aims:**
- **(1) Establish an approach for 3D imaging of innervation in colonic mucosal biopsies and computational quantitation of nerve fibers (NFs), enteric glial cells (EGCs), mast cells (MCs) and the proximity MCs to NFs**
- **(2) Compare measures between healthy controls (HCs) and IBS patients**
- **(3) Assess their correlations with IBS Symptom Severity Scale (IBS-SSS) and abdominal pain intensity and unpleasantness within 24 h of biopsies**

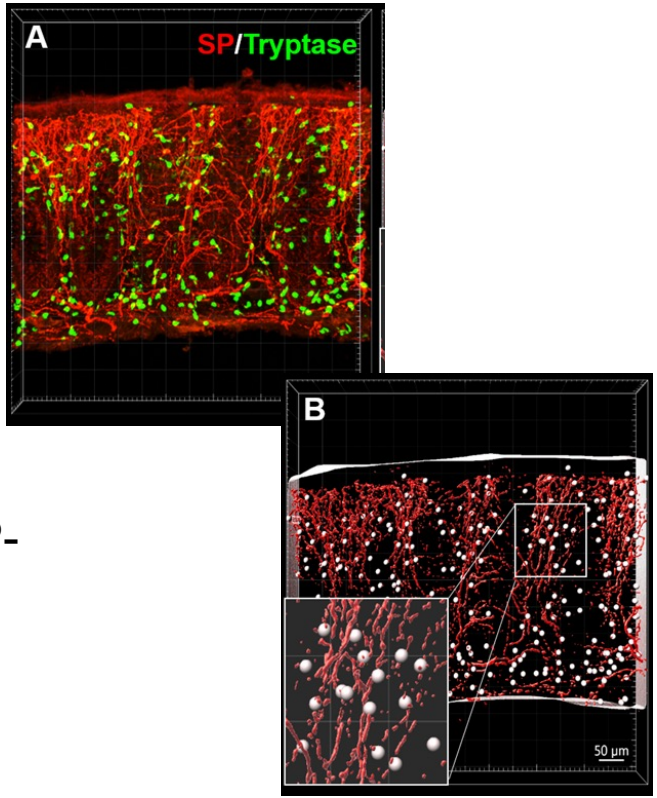
Methods: Specimen Collection and Processing

- Sigmoid mucosal biopsies collected from 12 HCs (age: 34±11 years, 6 females [F]) and 15 IBS (age: 34±10 years, 7 IBS-C [5F], 8 IBS-D [4F])
- Processed for CLARITY procedure and single or double immunolabeling with 10 marker antibodies

Antibodies	Marker for
Protein gene product (PGP) 9.5	pan-nerve fibers
Substance P (SP)	primary afferent nerve fibers
Calbindin (Calb)	intrinsic primary afferent nerve fibers
Tyrosine hydroxylase (TH)	extrinsic sympathetic nerve fibers
Neuropeptide (NPY)	sympathetic nerve fibers with extrinsic and intrinsic origin
Vasoactive intestinal peptide (VIP)	intrinsic secretory-motor nerve fibers
Vesicular acetylcholine transporter (VAChT)	extrinsic and intrinsic cholinergic nerve fibers
Human peripheral form of choline acetyltransferase (hpChAT)	intrinsic cholinergic nerve fibers
S100β	enteric gilal cells (EGCs)
Tryptase	mast cells (MCs)

Methods: 3D Imaging & Analysis

- Z-stack confocal images with 150-200 optical sections per sample generated 3D images
- Imaris 9.7 used to quantitate:
  - Densities of NFs, EGCs and MCs
  - Proximity of MCs to pan-NFs (PGP9.5 immunoreactive [ir])
  - Extrinsic and intrinsic primary afferent fibers (SP-ir and Calb-ir, respectively) expressed as % of MCs with shortest distance (≤5.2 µm) to NFs of total MCs (PGP9.5-MC, SP-MC, Calb-MC)

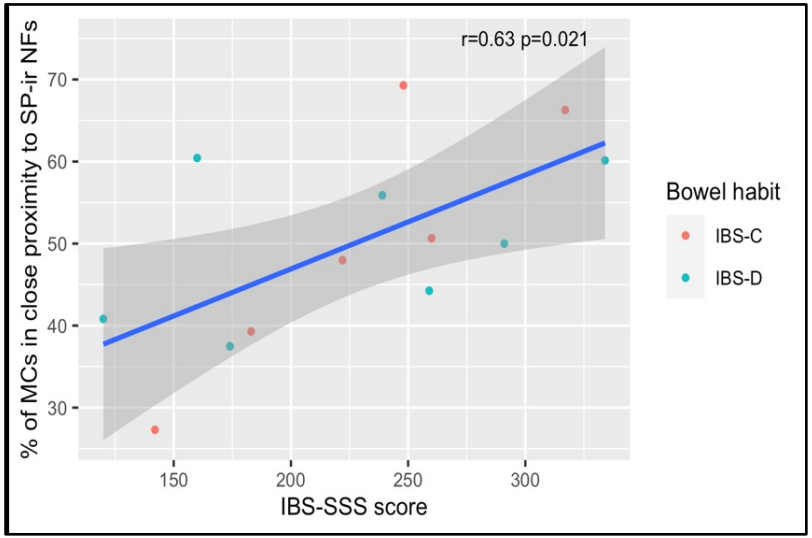


Results: Densities Differ Between IBS and Controls and Correlate With Symptoms

- Densities of NFs, EGCs and MCs did not show significant differences between IBS and HCs, but Calb-ir and hpChAT-ir densities tended to be lower in IBS vs HCs (P=0.07, P=0.05 respectively).
- In IBS, VIP-ir and NPY-ir densities (NF markers) negatively correlated with IBS-SSS (r=-0.67, P=0.013 and r=-0.57, P=0.042 respectively) and NPY with abdominal pain unpleasantness (r=-0.71, P=0.006).

Results: % of Mast Cells in Close Proximity to Nerve Fibers Correlate With IBS-SSS

- SP-MC positively correlated with IBS-SSS (r=0.63, P=0.021, pain intensity (r=0.61, P=0.026) and unpleasantness (r=0.57, P=0.041).
- **In IBS-D only**, similar findings were seen showing negative correlations of VIP-ir and NPY-ir densities with IBS-SSS (r=-0.9, P=0.006 and r=-0.57, P-0.042 respectively) and a positive correlation between SP-MC and pain intensity (r=0.8, P=0.03).



Conclusion

- Novel 3D imaging and computerized quantitation of colonic mucosal nerve fiber densities and immune cells revealed differences between IBS and HCs and particularly significant correlations of nerve fiber densities and MCs in close proximity to sensory nerves with IBS severity and current abdominal pain scores.
- Findings support alterations in peripheral neuronal signaling in IBS.
- These measures may become potential objective markers for IBS symptom severity and therapeutic response.
- *Supported by NIH/SPARC and Ironwood.*

Strengths & Limitations

- **Strengths**
  - Novel approach to examining the relationships between enteric nervous system, immune cells, and symptoms in IBS
  - Use of validated tools for symptom assessment to study correlations between biopsy findings and clinical symptoms
  - Inclusion of both healthy controls and volunteers with IBS
- **Limitations**
  - Small sample size
  - Random sampling, may benefit from longitudinal data

Small Intestinal Microbiome Dysbiosis May Underlie Abdominal Pain in Patients With Disorders of Gut Brain Axis Interaction

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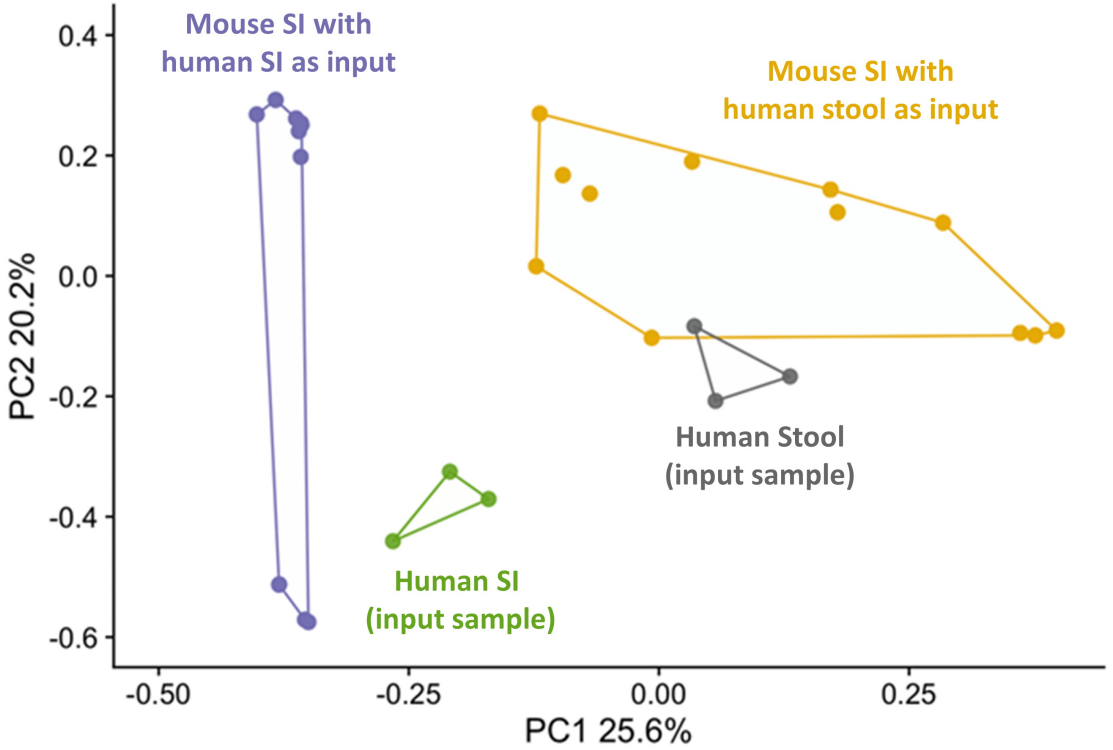
Background & Aims

- Current prevalent paradigm focuses on small intestinal (SI) bacterial overgrowth (SIBO) as a cause of gastrointestinal (GI) symptoms
- However, recent studies suggest alterations in SI microbial composition rather than SIBO may underlie GI symptoms in patients with disorders of gut-brain interaction (DGBI)
- Human stool is commonly used to recapitulate the human gut microbiome in germ free (GF) mice; however, it is unclear if stool can recapitulate SI microbiome in mice
- **Aim: To establish a mouse model that replicates the human SI microbiome and investigate the influence of the human SI microbiome on visceral sensitivity**

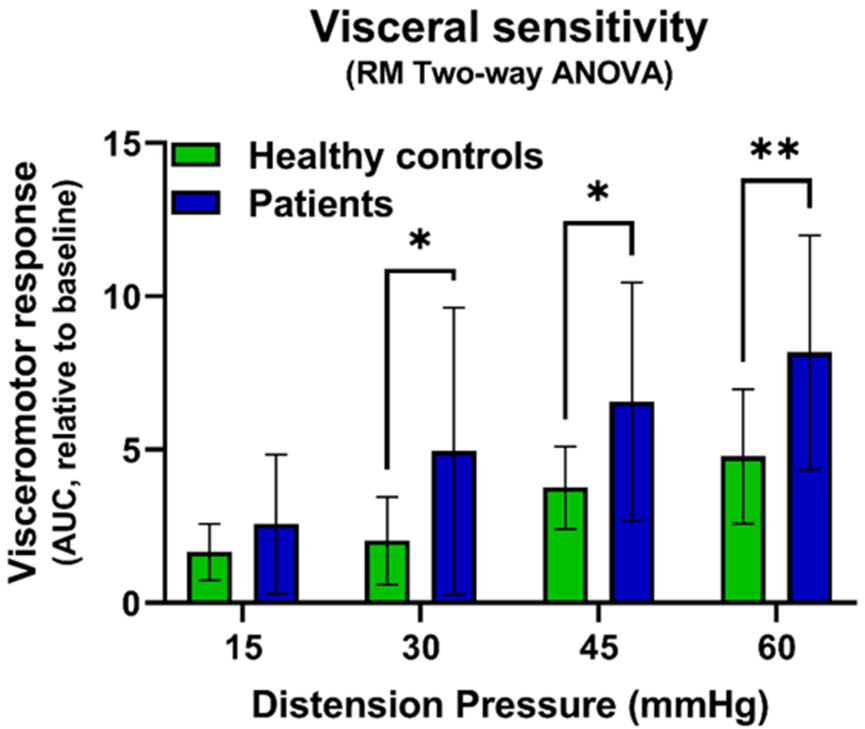
Methods

- Duodenal aspirate and stool samples collected from healthy controls (HC) and age/sex matched patients with abdominal pain (SIBO and bacterial pathogen culture negative)
- GF mice gavaged with human SI aspirate or stool and were maintained in gnotobiotic isolators or ISOcage™ system
- After 4 weeks, SI contents from mice were collected and processed with the human input samples for 16S rRNA sequencing
- In a subset of mice, visceromotor response (VMR) to colorectal balloon distension (CRD) were measured during 10-second distension intervals of 15, 30, 45 and 60 mmHg using a solid-state manometry catheter

Results: Colonization With Human SI Input Better Recapitulates Human SI Microbiome in Mice



Results: SI Dysbiosis Induces Visceral Hypersensitivity in Mice



- Mice with SI contents from patients with pain had higher VMR to CRD than mice colonized with SI aspirates from HC

Results: *Shigella* Spp. Is Associated With Visceral Sensitivity in Mice

- Sequencing of human and mouse SI contents from 1 abdominal pain patient and 2 HCs and found a *Shigella* spp. in the human and mouse SI content from the patient.
- Relative abundance of Shigella spp. in the mouse SI positively correlated with the VMR to CRD ($\rho=0.86$, $p<0.001$).

Conclusion

- Human SI contents are better than stool for replicating the human SI microbiome in mice
- Presence of *Shigella* spp. in the SI may underlie visceral hypersensitivity in patients with abdominal pain and represents an important therapeutic target

Strengths & Limitations

- **Strengths**
  - Inclusion of healthy controls and patients with abdominal pain
  - Combined assessment of microbiome composition and measurement of visceral sensation offer insight on microbial mechanisms of visceral pain
  - Analysis of both SI and colonic microbiomes to identify optimal approach to colonization experiments in mice
- **Limitations**
  - 16S rRNA sequencing may introduce larger bias when examining the microbiome of low-abundant sites (small intestine)
  - Small pool of human input samples
  - No direct assessment of the relationship between *Shigella* spp. and visceral hypersensitivity or pain in humans

A Double-Blind Placebo Controlled Study of Clonidine and Colesevelam for Fecal Incontinence (FI)

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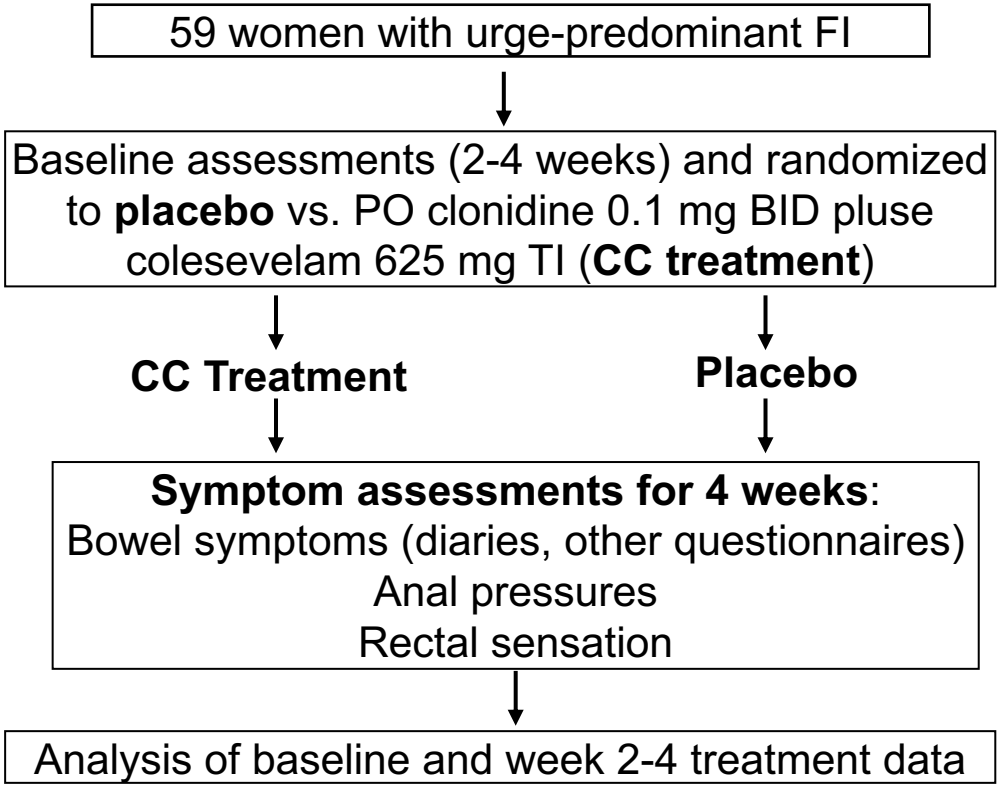
Background & Hypotheses

- Some women with urge-predominant fecal incontinence (FI) have a stiffer rectum and rectal hypersensitivity.
- In a phase 2 study, the a_2 adrenergic agonist clonidine, which increases rectal compliance and reduces rectal sensation, did not reduce FI in all women with urge FI, but had borderline significant effects in women with diarrhea and urge FI.
- Up to 25% of patients with idiopathic diarrhea have bile acid malabsorption, which may respond to bile acid sequestrants.
- **Hypotheses: Clonidine and colesevelam (CC) will improve fecal continence in women with urge FI.**

Methods: Study Procedures

- **Primary outcome:** Number of FI episodes
- FI Symptom Severity Score, FI Severity Index, and FI Quality of Life Scores calculated for <u>baseline and during</u> treatment



Results: Similar Baseline Characteristics

	Placebo (n=33)	Clonidine and colesevelam (n=26)	P values
Age, yr	47 ± 26	53 ± 29	.10
Body-mass index, kg/m^2	28.7. ± 6.3	28.7 ± 7.1	.40
Bowel habits			
Stool frequency/day, n	2.6 ± 1.9	2.9 ± 1.9	.08
Stool consistency, Bristol score	4.4 ± 1.4	4.6 ± 1.4	.75
BMs with Bristol score 5-7/week, n	1.4 ± 1.1	1.7 ± 1.6	.07
Duration for which defecation could be deferred, minutes	2.8 ± 7.8	3.7 ± 9.6	.68
Fecal incontinence			
FI episodes/week, n	7.7 ± 9.6	7.3 ± 6.7	.77
Only stain	3.7 ± 4.8	3.1 ± 3.3	.50
More than stain but less than full bowel movement	2.1 ± 3.6	2.0 ± 2.1	.84
Full bowel movement	2.1 ± 2.2	2.7 ± 6.0	.96
Proportion of bowel movements which were incontinent, %	45 ± 9%	40 ± 10%	.18
FI for Bristol form 5-7 (% stools)	61 ± 8%	76 ± 8%	.29
FISS score (max = 13)	9.3 ± 2.3	9.8 ± 1.5	.11
Anorectal manometry			
Anal resting pressure, mmHg	70 ± 32	72 ± 28	.78
Anal squeeze increment, mmHg	43 ± 33	44 ± 33	.87
Rectal sensory threshold for first sensation, mL	41 ± 21	39 ± 18	.66
Rectal sensory threshold for urgency, mL	65 ± 32	65 ± 25	.96
Rectal sensory threshold for discomfort, mL	103 ± 84	105 ± 43	.85

Mean ± SD

- On average patients had moderately severe FI
- After the baseline phase, 3, 1 and 51 patients completed 1, 2, and 4 weeks of therapy, respectively
- 1 eligible patient did not begin therapy and 3 patients not eligible

Results: FI Improved With Placebo; CC Improves FISS Over Placebo but Not Other Bowel Symptoms

		Placebo				Clonidine and colesevelam			p-value, ANCOVA, drug effects
Bowel habits	n	Before	During	P value	n	Before	During	P value	
Stool frequency/day	31	2.6 ± 2.3	2.4 ± 2.3	.26	23	3.3 ± 2.0	2.1 ± 2.0	.06	.24
Stool consistency (Bristol stool form score)	31	4.2 ± 1.9	4.1 ± 1.9	.47	23	4.5 ± 1.5	3.2 ± 1.5	.02	.44
Bristol score 5-7 stools, n per week	31	1.4 ± 0.7	1.0 ± 0.7	<.001	23	2.1 ± 1.1	1.15 ± 1.1	<.001	.35
Duration for which defecation could be deferred, minutes	31	3.7 ± 7.8	2.8 ± 7.8	<.001	23	3.4 ± 8.4	3.6 ± 8.4	.44	.56
Fecal incontinence									
All FI episodes, n per week	31	7.7 ± 4.4	4.2 ± 4.4	<.001	23	8.1 ± 3.7	4.8 ± 3.7	<.001	.55
Stain only, n per week	31	3.7 ± 1.8	2.4 ± 1.8	<.001	23	3.6 ± 3.0	3.3 ± 3.0	.64	.11
Moderate FI, n per week	31	2.0 ± 1.7	0.9 ± 1.7	.002	23	2.1 ± 2.6	2.0 ± 2.6	.94	.06
Full bowel movement, n per week	31	2.1 ± 2.2	1.3 ± 2.2	.006	23	2.7 ± 6.2	2.4 ± 6.2	.82	.36
Proportion of bowel movements which were incontinent (%)	31	45 ± 9%	27 ± 8%	.27	23	40 ± 10%	28 ± 9%	.22	.04
FI for Bristol form 5-7 (% stools)	31	61 ± 8%	67 ± 8%	.76	23	76 ± 8%	61 ± 10%	.007	.39
FISS symptom severity score (maximum = 13) [1]	33	9.3 ± 2.3	6 ± 3.2	<.001	26	9.8 ± 1.5	4.6 ± 3.6	<.001	.005
FISI (Rockwood score) [1]	33	33 ± 11	28 ± 15	.11	26	35 ± 11	22 ± 18	.001	.12
FISI-QoL (Rockwood score) [1]									
Lifestyle score	33	26 ± 9.0	24 ± 13	.19	26	24 ± 11	21 ± 14	.29	.67
Coping score	33	17 ± 5.2	15 ± 9.0	.33	26	15 ± 6.1	15 ± 10	.90	.80
Depression score	33	21 ± 4.5	18 ± 8.7	.15	26	20 ± 7.1	16 ± 10	.11	.49
Embarrassment score	33	7 ± 2.3	7 ± 3.8	.36	26	6 ± 3.0	5.7 ± 4	.40	.60
Loperamide tablets per week, n	31	1.5 ± 2	1.9 ± 2	.04	23	5 ± 4	6 ± 5	.28	.78
All parameters were computed from daily diaries except for those marked with [1] (pre and post treatment questionnaire)									

Results: No Difference in Primary Outcome ≥50% Reduction in FI Episodes) Between Groups

- The **primary outcome** (≥50% reduction in FI episodes) was not different between CC (13/24 [54%]) and placebo (17/32 [53%])
- Among 21 and 30 patients who completed 4 weeks of treatment, the change (treatment – baseline) in FI episodes during therapy was directly correlated with the rectal urge sensory threshold (r_s= 0.50, P =.03) in the CC but not in the placebo group (r_s= 0.17, P =.34)

Conclusion

- 53% of patients treated with placebo reported a >50% reduction in the number of FI episodes
- Effects of CC were not significant vs placebo
- CC did improve the FISS score which incorporates frequency, type, and amount of leakage and rectal urgency vs placebo
- CC but not placebo was more effective in pts with a higher rectal sensory threshold volume for urgency, which suggests that is more likely to be effective in pts without rectal hypersensitivity
- Future controlled trials should evaluate the utility of CC in patients who have documented bile acid malabsorption

Strengths & Limitations

- **Strengths**
  - Prospective, placebo, controlled trial
  - Detailed investigation of clinical symptoms and anorectal functions
- **Limitations**
  - High placebo response
  - Enrolled women with urge FI, but not specifically those with urge FI and diarrhea

A Randomized Parallel-Group Study of Self-Administered, Digital Gut-Directed Hypnotherapy vs. Muscle Relaxation for Irritable Bowel Syndrome

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Background & Aims

- Gut-directed hypnotherapy (GDH) is effective for treating irritable bowel syndrome (IBS), but access issues limit its widespread use.
- Preliminary studies also suggest that muscle relaxation might benefit patients with IBS.
- **Aim: To compare the safety and efficacy of a self-administered, digital GDH treatment program with that of digital muscle relaxation (MR) in adults with IBS.**

Methods: Study Participants & Design

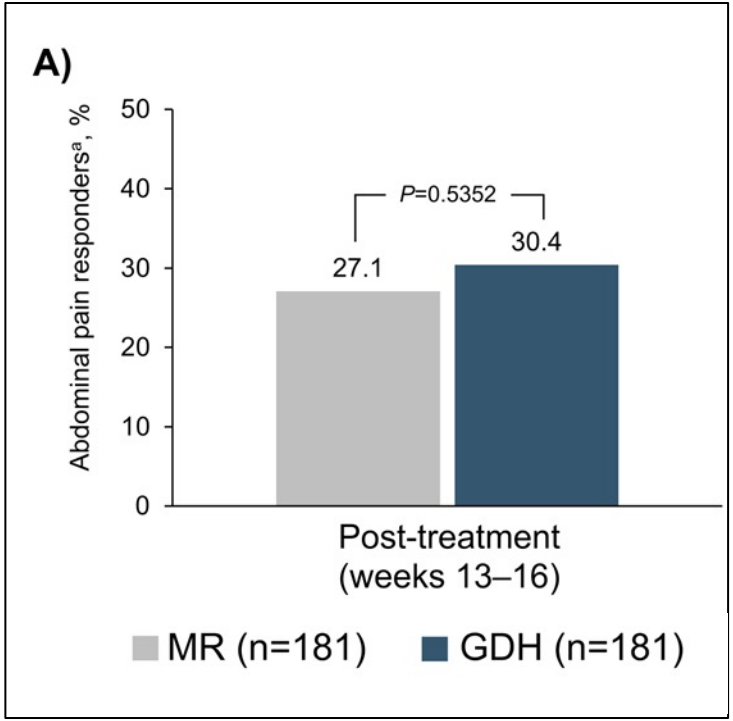
- **Study Design:** A multicenter, randomized, double-blind, controlled study enrolling patients from 26 centers in the USA from December 2019 to October 2020.
- **Eligibility:** Patients aged 18 to 70 years meeting the Rome IV criteria for IBS who reported an Average Worst Daily Pain Severity score of ≥3 on an 11-point scale over a 4-week run-in period.

Methods: Study Procedures

- Patients were randomized to 12 weeks of treatment with digital GDH via the North Carolina protocol or digital muscle relaxation (MR) control via a mobile app
- **Primary endpoint:** ≥30% reduction from baseline in average daily abdominal pain intensity 4 weeks post-treatment
- **Key secondary outcomes:** mean change from baseline abdominal pain, stool consistency and frequency

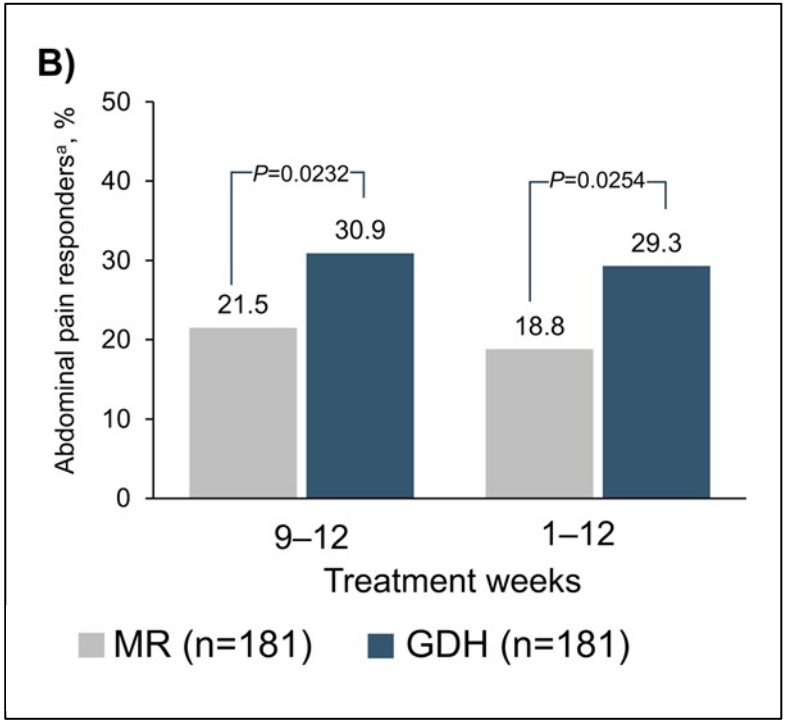
Results: No Significant Difference In % Of Responders Based on Primary Endpoint

- 362 of 378 randomized patients were treated and included in the efficacy analysis
- 30.4% of patients in the GDH group met the primary endpoint compared with 27.1% of those who received MR (*p*=0.532)
- **Assessment period:** post-period treatment weeks 13-16

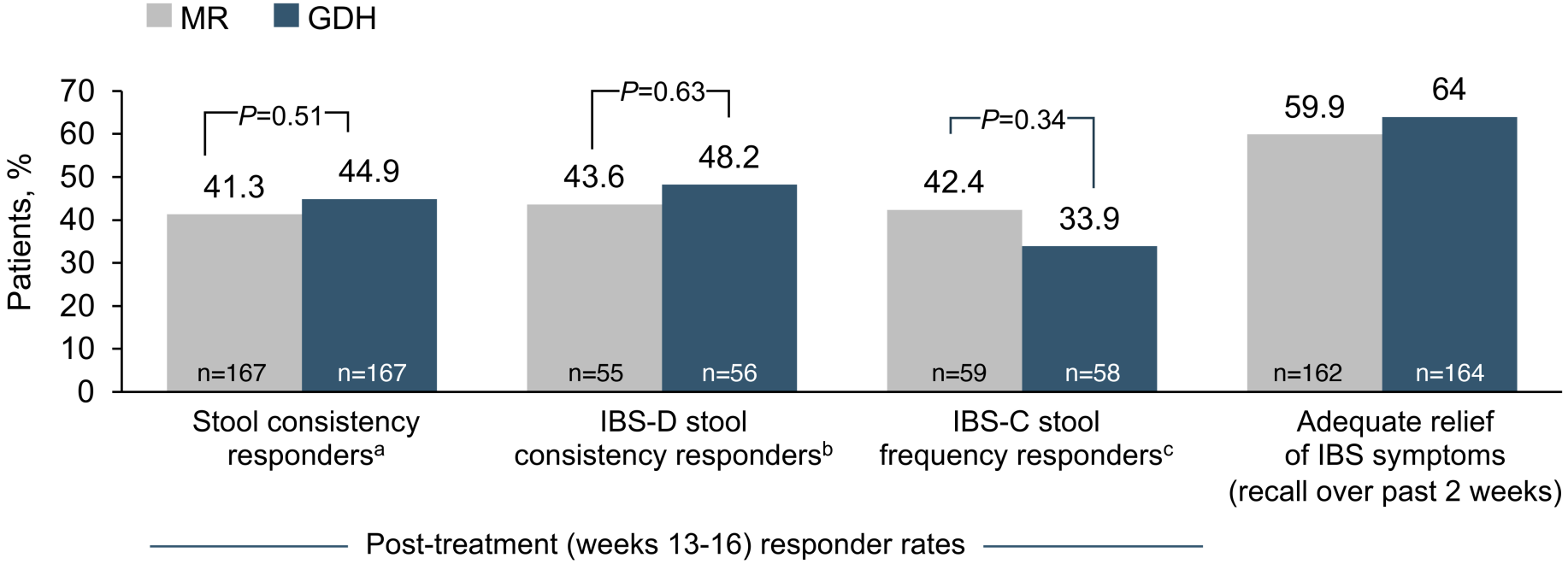


Results: Higher Rate of Responders With GDH During the Last 4 Weeks and Over the Entire Treatment Period

- Significantly more GDH-treated patients were abdominal pain responders during the **last 4 weeks of treatment** and the **entire treatment period** compared with those receiving MR



Results: No Significant Differences in Secondary and Exploratory Endpoints During Weeks 13–16 Post TX



Conclusions

- Benefits observed with this digital GDH were consistent with those described with in-person individual and group GDH in IBS
- Similar studies have shown symptom reduction with GDH vs. control interventions considered active treatments, including biofeedback, therapist or gastroenterologist led education, and low FODMAP diet
- Findings provide support for the digital delivery of GDH via the North Carolina protocol
- Treatment with a digital GDH program led to robust improvements in abdominal pain and stool symptoms in patients with IBS, supporting a role for this intervention as part of integrated care for IBS

Strengths & Limitations

- **Strengths:**
  - Large, randomized trial with rigorous study design
  - Use of active comparator
  - First study to assess all-digital program for delivery of GDH:
- **Limitations:**
  - Unclear effect of durability given lack of differences during the post-treatment assessment phase compared to MR
  - Further evaluation of clinical features that may enhance adherence or response needed

Long-Term Effectiveness of Two Different Carbohydrate-Restrictive Diets in Irritable Bowel Syndrome (IBS): The Caribs Trial

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Background & Aims

- Restrictive diets are often advocated in the treatment of IBS, but with unknown long-term effectiveness
- **Aim: To evaluate the long-term effects on IBS symptoms of <u>two different restrictive diets</u> within a randomized, controlled trial**

Methods & Aims: Participants & Design

- **Participants:** Adult patients with IBS (Rome IV) with at least moderate IBS symptom severity (IBS-SSS≥175)
- **Design:** Volunteers were randomized to one of three treatment options for 4 weeks (intervention period)
    1. Diet combining low- fermentable oligo-, di-, monosaccharides and polyols (FODMAP) and traditional dietary advice (LFTD)
    2. Low carbohydrate diet (LCD)
    3. Optimized medical treatment (OMT)

Methods: Study Procedures

- After the intervention period, patients in the LCD arm were informed about their allocated diet and patients in the LFTD arm received information about reintroduction of FODMAPs
- Follow-up visits scheduled 3- and 6-months post intervention for those receiving dietary treatment
- **Primary endpoint:** Reduction in IBS-SSS≥50
- **Dietary intake:** Four-day food records were used to assess energy and nutrient intake
- **Statistical Analysis:** Linear mixed models were used to assess symptom severity

Results: Participant Characteristics

- 304 participants randomized, 10 excluded, and 294 participants in ITT analysis
- Drop-out numbers during the intervention period was 6 (6%) in LFTD, 5 (5%) in LCD
- Drop-out at the 6-month follow-up visit 42 (43%) in LFTD and 35 (36%) in LCD

Results: Reduction in IBS-SSS With Both Low FODMAP and Low Carb Diet Interventions

- Significant reduction in IBS-SSS seen after the 4-week intervention ($p<0.001$ within groups; Nybacka et al DDW 2022) remained at the 6-month follow-up ($p<0.001$ within groups)
- No significant interaction effect at the different timepoints, i.e., both groups had a **similar change** in IBS-SSS over time

Table 1. Change in symptom severity within the two diet groups and difference in trajectory between the two diets taken time into account.

	Low FODMAP (LFTD)	*P*- time effect	Low carb (LCD)	*P*-time effect	*P*- group x time interaction
IBS-SSS total, baseline	322 ± 67		322 ± 69		0.98
Change week 4	-158 ± 112	0.001	-131 ± 109	0.001	0.20
Change month 3	-116 ± 95	0.001	-97 ± 104	0.001	0.15
Change month 6	-106 ± 111	0.001	-92 ± 115	0.001	0.10

IBS-SSS: irritable bowel syndrome severity scoring system

Results: Reduction in IBS-SSS With Both Low Fodmap and Low Carb Diet Interventions

Table 2. Symptom severity, energy intake, FODMAP and macronutrient distribution among responders and non-responders to a low FODMAP/traditional IBS diet and a low carbohydrate diet at baseline and at 3- and 6-months follow-up.

	Low FODMAP/traditional diet (LFTD)			Low carb diet (LCD)		
	Responders	*Non-responders*	*P-value*[1]	*Responders*	*Non-responders*	*P-value*[1]
Total IBS-SSS						
Baseline	329 ± 65	301 ± 68	0.036	332 ± 63	297 ± 80	0.023
Week 4[2]	134 ± 90**	301 ± 76	<0.001	152 ± 83**	298 ± 89	<0.001
Month 3[2]	170 ± 86**	295 ± 90	<0.001	202 ± 98**	258 ± 22	<0.001
Month 6[2]	159 ± 83**	305 ± 86	<0.001	208 ± 103**	263 ± 115	<0.001
Energy intake (kcal)						
Baseline[3]	1983 ± 434**	2053 ± 421*	0.49	1978 ± 536**	2149 ± 667	0.19
INTERVENTION	2308			2330		
Month 3[4]	1800 ± 331*	2024 ± 519	0.044	1784 ± 443*	1902 ± 555	0.32
Month 6[5]	1844 ± 414	2023 ± 750	0.26	2030 ± 686	1939 ± 536	0.58
Total FODMAP intake (g)						
Baseline[3]	16.4 ± 8.6**	18.8 ± 9.7**	0.25	17.8 ± 9.7	17.6 ± 9.3	0.96
INTERVENTION	3.4			16.6		
Month 3[4]	13.4 ± 7.1*	18.2 ± 7.5	0.020	13.7 ± 6.3*	14.7 ± 9.0*	0.57
Month 6[5]	12.7 ± 7.3*	16.4 ± 12.9	0.18	13.6 ± 8.6*	16.2 ± 8.6	0.27
Fat (E%)						
Baseline[3]	38.4 ± 5.8**	39.4 ± 6.3**	0.24	38.0 ± 6.6**	40.9 ± 5.6**	0.047
INTERVENTION	34.1			67.5		
Month 3[4]	38.2 ± 5.8	39.4 ± 4.9	0.43	43.7 ± 9.0**	43.7 ± 7.6	0.97
Month 6[5]	37.7 ± 5.5	38.1 ± 6.2	0.83	45.0 ± 8.9**	42.1 ± 6.9	0.18
Carbohydrate (E%)						
Baseline[3]	40.5 ± 6.4**	41.5 ± 6.3*	0.24	41.7 ± 7.0**	39.1 ± 7.7**	0.11
INTERVENTION	45.8			8.6		
Month 3[4]	40.0 ± 6.1	40.0 ± 4.2	0.98	33.5 ± 9.6**	35.5 ± 8.4	0.37
Month 6[5]	40.7 ± 4.8	40.6 ± 5.3	0.95	33.3 ± 10.1**	35.3 ± 8.0	0.43
Protein (E%)						
Baseline[3]	16.7 ± 3.8**	15.6 ± 2.1**	0.096	15.8 ± 3.3**	16.0 ± 4.4**	0.79
INTERVENTION	17.1			22.6		
Month 3[4]	17.1 ± 3.2	17.4 ± 3.5*	0.71	18.5 ± 4.4**	16.9 ± 3.9	0.12
Month 6[5]	17.4 ± 3.1*	18.2 ± 3.3	0.40	18.4 ± 5.2**	17.3 ± 3.5	0.37

- At 6 months, 67% in LFTD and 60% in LCD were still responders to treatment (n.s. difference between groups)
- Baseline dietary intake significantly different from intervention, except for FODMAP intake in the LCD diet and energy intake among non-responders to the LCD diet (no significant difference)

*P-values <0.05 **P-values <0.001

[1]P-values indicate difference between responders and non-responders using independent samples t-test

[2]Asterisk indicate difference between baseline symptom severity and week 4 using paired samples t-test

[3]Asterisk indicate difference between baseline intakes and intervention diet using paired samples t-test

[4]Asterisk indicate difference between baseline intakes and intakes at month 3 using paired samples t-test

[5]Asterisk indicate difference between baseline intakes and intakes at month 6 using paired samples t-test

Results: Intake After Dietary Intervention in LFTD and LCD Responders and Non-responders

Table 2. Symptom severity, energy intake, FODMAP and macronutrient distribution among responders and non-responders to a low FODMAP/traditional IBS diet and a low carbohydrate diet at baseline and at 3- and 6-months follow-up.

	Low FODMAP/traditional diet (LFTD)			Low carb diet (LCD)		
	Responders	*Non-responders*	*P-value*[1]	*Responders*	*Non-responders*	*P-value*[1]
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- Dietary intake during follow-up in LFTD and LCD was not significantly different between responders and non-responders at 6 months
- FODMAP intake was significantly lower among responders to LFTD diet at 6 months vs. baseline
- Macronutrient composition was significantly different among responders in LCD at 6 months vs. baseline

*P-values <0.05 **P-values <0.001

[1]P-values indicate difference between responders and non-responders using independent samples t-test

[2]Asterisk indicate difference between baseline symptom severity and week 4 using paired samples t-test

[3]Asterisk indicate difference between baseline intakes and intervention diet using paired samples t-test

[4]Asterisk indicate difference between baseline intakes and intakes at month 3 using paired samples t-test

[5]Asterisk indicate difference between baseline intakes and intakes at month 6 using paired samples t-test

Conclusions

- Both LFTD and LCD were effective in alleviating symptoms in patients with IBS during the 4-week intervention
- The effect persisted over a 6-month period
- Few differences were noted between responders and non-responders to the diets, but responders had altered their diets more
- Predictors of responders should be identified to personalize treatments in this large patient group

Strengths & Limitations

- **Strengths**:
  - Long-term follow-up of dietary intervention
  - Large sample size
  - Blinded intervention
- **Limitations**
  - All aspects of nutrient intake not described
  - Unblinding following intervention phase
  - Adherence to dietary interventions may have correlate with responsiveness for reasons other that dietary changes alone