Endoscopic sleeve gastroplasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial

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Summary

Background Endoscopic sleeve gastroplasty (ESG) is an endolumenal, organ-sparing therapy for obesity, with wide global adoption. We aimed to explore the efficacy and safety of ESG with lifestyle modifications compared with lifestyle modifications alone.

Methods We conducted a randomised clinical trial at nine US centres, enrolling individuals aged 21–65 years with class 1 or class 2 obesity and who agreed to comply with lifelong dietary restrictions. Participants were randomly assigned (1:1·5; with stratified permuted blocks) to ESG with lifestyle modifications (ESG group) or lifestyle modifications alone (control group), with potential retightening or crossover to ESG, respectively, at 52 weeks. Lifestyle modifications included a low-calorie diet and physical activity. Participants in the primary ESG group were followed up for 104 weeks. The primary endpoint at 52 weeks was the percentage of excess weight loss (EWL), with excess weight being that over the ideal weight for a BMI of 25 kg/m². Secondary endpoints included change in metabolic comorbidities between the groups. We used multiple imputed intention-to-treat analyses with mixed-effects models. Our analyses were done on a per-protocol basis and a modified intention-to-treat basis. The safety population was defined as all participants who underwent ESG (both primary and crossover ESG) up to 52 weeks.

Findings Between Dec 20, 2017, and June 14, 2019, 209 participants were randomly assigned to ESG (n=85) or to control (n=124). At 52 weeks, the primary endpoint of mean percentage of EWL was 49·2% (SD 32·0) for the ESG group and 3·2% (18·6) for the control group (p<0·0001). Mean percentage of total bodyweight loss was 13·6% (8·0) for the ESG group and 0·8% (5·0) for the control group (p<0·0001), and 59 (77%) of 77 participants in the ESG group reached 25% or more of EWL at 52 weeks compared with 13 (12%) of 110 in the control group (p<0·0001). At 52 weeks, 41 (80%) of 51 participants in the ESG group had an improvement in one or more metabolic comorbidities, whereas six (12%) worsened, compared with the control group in which 28 (45%) of 62 participants had similar improvement, whereas 31 (50%) worsened. At 104 weeks, 41 (68%) of 60 participants in the ESG group maintained 25% or more of EWL. ESG-related serious adverse events occurred in three (2%) of 131 participants, without mortality or need for intensive care or surgery.

Interpretation ESG is a safe intervention that resulted in significant weight loss, maintained at 104 weeks, with important improvements in metabolic comorbidities. ESG should be considered as a synergistic weight loss intervention for patients with class 1 or class 2 obesity. This trial is registered with ClinicalTrials.gov, NCT03406975.

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Introduction

Obesity is a global concern, with massive socioeconomic burdens. According to the US Centers for Disease Control and Prevention, the age-adjusted prevalence of obesity among US adults between 2017 and 2018 was 42·4%.[1] Obesity is a risk factor for important chronic diseases, including type 2 diabetes, heart disease, fatty liver disease, and multiple cancers, and it is a risk factor for severe COVID-19.[2,3] Available treatment options for obesity include lifestyle modifications of nutrition and activity, pharmacotherapies, endoscopic bariatric therapies, and surgeries such as sleeve gastrectomy and gastric bypass. Lifestyle modifications and pharmacological therapy have several limitations, and the use of bariatric surgery is hampered by its invasive nature and patient perceptions.[4] These limitations create treatment gaps that endoscopic bariatric therapies might address.[5] Endoscopic sleeve gastroplasty (ESG) is a reversible, endoluminal organ-sparing bariatric procedure that has gained widespread global adoption.[6–11] ESG is done with use of a commercially available, full-thickness endoscopic suturing device (Overstitch System; Apollo Endosurgery, Austin, TX, USA) approved by the US Food and Drug Administration, which imbricates the majority of the stomach by serial

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Research in context

Evidence before this study

We searched PubMed from inception to Dec 31, 2021, for literature in English, examining publications focused on obesity, available interventions, and those evaluating the efficacy of endoscopic sleeve gastroplasty (ESG). Keywords used include "obesity", "endoscopic sleeve gastroplasty", and "endoscopic bariatric therapies". We examined randomised trials and prospective and retrospective studies; we did not perform a strict systematic review. There is a clear and present need for effective bridging interventions between lifestyle interventions, pharmacological therapies, and bariatric surgery, which can be scalable, generalisable, and accepted by patients. The penetrance of bariatric therapies remains limited, and individuals without severe obesity, but with a metabolically important disease, might not be candidates for bariatric surgery, or interested in pursuing it when it is indicated. ESG is a transoral, anatomy-sparing endoscopic intervention that was developed to offer a minimally invasive bridge in obesity management. We did not find large randomised trials evaluating ESG in the management of obesity.

Added value of this study

We showed the efficacy of ESG, combined with lifestyle modifications, in achieving and maintaining important weight loss, despite doing the second half of the trial during the COVID-19 pandemic, with significant improvement in metabolic comorbidities. At 52 weeks, participants treated with ESG achieved an average of 12·6% decrease in percentage of total bodyweight compared with participants in the control group. Additionally, 80% of participants in the ESG group with baseline comorbidities had an improvement in one or more metabolic comorbidities. At 104 weeks, 68% of participants in the ESG group maintained 25% or more of excess weight loss. ESG-related serious adverse events occurred in 2% of participants, without mortality or need for intensive care or surgery.

Implications of all the available evidence

The MERIT study proves that ESG is scalable and can be offered in outpatient endoscopy practices by surgeons or gastroenterologists, with an excellent safety profile, without mortality, and with predictable conservatively managed adverse events.

interrupted sutures placed from the incisura to the cardia. In a meta-analysis that included 1772 patients, the average pooled total bodyweight loss at 6 months was 15·1% (95% CI 14·3–16·0) and at 12 months was 16·5% (15·2–17·8).[8] The influence of ESG over obesity pathophysiology has been shown to go beyond mechanical restriction, to affect satiation and metabolic dysregulation pathways.[12]

We aimed to explore the efficacy and safety of ESG in the multidisciplinary approach to obesity care. For this, we conducted a large, multicentre, randomised trial in patients with class 1 and class 2 obesity.

Methods

Study design and participants

The Multicentre ESG Randomised Interventional Trial (MERIT) enrolled adults from Dec 20, 2017, to Oct 24, 2019, at nine US academic and community centres (five gastroenterology centres and four bariatric surgery centres). Included individuals were aged 21–65 years, with BMI between 30 kg/m² and less than 40 kg/m², with a history of failure with non-surgical weight loss methods, and who agreed to comply with the lifelong dietary restrictions required by the procedure. Exclusion criteria included a history of gastrointestinal surgery and any inflammatory disease in the gastrointestinal tract; a full list of inclusion and exclusion criteria is presented in the appendix (pp 2–3).

See Online for appendix

Study sites and investigators were chosen to show the efficacy and safety of ESG across different practices (community, private, and academic centres), specialties (gastroenterology and surgery), and levels of previous experience with the procedure. All operators were proficient with endoscopic full-thickness suture applications using the Overstitch endoscopic suturing system. All operators, regardless of previous experience, underwent the same training programme for ESG. The principal investigator provided each site investigator with a training video showing the ESG technique. Additionally, an independent expert both with the suturing device and ESG procedure proctored the first two cases at every site. Each site obtained approval from an institutional review board.

Randomisation and masking

Before screening for eligibility, patients completed informed consent. After screening, they were randomly assigned to receive ESG plus moderate-intensity lifestyle modifications (ESG group) or moderate-intensity lifestyle modifications alone (control group) for 52 weeks. Randomisation was done with block randomisation (1:1·5) by use of stratified permuted blocks (appendix pp 3–4, 22). We created stratified block randomisation schedules using R, version 3.5.1. The schedules were uploaded to the REDCap (Research Electronic Data Capture) database. The planned randomisation ratio provided the power to examine participants in the control group who did not reach study success (<25% excess weight loss [EWL] at 52 weeks). This lifestyle modifications subgroup was offered the ESG and followed up for an additional 52 weeks.

Randomisation was requested by appropriate site personnel when an individual completed the screening visit and was found eligible for the study. We notified enrolled participants of treatment assignment at the time

of randomisation. This notification allowed the participants and site investigators to complete the necessary procedures for the two different treatment groups. However, clinical staff involved with the lifestyle management programme remained masked to treatment assignments for each participant. Given the absence of a sham endoscopy arm, the preparation for each group was different upon randomisation, and this could not be blinded. The study was not designed with a control group treated with a sham procedure that involved an upper endoscopy because of safety concerns raised by the literature regarding these sham procedures,[13] and the self-limited accommodative symptoms associated with ESG would impede blinding efforts. Therefore, double blinding was not possible.

Interventions

ESG is an incisionless, organ-sparing, transoral endoscopic procedure done in an outpatient setting under general anaesthesia (appendix pp 3–4). Lifestyle modifications included a low-calorie diet plan and physical activity counselling, which was customised for each participant's goals and lifestyle and provided during each study visit. Conditions to facilitate lifestyle modification compliance were identical in both groups. Furthermore, eligibility for crossover from the control group to the ESG group was linked to attendance to a minimum of two-thirds of the designated study visits, during which dietary and exercise plans were reiterated to incentivise lifestyle modification adherence in both groups (appendix p 4).

Patients in the ESG group were followed up for a total of 104 weeks. After the 52-week visit, some patients received an oesophagogastroduodenoscopy for retightening either on the basis of a suboptimal response to the primary intervention or at the discretion of the treating investigator (figure 1).

At 52 weeks, participants in the control group who did not reach the target primary weight loss goal (≥25% EWL) and completed the 52-week visit were offered crossover to receive ESG and were followed up for an additional 52 weeks after crossover (figure 1).

During the first year, 12 total visits were completed at week 1, week 4, and then every 4 weeks until the 52-week visit. Participants who underwent crossover ESG followed the same visit and data collection schedule as that of participants in the primary ESG group for the first year. Extended follow-up of participants in the primary ESG group consisted of six follow-up visits, one approximately every 6–8 weeks (appendix p 4).

Outcomes

The primary efficacy endpoint was percentage of EWL at 52 weeks, which was calculated with the following formula: (weight loss / baseline excess weight) × 100, where weight loss is defined as follow-up weight minus the initial weight, and baseline excess weight is defined as index weight minus ideal weight X (X=25 kg/m²). The primary endpoint was the comparison between the primary ESG and control groups at 52 weeks. After the completion of the primary endpoint, participants in the crossover ESG group were followed up for an additional 52 weeks and assessed separately for efficacy results. This group was also compared with the primary ESG group, as both had the same follow-up duration. Both primary and crossover ESG groups were combined for all safety endpoint analyses. Follow-up of the primary ESG group was extended an additional 52 weeks for a total of 104 weeks to evaluate the durability of the original procedure or the effect of retightening in individuals who received it.

Secondary efficacy endpoints were compared at 52 weeks and included weight loss measures such as proportion of patients with 25% or more EWL, percentage of total bodyweight loss, and the proportion of patients with 5% or more and 10% or more of total bodyweight loss. We assessed the effect of ESG on obesity comorbidities. The primary safety endpoint was defined as 5% or less of ESG-related serious adverse events. These were defined as grade 3 or higher on the Clavien-Dindo classification.[14] All severe adverse events were reviewed by a Data Safety Monitoring Board (DSMB) to evaluate the Clavien-Dindo grade and were followed up to 104 weeks. Protocol deviations in this study were mainly related to missed collection points or visits, often associated with the COVID-19 pandemic, and they had no effect on primary endpoints.

Post-hoc evaluation of the durability of ESG once goal weight was reached (≥25% of EWL) was done by use of a Kaplan-Meier survival analysis. Participants were censored from this analysis once their weight loss dropped and remained below the weight loss target, as they were no longer maintaining the desired weight loss goal established by the study. The only exception to this process was for participants who were retightened after the 52-week visit and reached the expected weight loss after retightening. These participants were removed at the next visit if the target weight loss was not reached after retightening. The planned analysis in the study to address durability was not feasible because the protocol was modified and only participants in the ESG group who did not meet the target weight loss had an oesophagogastroduodenoscopy for possible retightening. Therefore, a full assessment of durability was not possible for the entire population.

Statistical analysis

On the basis of reported ESG outcomes,[8] we made a conservative assumption of 25% EWL (SD 30%) in the ESG group at 52 weeks compared with 10% EWL (5%) in the control group. We planned a 1:1·5 randomisation scheme that allocated three patients to the control group for every two to the ESG groups at the time of randomisation. On the basis of a two-sample *t* test with unequal variances and two-sided $\alpha=0\cdot05$, there would be

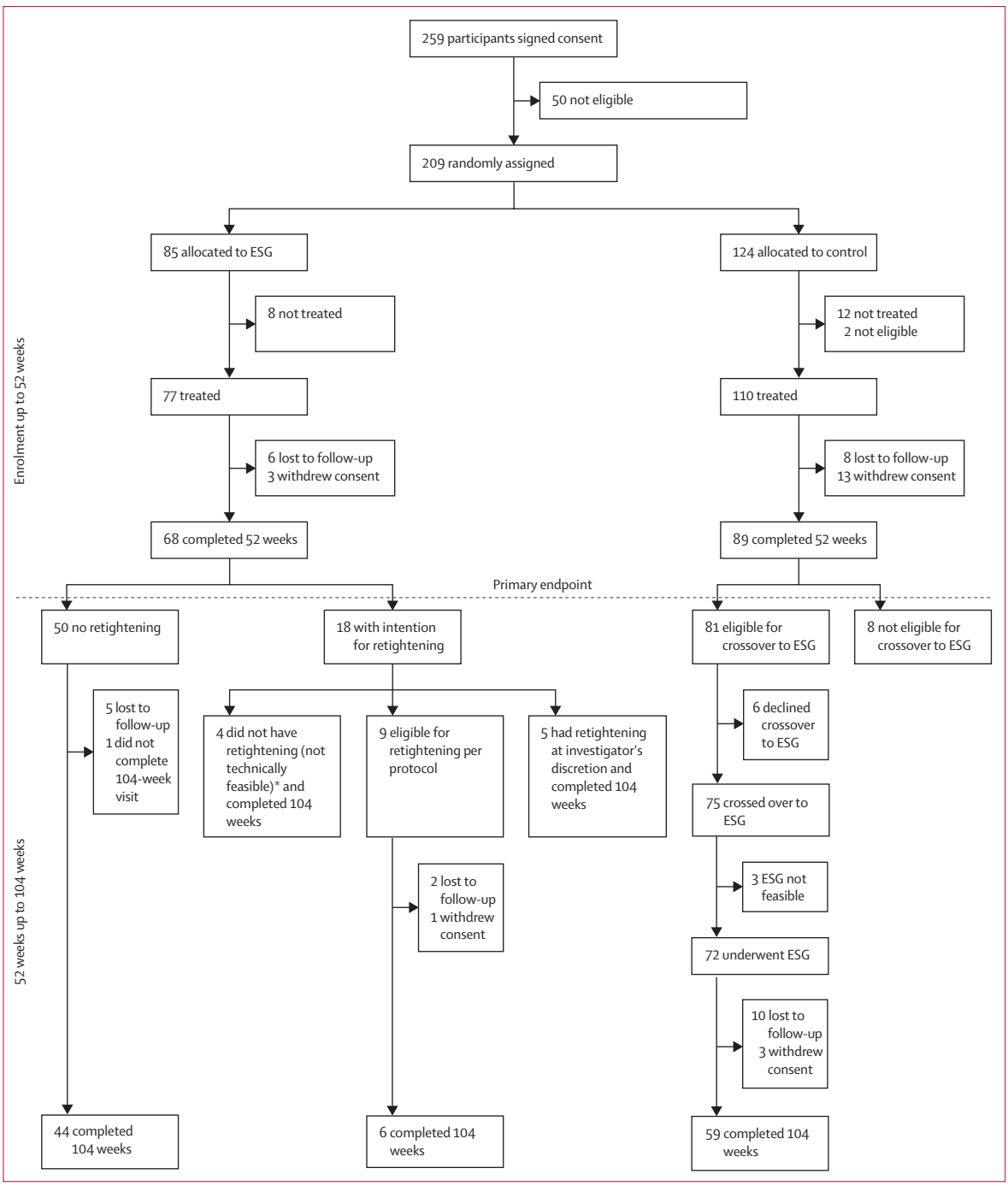

Figure 1: **Schematic overview of the study phases and participants' accountability by treatment group**
The first phase of the study started with randomised treatment and ended with the 52-week follow-up, which was the primary endpoint. An overview of reasons for ineligibility is provided in the appendix (pp 7–8). The COVID-19 pandemic started approximately at the time of the completion of the primary endpoint and was most prevalent in the follow-up period from 52 to 104 weeks. ESG=endoscopic sleeve gastroplasty. *Of the 18 participants who underwent evaluation for retightening, four did not undergo a retightening of the ESG because, upon observation, the sleeve was intact.

80% power to detect a difference of 15% in average EWL between groups with 34 patients allocated to ESG and 51 to control. 90% power would require group sizes of 45 patients to ESG and 68 to control. To allow for 45% dropout, we proposed an initial randomisation of 200 patients—80 to ESG and 120 to control. Therefore, we estimated that at least 77 patients would be eligible for crossover to the ESG group. The planned analysis was a

one-sample hypothesis that, of those offered ESG at 52 weeks, the average change in EWL would be at least 10%. On the basis of a one-sample *t* test with two-sided α=0·05 and SD of 30% at 104 weeks (52 weeks after ESG treatment), 70 patients completing ESG would result in 98% power to detect an effect of 25% reduction in EWL.

We did statistical analyses related to efficacy of randomised groups at 52 weeks on a per-protocol basis (completers, who were defined as participants who completed the 52 weeks visit) and a modified intention-to-treat (mITT) basis, which excluded participants who did not move forward with treatment for reasons unrelated to allocation. Patients who were randomly assigned but either did not complete the intervention or were identified as meeting exclusion criteria (as applied to both ESG and control groups) were excluded from the analysis.

We did statistical analysis for safety on all participants who underwent ESG (both primary and crossover ESG) up to 52 weeks.

We assessed the primary outcome of percentage of EWL over 52 weeks in the groups using a linear mixed-effects regression model. 11 planned post-randomisation study visits were modelled as discrete-time variables in the model, and regressions were adjusted for the prespecified prognostic variables of age, sex, baseline BMI, hypertension, and type 2 diabetes status to reduce residual variation and improve power. The primary outcome comparison at 52 weeks was estimated from a linear combination of treatment and time indicators and their interaction. The percentage of total bodyweight loss was assessed similarly.

We evaluated secondary endpoints at 52 weeks with descriptive statistics for each group and mixed-model effects modelling to assess the difference between each group, adjusted for age, sex, baseline BMI, hypertension, type 2 diabetes status, and baseline score of the questionnaire, if applicable. Key binary secondary endpoints assessed at the 104 weeks visit were compared between groups with the Pearson χ^2 test. For the secondary analysis, a per-protocol analysis compared the two randomised groups among participants who adhered to protocol—here, defined as those receiving the assigned study treatment and completing the 52-week visit.

Missing data were assumed missing at random (ignorable missingness) when analysed with linear mixed-effects models. Sensitivity analyses report comparisons using the last observation carried forward for missing data at study visits, which assumes the specified non-ignorable missing data pattern.

All analyses were done using SPSS (version 28) and SAS (version 9.4). This trial is registered with ClinicalTrials.gov, NCT03406975.

Role of the funding source

The funders provided grant support funding for data collection, statistical analysis, and editing support to collate the manuscript. Site investigators independently controlled the conduction of the study, analysis and interpretation of the data, decision to submit the manuscript, and final approval of the manuscript (scientific content in the manuscript).

Results

Between Dec 20, 2017, and June 14, 2019, 209 participants were randomly assigned to ESG (n=85) or to control (n=124). 20 participants were excluded from the mITT analysis because they did not move forward with treatment (eight in the ESG group and 12 in the control group). Additionally, two participants in the control group were removed from the mITT population after they completed at least one study visit because they were determined to be ineligible for the study (one due to age and the other because they had a history of binge eating). 77 participants underwent the ESG procedure and 110 initiated the lifestyle modifications programme alone, and they were included in the mITT analysis (figure 1, appendix p 2). Baseline characteristics of participants were similar between both groups (table 1). The ESG group had 68 (88%) women and nine (12%) men, and participants at baseline were aged a mean 47·3 years (SD 9·3) with mean BMI of 35·5 kg/m² (2·6). The control group had 92 (84%) women and 18 (16%) men, and participants at baseline were aged a mean 45·7 years (10·0) with mean BMI of 35·7 kg/m² (2·6). Of participants in the ESG group, 68 completed 52 weeks of follow-up. One patient requested ESG reversal during the study period, which was successfully done endoscopically. Of participants in the control group, 89 completed 52 weeks of follow-up, of whom 17 did not cross to the ESG group and were removed from continued study follow-up. 72 participants in the control group crossed to the ESG group and completed an additional 52 weeks.

The COVID-19 pandemic started in the middle of the study and had a substantial impact on study follow-up and participant retention (appendix p 22). Patients could not be followed up clinically in person, and the telemedicine approach was not mature at that point. During the initial period, lifestyle counselling continued, but monitoring of patients' weight, vitals, and laboratory workups were challenging. Eventually, measures were put in place to capture weight accurately through telemedicine visits, but other medical tests could not be completed. Clinics began to open 6–9 months after the initial closure, but participants were unwilling or unable to return for inpatient visits because of local restrictions and personal concerns regarding physical distancing. It is important to note that the pandemic affected not only the extended follow-up and crossover population but also some participants in the index ESG and control groups towards the 52 weeks visit.

The loss to follow-up rate was calculated as participants who did not complete the 52 weeks divided by those who were treated and was found to be 16%. The loss to follow-up rates were compared between the primary ESG

	Control	ESG
Demographics		
Participants	110	77
Age, years		
Mean	45·7 (10·0)	47·3 (9·3)
Median	45·5 (38·0–52·0)	49·0 (42·0–55·0)
Range	(23·0–65·0)	(22·0–64·0)
Sex		
Female	92 (84%)	68 (88%)
Male	18 (16%)	9 (12%)
Race		
White	62 (56%)	53 (69%)
African American	14 (13%)	11 (14%)
Asian	3 (3%)	0
Hispanic or Latino	18 (16%)	11 (14%)
Other	9 (8%)	1 (1%)
Deferred	4 (4%)	1 (1%)
Diabetic?		
Yes	36 (33%)	18 (23%)
No	74 (67%)	59 (77%)
Hypertensive?		
Yes	58 (53%)	38 (49%)
No	52 (47%)	39 (51%)
Weight characteristics		
Baseline BMI, kg/m²		
Participants	110	77
Mean	35·7 (2·6)	35·5 (2·6)
Median	35·8 (33·5–38·0)	35·8 (33·5–37·7)
Range	(30·1–39·9)	(31·0–39·9)
Baseline weight, kg		
Participants	110	77
Mean	99·1 (12·8)	98·4 (12·3)
Median	97·5 (91·0–106·5)	95·3 (90·5–107·9)
Range	(73·8–138·7)	(74·4–130·0)
Baseline waist circumference, cm		
Participants	63	28
Mean	109·7 (12·5)	110·3 (10·4)
Median	108·5 (99·0–119·0)	110·5 (102·9–118·2)
Range	(83·1–138·4)	(90·5–127·0)
Baseline hip circumference, cm		
Participants	63	28
Mean	119·5 (9·3)	119·7 (8·1)
Median	120·0 (113·0–126·8)	120·0 (114·7–124·2)
Range	(96·5–139·7)	(104·0–135·9)
Laboratory and vital signs characteristics		
Glucose, mg/dL		
Participants	80	57
Mean	98·6 (19·4)	101·7 (26·4)
Median	94·0 (87·3–103·0)	93·0 (88·0–107·5)
Range	(78·0–187·0)	(73·0–240·0)
$HgbA_{1c}$		
Participants	80	55
Mean	5·8 (0·8)	5·8 (0·8)

(Table 1 continues in next column)

(Continued from previous column)

	Control	ESG
Median	5·6 (5·3–6·2)	5·5 (5·3–5·9)
Range	(4·3–8·7)	(4·6–8·7)
Total cholesterol, mg/dL		
Participants	80	56
Mean	192·0 (37·3)	193·8 (41·0)
Median	191 (168–207)	192 (160–229)
Range	(125–310)	(114–291)
LDL, mg/dL		
Participants	79	56
Mean	111·9 (31·8)	115·0 (37·3)
Median	111 (87–133)	118 (85–141)
Range	(43–193)	(36–205)
HDL, mg/dL		
Participants	80	56
Mean	54·9 (14·0)	54·5 (15·5)
Median	52 (44–64)	54 (41–65)
Range	(31–104)	(32–106)
Triglycerides, mg/dL		
Participants	80	56
Mean	123·3 (51·5)	120·8 (63·1)
Median	112 (87–148)	113 (72–152)
Range	(45–341)	(32–363)
Systolic blood pressure, mm Hg		
Participants	103	77
Mean	131·6 (15·0)	134·2 (15·2)
Median	129 (121–142)	134 (124–143)
Range	(102–174)	(96–183)
Diastolic blood pressure, mm Hg		
Participants	103	77
Mean	80·9 (11·2)	82·4 (9·3)
Median	82 (74–87)	82 (75–88)
Range	(53–106)	(65–108)
Baseline medications for comorbid condition		
Participants	110	77
Diabetic medications		
Yes	38 (35%)	17 (22%)
No	72 (65%)	60 (78%)
Anti-hypertensive medications		
Yes	66 (60%)	40 (52%)
No	44 (40%)	37 (48%)
Lipid-lowering medications		
Yes	27 (25%)	13 (17%)
No	83 (75%)	64 (83%)

Data are n, mean (SD), median (IQR), or n (%), unless otherwise specified. ESG=endoscopic sleeve gastroplasty. $HgbA_{1c}$=glycated haemoglobin.

Table 1: **Descriptive statistics of baseline demographics and characteristics**

group and the control group, and we found no significant difference in their rates (p=0·18).

The primary endpoint at 52 weeks was mean percentage of EWL, which was 49·2% (SD 32·0) for the ESG group

and 3·2% (18·6) for the control group (p<0·0001; appendix p 11). Similarly, mean percentage of total bodyweight loss at 52 weeks was 13·6% (8·0) for the ESG group and 0·8% (5·0) for the control group (p<0·0001). After adjusting for age, sex, type 2 diabetes, hypertension, and baseline BMI in a mITT analysis with mixed-effects models, participants in the ESG group had a mean difference of 44·7% (95% CI 37·5–51·9) EWL and 12·6% (10·7–14·5) total bodyweight loss, compared with the control group at 52 weeks (p<0·0001 using last observation carried forward and p<0·0001 using mixed-model imputations for missing data). The weight loss trajectory by visit for each treatment group supported the difference between treatment groups (figure 2). The secondary endpoint—achieving 25% or more of EWL at 52 weeks—was observed in 59 (77%) participants in the ESG group compared with 13 (12%) in the control group. All weight loss parameters are presented in the appendix (pp 11–12). A group of participants was also followed up for an additional 52 weeks (end of follow-up at 104 weeks); this included the primary ESG cohort and the participants who crossed from the control group and received ESG at 52 weeks. Participants in the primary ESG group maintained 83% of the reached EWL at 104 weeks (11·4% [SD 8·4] total bodyweight loss and 41·0% [32·0] EWL; figure 2). By use of values from the last observation carried forward, four participants who did not reach 25% or more of EWL at the week 52 visit became weight loss responders at the week 104 visit, achieving 25% or more of EWL.

At 52 weeks, all participants in the primary ESG group were evaluated for suture reinforcement candidacy, and nine patients met the protocol-specific criteria to qualify for the reinforcement, having not met the primary endpoint (reached 25% or less of EWL). An additional five participants underwent a reinforcement procedure at the discretion of the treating investigator (figure 1, appendix p 13).

The weight loss trajectory of the crossover ESG group improved substantially, with participants achieving a mean 44·1% (SD 35·7) EWL at 52 weeks from crossover (figure 2, appendix p 14). The mean EWL of all participants who underwent the ESG procedure (both primary ESG and crossovers) at week 52 post procedure was 46·7% (33·8).

After 52 weeks, participants in the primary ESG group were followed up for an additional 52 weeks (study week 104). Of 60 participants who reached 25% or more of EWL, 41 (68%) maintained the reached EWL at 104 weeks (figure 2). Additionally, patients in the control group who did not reach the primary endpoint at 52 weeks, and who thus received crossover ESG, were followed up until week 104, along with the primary ESG group (figure 2). To understand performance in patients in the crossover ESG group, who completed a full year of lifestyle intervention before they received the procedure, we compared the results of participants in the primary ESG group in their first 52 weeks with the crossover patients who were followed up for an identical period. However, the conditions of follow-up were different between the groups, wherein the participants who crossed to ESG were followed up during the height of the COVID-19 pandemic.

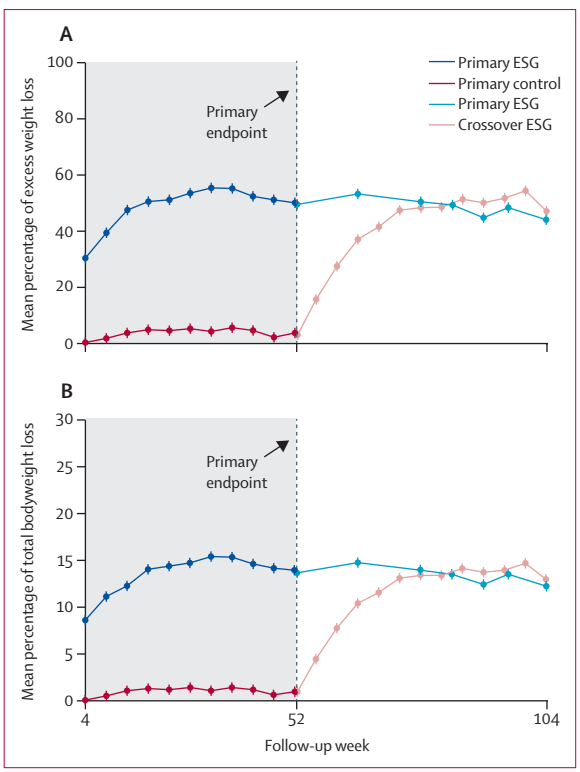

Figure 2: **Mean percentage of excess weight loss (A) and percentage of total bodyweight loss (B) by study group over time from initial treatment**
Error bars are 95% CI. After the conclusion of the 52-week visit, participants in the control group who met predefined criteria were eligible for crossover ESG. ESG=endoscopic sleeve gastroplasty.

In the primary ESG group, 55 (81%) of 68 participants reached the primary endpoint (≥25% EWL) at 52 weeks, compared with 46 (72%) of 64 in the crossover ESG group with a similar follow-up period. We found no statistical difference between the two groups using Mantel-Cox log rank test (p=0·21; appendix p 24).

We assessed the effect of the interventions on associated comorbidities. Our definition of amelioration or worsening of an associated comorbidity is relayed in the appendix (p 10). Fasting glucose concentrations, and the Homeostatic Model Assessment for Insulin Resistance significantly improved in the ESG group (primary and crossover) compared with the control group in all participants. For those with diabetes, HbA_{1c} levels significantly improved in the ESG group compared with the control group. Importantly, diabetes improved clinically in 25 (93%) of 27 participants in the ESG group compared with only four (15%) of 27 participants in the control group. None of the participants in the ESG group had clinical worsening of diabetes, whereas almost half of participants in the control group (12 [44%]) had clinical worsening of diabetes at the end of follow-up (table 2).

	ESG (primary)	Control	Rate difference*	p value†	ESG (primary and crossover)
Diabetes					
Improving	92% (12/13; 65 to 100)	15% (4/27; 5 to 33)	−77·5 (10·1; −91·4 to −47·4)	<0·0001	93% (25/27; 76 to 99)
Worsening	0% (0/13; 0 to 27)	44% (12/27; 28 to 63)	44·4 (9·6; 16·1 to 60·2)	0·0041	0% (0/27; 0 to 15)
Hyperlipidaemia					
Improving	40% (6/15; 20 to 64)	32% (8/25; 17 to 52)	8·0 (15·7; −37 to −22)	0·61	30% (7/23; 10 to 15)
Worsening	27% (4/15; 11 to 52)	28% (7/25; 14 to 48)	1·3 (14·9; −28 to 28)	0·93	30% (7/23; 10 to 15)
Hypertension					
Improving	67% (24/36; 50 to 80)	40% (19/48; 27 to 54)	−27·1 (10·6; −46·1 to 5·5)	0·014	60% (39/65; 48 to 71)
Worsening	6% (2/36; 1 to 19)	23% (11/48; 13 to 37)	17·4 (7·2; 1·5 to 30·7)	0·029	9% (6/65; 4 to 19)
Metabolic syndrome					
Improving	83% (24/29; 65 to 93)	35% (10/29; 20 to 53)	−48·3 (11·3; −67·0 to −23·3)	0·0002	83% (35/42; 69 to 92)
Worsening	0% (0/29; 0 to 14)	38% (11/29; 23 to 56)	37·9 (9·0; 17·2 to 53·7)	0·0002	5% (2/42; 1 to 17)
Effect on multiple comorbid conditions					
Improved at least 1 condition	41 (80%; n=51)	28 (45%; n=62)	..	..	70 (78%; n=90)
Worsened at least 1 condition	6 (12%; n=51)	31 (50%; n=62)	..	..	15 (17%; n=90)

Data are rate (n/N; 95% CI), rate difference (SE; 95% CI) or n (%; N). ESG=endoscopic sleeve gastroplasty. A negative rate difference indicates that the ESG rate was greater than the control rate. *Mean difference was calculated as the difference between the rate for the control group minus ESG group. †The p value was determined with an independent samples proportions test to evaluate differences between two rates.

Table 2: **Comorbidity 52-week change from baseline for randomly assigned participants**

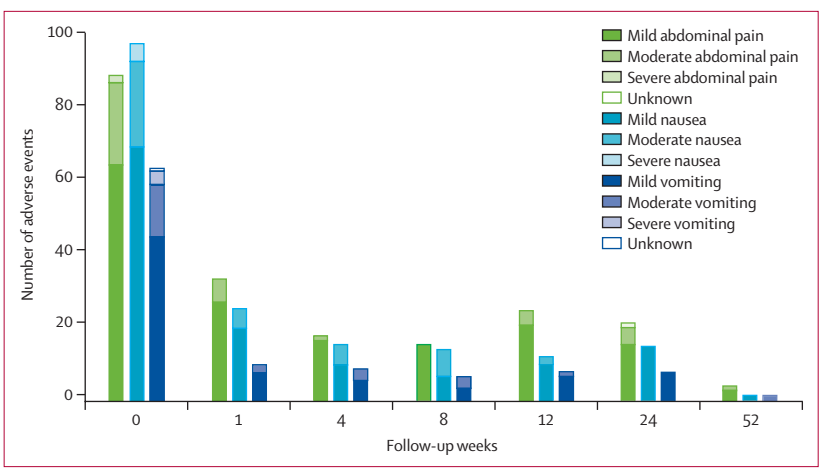

Figure 3: **Prevalent adverse events (device-related or procedure-related) associated with accommodative symptoms by severity and time from the ESG procedure**
The graph includes adverse events occurring after both primary and crossover ESG. ESG=endoscopic sleeve gastroplasty.

We observed a similar significant clinical improvement in terms of hypertension status, improving in 39 (60%) of 65 participants in the ESG group, compared with 19 (40%) of 48 in the control group. In terms of hypertension worsening, this occurred in 11 (23%) participants in the control group compared with only four (9%) participants in the ESG group. Similarly, those in the ESG group had HDL increase, triglycerides decrease, and improvement in waist-to-hip ratio compared with participants in the control group. Metabolic syndrome significantly improved in 35 (83%) of 42 participants in the ESG group, compared with only ten (35%) of 29 in the control group; 11 (38%) participants in the control group had a clinical worsening in terms of metabolic syndrome compared with two (5%) participants in the ESG group. ESG led to significantly improved levels of liver transaminases, hepatic steatosis index, aspartate transaminase-to-platelets ratio index, and C-reactive protein compared with control (appendix pp 16–17). Only six (12%) of 51 participants in the primary ESG group had worsening of at least one comorbidity during 52 weeks of follow-up, compared with 31 (50%) of 62 participants in the control group. Conversely, 41 (80%) participants in the primary ESG group had improvement in at least one comorbidity, compared with 28 (45%) participants in the control group during the same follow-up. Hyperlipidaemia accounted for most of the worsening comorbidities in the ESG group, rather than this being attributed to diabetes or hypertension. Gastroesophageal reflux disease symptoms did not worsen in the ESG group compared with the control group, as measured by monthly administration of a validated questionnaire (appendix p 28). Additionally, quality of life, eating behaviours, depression improvement, and patients' satisfaction were all superior in the ESG group compared with the control group.

ESG-related adverse events are reported for participants who underwent a completed or attempted ESG procedure (appendix pp 18–21). 927 events were reported in 138 (92%) of 150 participants in the primary and crossover ESG group. Two-thirds (612 [66%] of 927) of reported adverse events were accommodative gastrointestinal symptoms expected in the post-procedural acclimation period, including pain, heartburn, nausea, and vomiting. Most of these symptoms resolved within 1 week (figure 3). Three participants (2%) who underwent ESG had a

device-related or procedure-related adverse event that met the criteria of grade 3 (requiring surgical, endoscopic, or radiological intervention) or higher on the Clavien-Dindo classification scale. These events included abdominal abscess, managed endoscopically; upper gastrointestinal bleed, managed conservatively without transfusion; and a case of malnutrition requiring endoscopic reversal of the ESG. Six (4%) of 150 participants required subsequent hospital admission for medical management of accommodative symptoms. All participants with serious adverse events fully recovered, and the primary safety objective of 5% or less observed device-related or procedure-related serious adverse events was met.

Discussion

In this randomised trial, ESG with lifestyle modifications, compared with lifestyle modifications alone, resulted in significant improvements in terms of weight loss, metabolic comorbidities, quality of life, eating behaviours, and depression, with high participant satisfaction. Furthermore, gastroesophageal reflux disease incidence did not appear to be increased, as seen with other bariatric interventions, possibly due to the angle of His preservation, autonomic nervous integrity, and antral preservation.[15–17] Participants in the ESG group maintained a clinically-relevant weight loss at 2 years despite a pandemic that restricted activities, through quarantines, physical distancing, and emotional stress.[18,19] Participants in the ESG group were significantly more likely to have meaningful improvements in metabolic comorbidities, whereas 50% of participants in the control group had worsening of metabolic health during this time period. Bariatric surgery can also achieve significant and durable weight loss; however, penetration of surgery in severe obesity (BMI >40) is low and negligible for individuals with class 1 or class 2 obesity,[20] and the latter groups include the highest contributors to the global disease burden in terms of comorbidities and overall mortality.[21]

The COVID-19 pandemic affected this study, restricting in-person clinical follow-up visits. Additionally, crossover ESG procedures were delayed 1–6 months because medical facilities differed in their positions related to elective procedures during this time. It is important to note that participants in the control group who did not reach the weight loss target and who thus received crossover ESG did well despite the pandemic and reached similar weight loss to the primary ESG group over 52 weeks' follow-up. First, this shows that, despite the pandemic limiting healthy lifestyle activities, these participants reached similar weight loss, suggesting that the ESG efficacy might have an inherent patho-physiological basis, in addition to synergism with lifestyle modifications. Second, this good performance suggests that there is no advantage in delaying intervention to favour a lifestyle-change first approach. Participants in the control group were only offered crossover if they strictly adhered to their scheduled visits, despite their suboptimal weight response, for a full year. Despite this rigorous adherence, these participants did not have an amplified weight loss response when ESG was added and did not do better compared with those randomly assigned directly to receive ESG. This is consistent with previous literature relaying that enforced conservative weight management before bariatric surgery has no effect on post-intervention outcomes.[22] Therefore, it can be gleaned that a delay in ESG might not be additive to the patient's overall weight loss experience, and a so-called failure of lifestyle approach should not be a prerequisite for ESG.

Our study has some limitations. These include the absence of a sham intervention group, which is an inherent limitation, given the expected early accommodative symptoms after ESG.[23] Another limitation is the restricted nature of durability assessment and the absence of a comparative group between 52 weeks and 104 weeks. However, it is unlikely that the control group would reach a different trajectory in 2 years than what was observed at 52 weeks, especially with COVID-19 restrictions. Other limitations include an inadequate cohort size and follow-up to detect differences in the incidence of end-organ and cardiovascular outcomes and mortality. We should note that ESG was offered to enrolled participants at no cost. Therefore, having no financial investment in the weight loss intervention programme might have affected patient compliance, and results might have been even more robust if a financial incentive was in play. Additionally, our results are generalisable, as the trial was done in both academic and community settings, and procedures were done by gastroenterologists or bariatric surgeons with a range of experience and technical proficiency.

ESG is a minimally invasive alternative to laparoscopic sleeve gastrectomy that can be done at a lower BMI, offering a safe and effective option for individuals wishing to avoid surgery. Moreover, recent impressive findings achieved in the domain of pharmacological treatments have resulted in a new category of treatment options. In a recent phase 3 randomised controlled trial, a high dose of 2·4 mg subcutaneous semaglutide (a GLP-1 receptor agonist), given once per week, achieved a 9·6% decrease in mean bodyweight at 68 weeks compared with placebo.[24,25] In another recent randomised controlled trial, tirzepatide, a new GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide, resulted in significant weight loss at 72 weeks, up to 21% at a 15 mg once per week dose compared with only 3·1% weight loss in the placebo group.[26] However, these medications require an injection, and these weight loss results were only achieved at the highest dose. Additionally, gastrointestinal symptoms are often associated with these medications and can lead to the discontinuation of therapy. Furthermore, discontinuation of semaglutide was shown to result in a two-thirds weight regain and the return of some cardiometabolic parameters that approach baseline.[27] Although similar gastrointestinal

symptoms are reported with ESG, these symptoms are predominantly short-lived, and ESG was shown to maintain weight loss for 2 years after the procedure.

Obesity is a multifactorial chronic condition that cannot be managed the same way for everyone or with only one treatment intervention for the same person. The consideration of ESG in the treatment paradigm provides an option for a non-surgical, non-pharmacological solution for weight loss and management of comorbid conditions, especially for individuals who are not willing to consider or do not qualify for surgery as a treatment option. However, ESG might also allow for combination treatment with pharmacological options, depending upon personal goals of individuals.

The ESG with the OverStitch System meets and exceeds the minimum safety and effectiveness thresholds for endoscopic bariatric therapies defined by the joint task force convened by the American Society for Gastrointestinal Endoscopy and the American Society for Metabolic and Bariatric Surgery.[28,29] ESG induced clinically meaningful weight loss with improvements in obesity-related comorbid conditions of metabolic syndrome, type 2 diabetes, hypertension, quality of life, eating behaviours, and depression, and did not lead to worsening of gastroesophageal reflux disease, while maintaining a high patient satisfaction. In a multidisciplinary effort, ESG should be considered as a synergistic weight loss intervention for patients with class 1 or class 2 obesity.

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Contributors
BKAD and EBW conceptualised the study. BKAD, FB, EJV, RZS, CCT, BCT, AFT, CGC, VK, MBU, ACS, AJA, OG, TK, MM, MMC, KG, DB, PJ, and EBW were principal investigators or staff involved in the investigation. BKAD, FB, EJV, CD, and EBW designed the study or aspects of the methods. CD, CLK, and ARR curated, reviewed, and cleaned the data. JA and CD did the formal statistical analysis. BKAD acquired funding. BKAD, CLK, ARR, and EBW managed and coordinated the study. FB, JA, and BKAD wrote the original draft, and all authors critically reviewed and edited the manuscript. MGN, NSB, TDW, and NZ provided oversight and leadership, including mentorship or other study-crucial activities. BKAD, JA, and CD verified the analysed data and had full access to all information and data. All authors verify that this study was done according to protocol and vouch for the completeness, accuracy, and integrity of the data.

Declaration of interests
BKAD reports a consultant role for Endogenex, Endo-TAGSS, Metamodix, and BFKW; a consultant role and grants or research support from USGI, Spatz Medical, and Boston Scientific; speaker roles for Olympus and Johnson and Johnson; speaker fees and grant or research support from Medtronic and Endogastric Solutions; and research support from Apollo Endosurgery, Cairn Diagnostics, and Aspire Bariatrics. EBW reports grants or research support from Apollo Endosurgery and Activ Surgical; and honoraria from Intuitive, Covidien, Johnson & Johnson, and Gore Medical. RZS reports a consultant role and research support from Boston Scientific, Cook Medical, Olympus, and Lumendi. EJV reports unpaid leadership roles in the American Gastroenterological Association Trainee and Early Career Committee and American College of Gastroenterology and US Food and Drug Administration Related Matters Committee. CCT reports a consultant role for Apollo Endosurgery, Boston Scientific, Enterasense, EnVision Endoscopy, Fractyl, USGI Medical, Medtronic/Covidien, Olympus/Spiration, and GI Dynamics; being an advisory board member for USGI Medical and Fractyl; having received research grant and support from USGI Medical, Apollo Endosurgery, Boston Scientific, ERBE, FujiFilm, Lumendi Olympus/Spiration, Aspire Bariatrics, and GI Dynamics; having served as a general partner for Blueframe Healthcare; having served as a founder for Enterasense, EnVision Endoscopy, and GI Windows; and holding stock and royalties for GI Windows. CGC reports a consultant role for Boston Scientific, Apollo Endosurgery, and Olympus Corporation; a speaker role for Apollo Endosurgery, AbbVie, Boston Scientific, and Olympus; support for attending meetings from Boston Scientific, Apollo Endosurgery, and AbbVie; being a data safety and monitoring board (DSMB) member for BFKW, ERBE, and Nitinotes Surgical. VK reports a consultant role for ERBE, Apollo Endosurgery, Boston Scientific, FujiFilm, and Medtronic. MBU reports a consultant role for Boston Scientific, Cook, and Olympus; a speaker role for Apollo Endosurgery, Gore, Medtronic, and ERBE; and grants from Boston Scientific, Gore, and Medtronic. ACS reports research grant support from Apollo Endosurgery, Boston Scientific, Endogenex, Endo-TAGSS, and Enterasense; and a consultant role for Apollo Endosurgery, Boston Scientific, ERBE Elektromedizin, GI Dynamics, Intuitive Surgical, and Olympus. AJA reports a consultant role for Rhythm Pharmaceuticals, General Mills, and Amgen Pharmaceuticals; and holding shares of Gila Therapeutics and Phenomix Sciences. MM reports grants from Nestle, VectivBio, Zealand, Fresnius Kabi, and Realfood Blends; a consultant role for Baxter; being a DSMB member for EndoBarrier; and a leadership role at Oley Foundation. PJ reports a consultant role for Apollo Endosurgery, Spatz Medical, ERBS, and GI Dynamics; support for attending meetings from Endogastric Solutions; being a DSMB member for Spatz Medical; grants from Boston Scientific and ASGE; and a financial interest in USGI Medical, GI Dynamics, and Fractyl. NSB, TDW, and NZ were members of the DSMB for this study. ARR and CLK provided administrative assistance to the DSMB. CLK reports a leadership role in the American Society of Metabolic and Bariatric Surgery (ASMBS) Advance Practice Providers Committee, a role as co-chair of the ASMBS Programs Committee, and a vice president role with the Texas Association of Bariatric Surgery–Integrated Health. LE received research grant support from Mayo Clinic and is a consultant for Apollo Endosurgery. JA received research grant support from Mayo Clinic and was a consultant for Apollo Endosurgery at the time of the study; currently, JA is employed by Apollo Endosurgery as Senior Director, Global Clinical Affairs. MGN reports a consultant role for Apollo EndoSurgery, GI Dynamics, Keyron, and USGI; and a speaker role with Erbe. NZ was the DSMB chair for this study, and reports a consultant role for Ethicon, Medtronic, Olympus, GI Windows, Apollo Endosurgery, Boheringer, and LivsMed. DB, FB, BCT, AFT, OG, TK, MMC, CD, and KG declare no competing interests.

Data sharing
The study data are available from Prof Barham K Abu Dayyeh (abudayyeh.barham@mayo.edu) after the publication of the study. Individual participant data (de-identified), the coding dictionary, and other specific sets of data are available. The protocol, analysis plan, and informed consent document are also available upon request. Any other special data requests will require a proposal for approval, as well as a signed data share agreement.

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writing, and research support under a grant supported by the Mayo Clinic. VK is currently the chair of the Division of Gastroenterology and Hepatology at Mayo Clinic, Jacksonville, FL; however, he performed the work on this study at Johns Hopkins University. JA is currently Senior Director, Global Clinical Affairs at Apollo Endosurgery; however, she performed the work on this study through Pivotal Research Solutions, which was supported by a grant from Mayo Clinic.

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