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# Diabetic gastroenteropathy: Associations between gastrointestinal symptoms, motility, and extraintestinal autonomic measures

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## Abstract

**Background:** Diabetic gastroenteropathy can cause significant diagnostic challenges. Still, it remains unknown if measures of extraintestinal autonomic function reflect diabetic gastroenteropathy. We aimed to assess the associations between (1) gastrointestinal symptoms and motility measures and (2) gastrointestinal symptoms/motility measures and extraintestinal autonomic markers.

**Methods:** We included 81 persons with type 1 or type 2 diabetes (65% female, mean age 54) with gastrointestinal symptoms and autonomic neuropathy. The Gastroparesis Cardinal Symptom Index (GCSI) and the Gastrointestinal Symptom Rating Scale (GSRS) assessed gastrointestinal symptoms. The wireless motility capsule (Smartpill™) assessed panenteric transit times and motility indices. Cardiovascular reflex tests (VAGUS™) and cardiac vagal tone (eMotion Faros) estimated cardiovascular autonomic neuropathy, while the SUDOSCAN™ evaluated sudomotor function.

**Key Results:** Proximal gastrointestinal symptoms were positively associated with the gastric motility index (GCSI: 1.18 (1.04–1.35), $p=0.01$; GSRS: 1.15 (1.03–1.29), $p=0.02$; median ratio (95% CI)), while only satiety correlated with gastric emptying time (1.24 (1.03–1.49), $p=0.02$). Diarrhea was associated with decreased small bowel transit time (0.93 (0.89–0.98), $p=0.005$), while constipation were associated with prolonged colonic transit time (1.16 (1.03–1.31), $p=0.02$). Gastrointestinal symptoms increased with the degree of abnormal cardiovascular reflex tests (GCSI: 0.67 (0.16–1.19), $p=0.03$; GSRS: 0.87 (0.30–1.45), $p=0.01$; mean difference (95% CI)) but not with motility measures. Cardiac vagal tone and sudomotor function were not associated with gastrointestinal markers.

**Conclusions & Inferences:** Gastrointestinal and extraintestinal autonomic measures were not associated. However, proximal gastrointestinal symptoms were associated with the gastric motility index and cardiovascular reflex tests. Hence,

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the latter may contribute to evaluating whether proximal gastrointestinal symptoms are autonomically derived.

**KEYWORDS**
cardiovascular diagnostic technic, diabetic autonomic neuropathy, enteric neuropathy, gastrointestinal motility, gastrointestinal transit, signs and symptoms, digestive

## 1 | INTRODUCTION

Autonomic neuropathy affecting multiple organs is a common and severe complication of diabetes.[1] Neuropathy of the autonomic nerve fibers and enteric nervous system can affect the entire gastrointestinal tract, causing mild to severe symptoms.[2] Furthermore, unpredictable delivery of gastric content to the small bowel can cause unreliable drug absorption, blood glucose fluctuations, and even malnutrition.[3,4] The correlation between gastrointestinal symptoms and underlying pathophysiology is generally weak, so objective assessment is important to guide treatment.[5–8] Methods for direct evaluation of enteric neuropathy are not yet available in clinical practice.[9] Hence, gastrointestinal transit times and contractile activity are used as proxies for enteric autonomic dysfunction.[3,10] Evaluation should preferably be panenteric, and only two ingestible capsule systems, the wireless motility capsule, and the Motilis 3D-Transit system, qualify for this.[6] Unfortunately, the wireless motility system is being decommissioned, and the Motilis 3D-Transit system is not commercially available. Magnetic Resonance Imaging (MRI) has shown promising results for assessing panenteric motility and transit time measures; however, these protocols can only be performed at specialist centers.[11,12] This leaves clinicians with insufficient tools to diagnose enteric neuropathy. However, autonomic neuropathy is a systemic complication of diabetes, and tests of autonomic function from other organ systems could potentially represent proxies for objective assessment of enteric neuropathy. Tests for cardiovascular and sudomotor function are generally available. Still, before results from such tests can be used to qualify a diagnosis of enteric neuropathy, their association with tests of gastrointestinal function needs to be firmly established.

The function of the autonomic nervous system can be evaluated by direct assessment of autonomic nerve signals, limited by its invasive and time-consuming character. Instead, cardiovascular autonomic reflex testing is considered the gold standard for indirectly evaluating the presence of autonomic neuropathy by measuring, for example, heart rate response to physiological provocative maneuvers.[13] Likewise, long-term heart rate variability measurements are widely used, where parasympathetic activity can be differentiated from combined sympathetic and parasympathetic activity.[14] A validated short-term alternative is the cardiac vagal tone, evaluating the parasympathetic efferent activity by detecting phase shifts in the intervals between subsequent heartbeats by five-min recordings.[15] Furthermore, sweat tests for assessing the sudomotor function indirectly measure sympathetic activity by stimulating the sympathetically innervated sweat glands.[16] Cardiovascular autonomic tests have previously been used as indirect markers of enteric autonomic function in diabetes, with studies showing inconsistent correlations to gastric emptying times, and only minimal data are available for associations with gastrointestinal contractile activity.[17–19] Hence, it is unknown to what extent cardiovascular autonomic measurements reflect panenteric gastrointestinal transit times and contractile activity.

**Key points**

- Gastrointestinal and extraintestinal measures of autonomic neuropathy were not associated.
- Gastrointestinal symptoms increased with the severity of cardiovascular autonomic neuropathy.
- Gastrointestinal symptoms were associated with the gastric motility index and intestinal transit times.

We have recently collected a dataset on individuals with diabetes, moderate to severe gastrointestinal symptoms, and symptoms or markers of autonomic neuropathy. We used panenteric transit times and motility indices obtained with the wireless motility capsule as markers of gastrointestinal autonomic neuropathy. Cardiovascular autonomic reflex tests measured with the VAGUS device, cardiac vagal tone obtained with the eMotion Faros device, and sudomotor function evaluated with the SUDOSCAN device were used as markers of extraintestinal autonomic neuropathy.[20]

For the present study, our first aim was to assess if gastrointestinal symptoms were associated with gastrointestinal transit times or contractile activity. Our second aim was to examine whether gastrointestinal symptoms, transit times, or contractile activity were associated with either cardiovascular autonomic reflex tests, cardiac vagal tone (mainly a test of parasympathetic activity), or sudomotor function (primarily a test of sympathetic activity) (Figure 1).

## 2 | MATERIALS AND METHODS

### 2.1 | Study participants

Data were obtained from a randomized, sham-controlled, multicenter trial investigating the effect of non-invasive vagal nerve stimulation for treating gastrointestinal symptoms in individuals

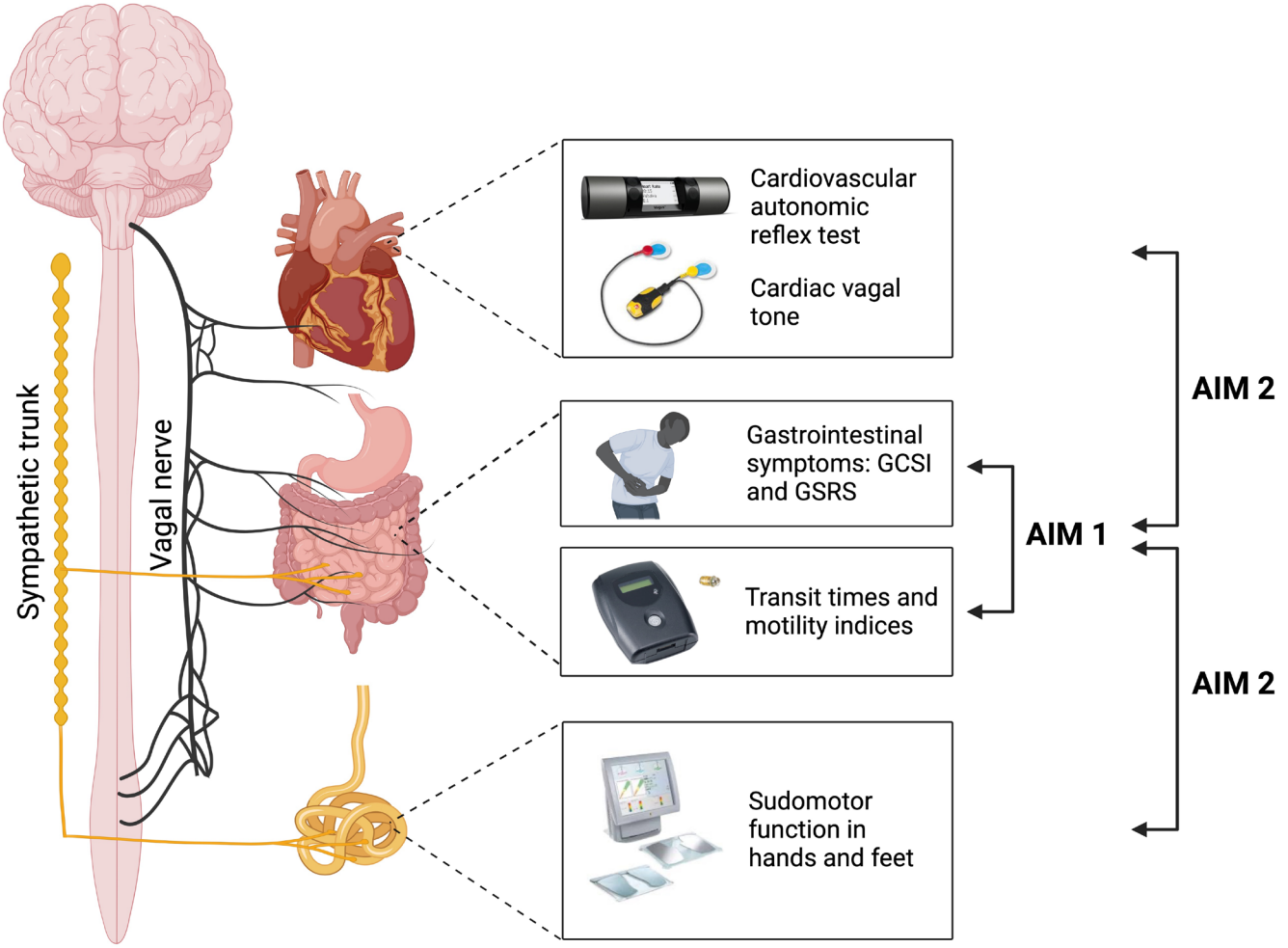


**FIGURE 1** Overview of the methods used to assess cardiovascular, gastrointestinal, and sudomotor functions while also schematically presenting the study aims.

with diabetes (clinical trial registration: NCT04143269).[21] The study consisted of two study periods separated by a two-week washout period. The present data represents the baseline recordings of the second study period, where the wireless motility capsule recordings were obtained.

Participants were recruited through social media, patient forums, or outpatient gastroenterology and endocrinology clinics at the Danish University Hospitals in Aalborg, Aarhus, and Copenhagen. The participants were adults, had type 1 or type 2 diabetes for a minimum of 1 year, and had gastrointestinal symptoms, as presented in Figure 2. The cut-off for having gastrointestinal symptoms was based on the Gastroparesis Cardinal Symptom Index (GCSI) and the Gastrointestinal Symptom Rating Scale (GSRS) in healthy cohorts.[21] Furthermore, autonomic neuropathy was confirmed by either a Composite Autonomic Symptoms Score (COMPASS-31) above 16,[22] at least one abnormal cardiovascular reflex test (VAGUS™),[23,24] or a decreased sudomotor function (SUDOSCAN™) defined as electrochemical chloride conduction <70μS for the feet and <50μS for the hands.[25] Individuals with known gastrointestinal or cardiovascular disease besides autonomic neuropathy complications were excluded. All examinations were performed at the hospital in a quiet room, with participants refraining from smoking, eating, and drinking caffeine overnight. Stable habitual medication intake was required in the randomized trial. Thus, regular intake of drugs affecting gastrointestinal motility was continued.

The study received ethical approval from the North Denmark Region Committee on Health Research Ethics (N-20190020) and the Danish Medicines Agency (CIV-19-07-029105). An independent Good Clinical Practice unit monitored the study, and it was registered at ClinicalTrials.gov (NCT04143269). All individuals provided written informed consent.

## 2.2 | Gastrointestinal symptoms

Two questionnaires were used to evaluate gastrointestinal symptoms, demonstrating good internal consistency and reliability between tests. The GCSI comprises nine questions from The Patient Assessment of Upper Gastrointestinal Symptom Severity Index rated on a Likert scale from 0 to 5, representing no to very severe

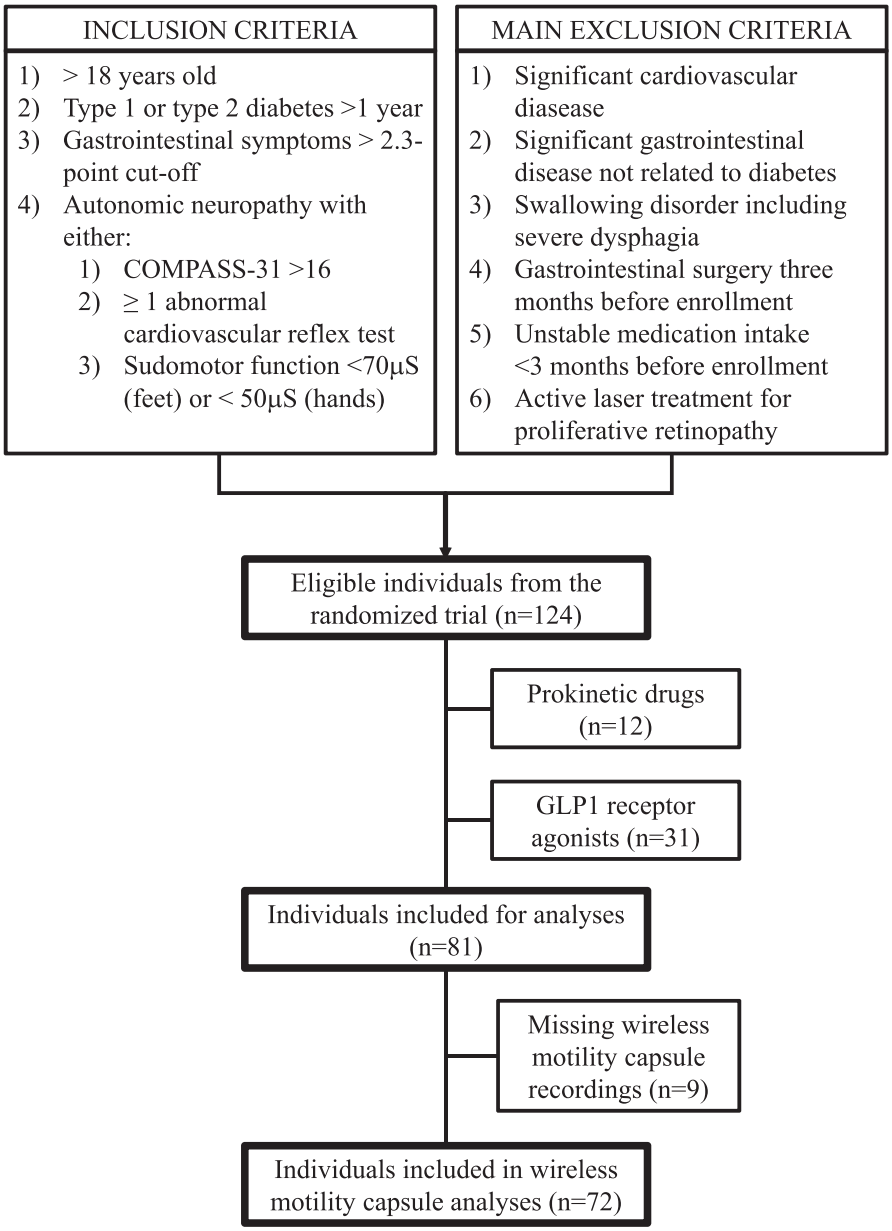


**FIGURE 2** Flowchart presenting the inclusion and exclusion criteria applied in the randomized trial followed by the extended exclusion criteria applied in the present secondary analysis.

symptoms.[26] The GCSI can be subdivided into nausea/vomiting, bloating, and postprandial fullness scores.[27] The GSRS includes 15 questions on a Likert scale from 1 to 7, representing no discomfort to very severe discomfort, and evaluates the symptom severity across reflux, abdominal pain, indigestion, diarrhea, and constipation scores.[28] The average value of the symptom sub-scores determined the total scores in the questionnaires.

## 2.3 | Gastrointestinal motility

The wireless motility capsule (SmartPill™, Medtronic, Minneapolis, Minnesota, USA) was used to evaluate objective measures of gastrointestinal motility, including segmental gastrointestinal transit times and contractile activity.[29–31] To induce a postprandial state, capsule ingestion was preceded by consumption of a standardized 260 kcal SmartBar followed by 6 hours of fasting. Data were continuously transmitted to a portable receiver, with the capsule measuring temperature, pH, and pressure while passing through the gastrointestinal tract. Two independent investigators used the related software (Medtronic MotiliGI™ version 3.1) to determine the physiological landmarks defining the transition between gastrointestinal segments and reached a consensus on discrepancies.[31] A temperature rise defined capsule ingestion, while specific pH changes defined the capsule transition between segments. An abrupt temperature drop, a sudden signal loss following a registered bowel movement, or total data loss defined capsule expulsion.[31] When severe data loss limited the evaluation of segmental transition, the segmental data before and after was excluded. The complementary software calculated segmentally divided motility indices by combining information on contraction amplitudes and frequencies, using solely contractions

measures between 10 mmHg and 300 mmHg.[32] To determine pathologically fast or prolonged segmental transit times and motility indices, data were compared to our previously published normative data using the 5th percentile (lower limit) and the 95th percentile (upper limit), respectively.[29,30]

### 2.4 | Cardiovascular autonomic reflex tests

Cardiovascular autonomic neuropathy can be diagnosed based on cardiovascular autonomic reflex testing. The hand-held VAGUS™ device (Medicus Engineering, Aarhus, Denmark) was used to conduct three standardized cardiovascular autonomic reflex tests. Two intra-device electrocardiogram electrodes continuously measure the interval between subsequent heartbeats (R-R interval) in response to (1) posture change from lying to standing (lying-to-standing test), (2) deep breathing with six breaths/minute (expiration/inspiration test), and (3) forced 15-second expiration against a standardized resistance mouthpiece followed by 45 s relaxed breathing (Valsalva maneuver).[23] The outputs represent the ratios between the shortest and longest R-R interval or the mean R-R interval at standardized test sequences.[33] Each test result was compared to pre-defined age-matched cut-off values in healthy individuals.[34] Three normal tests indicate no cardiovascular autonomic neuropathy, one abnormal test suggests early-stage neuropathy, while two or three abnormal tests indicate manifest neuropathy.[24]

### 2.5 | Cardiac vagal tone

The cardiac vagal tone was assessed with the eMotion Faros device (Mega Electronics, Kuopio, Finland), an electrocardiogram monitor receiving signals from three standard chest-placed electrodes. It evaluates the parasympathetic efferent nervous signal by detecting phase shifts in the intervals between subsequent heartbeats for 5 min while the participants are resting.[15,35,36] The cardiac vagal tone is measured on a linear vagal scale, with 0 indicating a total parasympathetic acetylcholine neurotransmitter blockage, calculated by the ProBioMetrics online application (ProBioMetrics, Version 1.0, Kent, UK).[13] Each 5-min recording typically contains 300 data points. Artifacts were removed as previously described.[36] A cardiac vagal tone cut-off value of 3.18 was used to dichotomize the data in pathological and non-pathological, as a value below this cut-off indicates established cardiovascular autonomic neuropathy.[36]

### 2.6 | Sudomotor function

The SUDOSCAN™ device (Impeto Medical, California, San Diego, USA) assessed the functionality of the sympathetically innervated sweat glands, suggested to be an early indicator of small fiber neuropathy.[37] The sudomotor function is represented by the electrochemical skin conductance of sweat chloride induced by applying a low voltage current (<4 V) to the hands and feet by two stainless steel electrodes.[38] The scores provided represent the measured and applied current ratio, averaged between the left and right sides in micro-Siemens (μS). To detect abnormal sudomotor function, cut-offs of 50μS for hands and 70μS for feet were applied.[25]

### 2.7 | Statistical analyses

The electronic data management tool REDCap was used for data collection. Visual inspection of QQ plots and histograms was used to evaluate data distribution. Normally distributed baseline data were reported as means with 95% confidence intervals (95% CI), non-normally distributed baseline data as medians with interquartile ranges (IQR), and baseline counts were reported with frequencies.

Linear regression analyses explored the relationship between wireless motility capsule measurements as outcome variables using the following predictor variables: (1) gastrointestinal symptoms, (2) cardiovascular autonomic neuropathy score, (3) cardiac vagal tone, and (4) sudomotor function. Furthermore, gastrointestinal symptoms were used as the outcome variable, with the cardiovascular autonomic neuropathy score, cardiac vagal tone, and sudomotor function as predictor variables. HbA1c was likewise used as the outcome variable in linear regression analysis, with gastrointestinal symptoms, motility measures, and extraintestinal autonomic measures as predictor variables. The regression outputs were mean differences (MD) with 95% CI for outcome variables with normally distributed residuals. However, logarithmic transformations were performed before running the analyses when the residuals were skewed, followed by post-analysis retransformation, leading to median ratios (MR) with 95% CI as outputs. The MD and MR measures represent the change in the outcome variable for every 1-point increase in the predictor variable. The *p*-values were obtained with an *F*-test for the categorical cardiovascular autonomic neuropathy score, describing whether any group significantly differed from the reference group (no cardiovascular autonomic neuropathy).

The abovementioned analyses were repeated after the exclusion of those taking laxatives. Two severely prolonged gastric emptying times were observed, and sensitivity analyses were done without those. Two-sided *p*-values without adjustments for multiple comparisons were presented, as the analyses were explorative. Statistical analyses were done in Stata version 17.0 (StataCorp, TX, USA).

## 3 | RESULTS

### 3.1 | Participant characteristics

Data on 124 participants were available from the randomized study (Figure 2). Twelve individuals using prokinetic drugs (metoclopramide, domperidone, or prucalopride) and 31 using GLP1 receptor

**TABLE 1** Baseline demographic and clinical characteristics.

| | All ($n=81$) | Type 1 diabetes ($n=52$) | Type 2 diabetes ($n=29$) |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, mean (95% CI), years | 54 (50–57) | 49 (44–53) | 62 (59–66) |
| Female sex, *n* (%) | 53 (65) | 41 (79) | 12 (41) |
| BMI, mean (95% CI), kg/m$^2$ | 29 (27–30) | 28 (26–29) | 31 (29–32) |
| Smoking | | | |
| Current, *n* (%) | 10 (12) | 7 (13) | 3 (10) |
| Previous, *n* (%) | 31 (45) | 20 (47) | 11 (42) |
| Clinical characteristics | | | |
| Diabetes duration, median (IQR), years[a] | 18 (10–36) | 29 (17–39) | 11 (5–15) |
| HbA1c, mean (95% CI), mmol/mol | 61 (58–63) | 62 (58–65) | 59 (54–63) |
| Creatinine, median (IQR), μmol/l[a] | 69 (59–80) | 67 (59–79) | 72 (57–80) |
| Estimated glomerular filtration rate (eGFR) <60 mL/min, *n* (%) | 8 (10) | 4 (8) | 4 (14) |
| Systolic blood pressure, mean (95% CI), mmHg | 135 (132–138) | 135 (130–139) | 136 (131–141) |
| Diastolic blood pressure, mean (95% CI), mmHg | 80 (78–82) | 81 (77–84) | 79 (76–82) |
| Pulse, mean (95% CI), beats per minute | 70 (67–73) | 70 (66–73) | 71 (65–76) |
| Charlson Comorbidity Index Score, median (IQR) | 2 (2–2) | 2 (2–2) | 2 (1–2) |
| Gastroparesis Cardinal Symptom Index, mean (95% CI)[b] | 1.87 (1.65–2.10) | 2.07 (1.81–2.33) | 1.51 (1.11–1.91) |
| Gastrointestinal Symptom Rating Scale, mean (95% CI)[b] | 2.84 (2.59–3.10) | 2.92 (2.63–3.20) | 2.70 (2.17–3.23) |

[a]Data on 80 participants, including 51 with type 1 diabetes.
[b]Data on 80 participants, including 52 with type 1 diabetes.

agonists (30 with type 2 diabetes) were excluded due to their effects on gastrointestinal motility. Table 1 shows the demographic and clinical characteristics of the remaining 81 participants, further stratified by type of diabetes. Table 2 presents autonomic and gastrointestinal characteristics, with 85% of participants having autonomic neuropathy based on the COMPASS-31 score and 60% having cardiovascular autonomic neuropathy based on at least one abnormal reflex test. A low cardiac vagal tone was seen in 45%, and an abnormal sudomotor function in approximately 40%. The median segmental transit times were below the 95 percentiles for healthy individuals.[29] Pathologically prolonged gastric emptying, small bowel transit, and colonic transit times were seen in 24%, 18%, and 31%, while pathologically fast transit times were seen in 15%, 21%, and 3%, respectively. The median motility indices were within the normative values (below the 95th and above the 5th percentiles) for healthy individuals, and the frequencies of pathologically low or high indices were all below 12%. Participants with type 1 diabetes generally had longer transit times and higher gastric motility indices compared to those with type 2 diabetes. Otherwise, the remaining gastrointestinal and extraintestinal autonomic characteristics were comparable across diabetes types.

## 3.2 | Missing data

Wireless motility capsule data were available for 72 participants; missing data were caused by two inadequately saved recordings, three malfunctioning capsules/receivers, and three participants unable to swallow the capsule. Additionally, one recording was excluded due to gastric emptying time ten standard deviations above the mean, followed by subsequent battery loss. In contrast, two less severe gastric emptying time outliers were included, but a sensitivity analysis without these outliers yielded no key result changes. In the cardiovascular autonomic neuropathy score, device issues caused

**TABLE 2** Measurements of autonomic and gastrointestinal function.

| | All | Type 1 diabetes | Type 2 diabetes |
|---|---|---|---|
| *Autonomic characteristics* | *n* = 81 | *n* = 52 | *n* = 29 |
| Composite Autonomic Symptom Score 31 (COMPASS-31), mean (95% CI) | 36 (32–39) | 35 (31–39) | 36 (29–43) |
| COMPASS 31 > 16, n (%) | 69 (85) | 45 (87) | 24 (83) |
| Cardiovascular autonomic neuropathy score (CAN) | | | |
| No CAN, n (%) | 32 (40) | 19 (37) | 13 (45) |
| Early CAN, n (%) | 22 (27) | 14 (27) | 8 (28) |
| Manifest CAN, n (%) | 27 (33) | 19 (37) | 8 (28) |
| SUDOSCAN | | | |
| Electrochemical chloride conductance for the hands, median (IQR), μS | 61 (45–74) | 57 (44–74) | 68 (47–73) |
| <50μS, n (%) | 32 (40) | 22 (42) | 10 (34) |
| Electrochemical chloride conductance for the feet, median (IQR), μS | 77 (55–85) | 74 (52–82) | 79 (70–86) |
| <70μS, n (%) | 31 (38) | 23 (44) | 8 (28) |
| Cardiac vagal tone (CVT), median (IQR)[a] | 3.29 (2.22–5.63) | 3.45 (2.46–5.98) | 2.97 (2.07–4.81) |
| CVT <3.18, n (%) | 31 (45) | 18 (40) | 13 (54) |
| *Gastrointestinal characteristics* | *n* = 72 | *n* = 45 | *n* = 27 |
| Gastric emptying time, median (IQR), min | 200 (156–292) | 219 (157–313) | 189 (143–229) |
| Pathologically fast: <112 min (female) or < 102 min (male), n (%) | 11 (15) | 7 (16) | 4 (15) |
| Pathologically slow: > 298 min (female) or > 293 min (male), n (%) | 17 (24) | 13 (29) | 4 (15) |
| Small bowel transit time, median (IQR), min | 282 (224–333) | 287 (230–332) | 251 (213–334) |
| Pathologically fast: < 136 min (female) or < 146 min (male), n (%) | 15 (21) | 9 (20) | 6 (22) |
| Pathologically slow: > 522 min (female) or > 345 min (male), n (%) | 13 (18) | 10 (22) | 3 (11) |
| Colonic transit time, median (IQR), min | 2208 (1040–3751) | 2572 (1396–4232) | 1069 (846–2274) |
| Pathologically fast: < 448 min (female) or < 259 min (male), n (%) | 2 (3) | 1 (2) | 1 (4) |
| Pathologically slow: > 2977 min (female) or > 3032 min (male), n (%) | 22 (31) | 17 (38) | 5 (19) |
| Whole gut transit time, median (IQR), min | 2776 (1461–4622) | 3299 (2351–4848) | 1561 (1380–2776) |
| Pathologically fast: < 812 min (female) or < 626 min (male), n (%) | 1 (2) | 0 (0) | 1 (4) |
| Pathologically slow: > 4360 min (female) or > 3928 min (male), n (%) | 20 (28) | 15 (33) | 5 (19) |
| Gastric motility index, median (IQR) | 61 (41–88) | 66 (45–98) | 58 (34–83) |
| Pathologically low: < 14 (female) or < 13 (male), n (%) | 0 (0) | 0 (0) | 0 (0) |
| Pathologically high: > 175 (female) or > 138 (male), n (%) | 5 (7) | 5 (11) | 0 (0) |
| Small bowel motility index, median (IQR)[b] | 153 (94–239) | 166 (94–233) | 139 (98–245) |
| Pathologically low: < 63 (female) or < 47 (male), n (%) | 6 (8) | 5 (11) | 1 (4) |
| Pathologically high: > 381 (female) or > 263 (male), n (%) | 7 (10) | 4 (9) | 3 (11) |
| Colonic motility index, median (IQR)[b] | 187 (122–273) | 183 (118–257) | 188 (131–273) |
| Pathologically low: < 52 (female) or < 70 (male), n (%) | 3 (4) | 1 (2) | 2 (7) |
| Pathologically high: > 383 (female) or > 399 (male), n (%) | 3 (4) | 2 (5) | 1 (4) |
| Delta ileocecal junction pH-drop, mean (95% CI)[c] | 1.8 (1.5–2.1) | 1.8 (1.5–2.1) | 1.8 (1.4–2.0) |

[a]Data on 69 participants, 45 with type 1 diabetes.

[b]Data on 71 participants, 44 with type 1 diabetes.

[c]Data on 70 participants, 43 with type 1 diabetes.

Previously published normative 5th percentiles (lower limit) and 95th percentiles (upper limit) are registered for each gastrointestinal segment and were used to determine whether segmental transit times and motility indices were pathologically fast or prolonged.

15 missing Valsalva test values. Nevertheless, all 81 scores were available for analysis based on the remaining two tests. Seven cardiac vagal tone recordings were excluded due to poor data quality, and five were missing due to electrode signal loss, leaving 69 recordings for analysis.

### 3.2.1 | Associations between gastrointestinal symptoms and motility

For the transit times, a higher satiety sub-score was associated with a longer median gastric emptying time (Table 3). However,

**TABLE 3** Associations between gastrointestinal symptoms and objective gastrointestinal markers.

| | Gastric emptying time | | Small bowel transit time | | Colonic transit time | |
|---|---|---|---|---|---|---|
| | Median ratio (95% CI) | *p* value | Median ratio (95% CI) | *p* value | Median ratio (95% CI) | *p* value |
| Gastroparesis Cardinal Symptom Index | 1.20 (0.96–1.51) | 0.11 | 1.00 (0.92–1.08) | 0.96 | 1.03 (0.84–1.27) | 0.77 |
| Nausea/vomiting sub-score | 1.07 (0.82–1.39) | 0.62 | 0.93 (0.85–1.01) | 0.09 | 1.05 (0.84–1.33) | 0.65 |
| Bloating sub-score | 1.07 (0.92–1.25) | 0.36 | 1.01 (0.96–1.07) | 0.59 | 0.97 (0.85–1.11) | 0.68 |
| Satiety sub-score | 1.24 (1.03–1.49) | **0.02** | 1.01 (0.95–1.08) | 0.66 | 1.08 (0.91–1.27) | 0.36 |
| Gastrointestinal Symptom Rating Scale | 1.08 (0.88–1.32) | 0.45 | 0.96 (0.90–1.03) | 0.25 | 1.00 (0.84–1.20) | 0.96 |
| Reflux sub-score | 1.16 (0.98–1.37) | 0.08 | 0.95 (0.90–1.01) | 0.09 | 0.93 (0.80–1.08) | 0.36 |
| Abdominal pain sub-score | 1.04 (0.88–1.23) | 0.63 | 0.97 (0.92–1.03) | 0.36 | 1.00 (0.86–1.15) | 0.97 |
| Indigestion sub-score | 1.07 (0.92–1.26) | 0.37 | 0.98 (0.93–1.03) | 0.43 | 1.01 (0.88–1.16) | 0.88 |
| Diarrhea sub-score | 0.93 (0.80–1.08) | 0.34 | 0.93 (0.89–0.98) | **0.005** | 0.90 (0.79–1.03) | 0.13 |
| Constipation sub-score | 1.07 (0.93–1.24) | 0.34 | 1.04 (0.99–1.09) | 0.16 | 1.16 (1.03–1.31) | **0.02** |

| | Gastric motility index | *p* value | Small bowel motility index | *p* value | Colonic motility index | *p* value |
|---|---|---|---|---|---|---|
| Gastroparesis Cardinal Symptom Index | 1.18 (1.04–1.35) | **0.01** | 1.00 (0.87–1.14) | 0.96 | 0.96 (0.83–1.11) | 0.57 |
| Nausea/vomiting sub-score | 1.23 (1.06–1.43) | **0.007** | 1.06 (0.92–1.24) | 0.41 | 0.96 (0.82–1.13) | 0.65 |
| Bloating sub-score | 1.08 (0.99–1.18) | 0.07 | 0.98 (0.90–1.07) | 0.69 | 0.97 (0.88–1.07) | 0.53 |
| Satiety sub-score | 1.10 (0.99–1.23) | 0.08 | 0.99 (0.89–1.10) | 0.83 | 0.98 (0.88–1.11) | 0.78 |
| Gastrointestinal Symptom Rating Scale | 1.15 (1.03–1.29) | **0.02** | 0.97 (0.86–1.09) | 0.62 | 0.95 (0.84–1.08) | 0.41 |
| Reflux sub-score | 1.18 (1.08–1.30) | **0.001** | 0.99 (0.90–1.10) | 0.91 | 0.99 (0.86–1.10) | 0.79 |
| Abdominal pain sub-score | 1.13 (1.02–1.23) | **0.02** | 0.99 (0.90–1.10) | 0.88 | 0.95 (0.86–1.06) | 0.35 |
| Indigestion sub-score | 1.08 (0.98–1.18) | 0.12 | 1.01 (0.92–1.11) | 0.88 | 0.94 (0.85–1.04) | 0.24 |
| Diarrhea sub-score | 1.10 (1.00–1.20) | **0.04** | 0.97 (0.88–1.06) | 0.44 | 0.92 (0.84–1.01) | 0.08 |
| Constipation sub-score | 1.01 (0.93–1.10) | 0.76 | 0.96 (0.88–1.04) | 0.33 | 1.04 (0.95–1.13) | 0.42 |

*Note*: The results represent the change in segmental transit times and motility indexes for each 1-point increase in gastrointestinal symptom scores. Bold values represent *p*-values < 0.05.

this association lost significance when the two gastric emptying time outliers were excluded. Each 1-point increase in the diarrhea sub-score was associated with an estimated 7% (MR 0.93, 95% CI 0.89–0.98, $p=0.005$) reduction of the small bowel transit time, while every increase in the constipation sub-score was associated with an estimated 16% (MR 1.16, 95% CI 1.03–1.31, $p=0.02$) longer colonic transit time (Figure 3).

For the motility indices, each 1-point increase in the GCSI and the GSRS was associated with an estimated 18% (MR 1.18, 95% CI 1.04–1.35, $p=0.01$) and 15% (MR 1.15, 95% CI 1.03–1.30, $p=0.02$) increase in the gastric motility index, respectively (Figure 3). Except for the constipation sub-score, the increase of the gastric motility index with symptoms was persistent across all symptom-specific sub-scores, even though the bloating, satiety, and indigestion sub-scores did not reach statistical significance. The remaining small bowel and colonic transit times and motility indices were not associated with symptoms. The exclusion of nine participants taking laxatives and the two gastric emptying time outliers did not affect these results. No associations were observed between HbA1c and gastrointestinal symptoms, transit times, or motility indices (data not shown).

### 3.2.2 | Associations between gastrointestinal symptoms and extraintestinal autonomic measures

Table 4 and Figure 4 show increased gastrointestinal symptoms with every rise in the cardiovascular autonomic neuropathy score. The mean GCSI was 0.67 (95% CI 0.16–1.19, $p=0.03$) points higher, and the mean GSRS was 0.87 (95% CI 0.30–1.45 $p=0.01$) points higher in individuals with manifest cardiovascular autonomic neuropathy compared to those without. The symptomatic increase was more prominent for manifest than for early cardiovascular autonomic neuropathy. Proximal gastrointestinal symptoms drove these correlations, as the increased diarrhea sub-score across cardiovascular autonomic neuropathy categories was insignificant, and the constipation sub-score remained

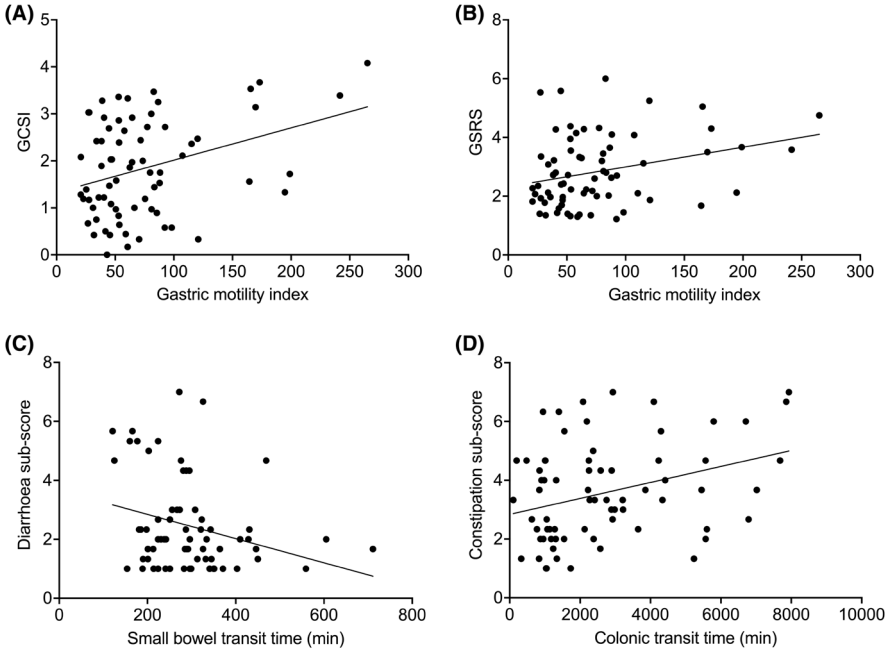


**FIGURE 3** (A) Scatterplot visualizing the association between the gastric motility index and the Gastroparesis Cardinal Symptom Index (GCSI), $n = 70$, (B) between the gastric motility index and the Gastrointestinal Symptom Rating Scale (GSRS), $n = 71$, (C) between the diarrhea sub-score and the small bowel transit time, $n = 71$, and (D) between the constipation sub-score and the colonic transit time, $n = 71$.

**TABLE 4** Gastrointestinal measurements in individuals with no, early, or manifest cardiovascular autonomic neuropathy.

| | No cardiovascular autonomic neuropathy (CAN 0) | Early cardiovascular autonomic neuropathy (CAN 1) | Manifest cardiovascular autonomic neuropathy (CAN 2/3) | *p* value |
|---|---|---|---|---|
| Gastrointestinal symptoms | | | | |
| Gastroparesis Cardinal Symptom Index, mean (95% CI) and mean difference (95% CI) | 1.58 (1.23–1.94)<br>0.0 | 1.79 (1.38–2.20)<br>0.21 (−0.33–0.75) | 2.26 (1.88–2.63)<br>0.67 (0.16–1.19) | **0.03** |
| Gastrointestinal Symptom Rating Scale, mean (95% CI) and mean difference (95% CI) | 2.49 (2.10–2.88)<br>0.0 | 2.69 (2.22–3.15)<br>0.19 (−0.41–0.80) | 3.37 (2.95–3.79)<br>0.87 (0.30–1.45) | **0.01** |
| Diarrhea sub-score, mean (95% CI) and mean difference (95% CI) | 2.09 (1.55–2.62)<br>0.0 | 2.20 (1.56–2.84)<br>0.11 (−0.72–0.95) | 2.93 (2.35–3.50)<br>0.84 (0.05–1.63) | 0.09 |
| Constipation sub-score, mean (95% CI) and mean difference (95% CI) | 3.58 (2.99–4.17)<br>0.0 | 3.26 (2.55–3.96)<br>0.32 (−1.24–0.60) | 3.93 (3.29–4.56)<br>0.35 (−0.52–1.22) | 0.37 |
| Transit times | | | | |
| Gastric emptying time, median (95% CI) and median ratio (95% CI), minutes | 180 (124–262)<br>1.0 | 270 (174–418)<br>1.50 (0.84–2.66) | 281 (190–415)<br>1.56 (0.91–2.68) | 0.21 |
| Small bowel transit time, median (95% CI) and median ratio (95% CI), minutes | 268 (234–306)<br>1.0 | 286 (245–334)<br>1.07 (0.87–1.31) | 270 (235–310)<br>1.01 (0.83–1.22) | 0.79 |
| Colonic transit time, median (95% CI) and median ratio (95% CI), minutes | 1721 (1228–2411)<br>1.0 | 1853 (1252–2742)<br>1.08 (0.64–1.81) | 2217 (1561–3148)<br>1.29 (0.79–2.10) | 0.57 |
| Whole gut transit time, median (95% CI) and median ratio (95% CI), minutes | 2367 (1826–3068)<br>1.0 | 2800 (2072–3786)<br>1.18 (0.79–1.76) | 3036 (2319–3975)<br>1.28 (0.88–1.86) | 0.40 |
| Motility indexes | | | | |
| Gastric motility index, median (95% CI) and median ratio (95% CI) | 54 (43–68)<br>1.0 | 66 (50–85)<br>1.22 (0.86–1.72) | 72 (57–91)<br>1.34 (0.96–1.85) | 0.21 |
| Small bowel motility index, median (95% CI) and median ratio (95% CI) | 139 (110–174)<br>1.0 | 169 (129–221)<br>1.22 (0.85–1.74) | 136 (107–172)<br>0.98 (0.71–1.36) | 0.44 |
| Colonic motility index, median (95% CI) and median ratio (95% CI) | 143 (112–182)<br>1.0 | 203 (155–267)<br>1.42 (0.99–2.04) | 173 (125–220)<br>1.21 (0.86–1.70) | 0.16 |

*Note*: The results represent the change in gastrointestinal symptoms and objective markers for each 1-point cardiovascular autonomic neuropathy score increase. Bold values represent *p*-values < 0.05.

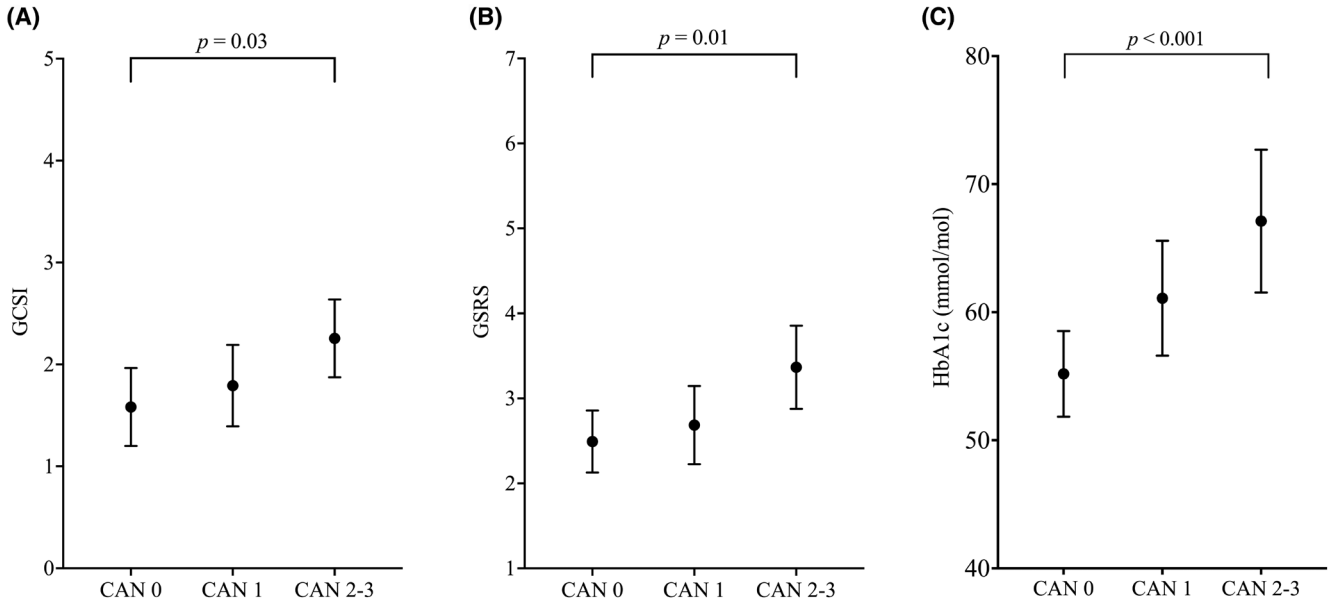


FIGURE 4 (A) The mean Gastroparesis Cardinal Symptom Index (GCSI) with 95% CI presented for each severity category of the cardiac autonomic neuropathy score (CAN), $n = 79$, (B) the mean Gastrointestinal Symptom Rating Scale (GSRS) with 95% CI for each CAN severity category, $n = 80$, and (C) the mean HbA1c level with 95% CI for each CAN severity category, $n = 81$. CAN 0 represents no cardiovascular autonomic neuropathy, CAN 1 early-stage, and CAN 2–3 manifest.

unchanged. Neither cardiac vagal tone nor sudomotor function were associated with gastrointestinal symptoms Table (S1). Interestingly, the HbA1c levels likewise increased with the severity of the cardiovascular autonomic neuropathy score (Figure 4).

### 3.2.3 | Associations between gastrointestinal motility and extraintestinal autonomic measures

The cardiovascular autonomic neuropathy score: The gastric motility index was estimated to be 34% (MR 1.34, 95% CI 0.96–1.85, $p = 0.21$) higher, and the gastric emptying time was estimated to be 56% (MR 1.56, 0.91–2.68, $p = 0.21$) higher in the group with manifest cardiovascular autonomic neuropathy compared to those without cardiovascular autonomic neuropathy. Notably, these associations were not statistically significant. Neither the small bowel motility index, the colonic motility index, nor the remaining segmental transit times correlated to the cardiovascular autonomic neuropathy score severity (Table 4).

Cardiac vagal tone and sudomotor function: Each 1-point increase in the cardiac vagal tone was associated with an estimated 6% (MR 0.86–1.01, $p = 0.10$) non-significant reduction in the gastric emptying time and an estimated 3% (MR 0.97, 95% CI 0.94–1.00, $p = 0.03$) reduction in the small bowel transit time. The cardiac vagal tone is considered pathological when low. Thus, it may be associated with prolonged gastric and small bowel transit times, while no associations were seen with the colonic transit times or motility indices. Neither the sudomotor function in the hands nor the feet was associated with gastrointestinal transit times or motility indices Table S1. Figure 5 provides an overview of the primary findings.


FIGURE 5 Schematic overview of the observed associations between gastrointestinal symptoms, motility, and extraintestinal autonomic measures. The double arrow represents an association between the two measures.

## 4 | DISCUSSION

We have investigated a group of individuals with diabetes, symptoms of gastrointestinal dysfunction, and symptoms or signs of autonomic neuropathy. We found symptoms from the proximal

gastrointestinal tract positively associated with the gastric motility index. In addition, the severity of diarrhea-related symptoms was associated with fast small bowel transit time, and the severity of constipation-related symptoms was associated with slow colonic transit time. No significant association between gastrointestinal motility and the presence of extraintestinal autonomic neuropathy was observed, but the cardiovascular autonomic neuropathy score was related to symptoms from the proximal gastrointestinal tract and poor glycemic regulation. In contrast, no associations were observed between gastrointestinal symptoms and cardiac vagal tone or sudomotor function. Hence, the methods for assessing extraintestinal autonomic neuropathy, while indicating some pathological changes in gastrointestinal motility, cannot likely substitute objective evaluation of gastrointestinal transit and contractility in patients with diabetes and gastrointestinal symptoms. Still, the cardiovascular autonomic neuropathy score may be utilized to qualify whether symptoms from the proximal gastrointestinal tract are plausibly autonomic-derived.

### 4.1 | Associations between gastrointestinal symptoms and motility

In diabetes, the delicate intrinsic and extrinsic autonomic coordination of the gastrointestinal tract is disrupted at multiple levels, which often causes dysmotility observed as either rapid or prolonged transit times. It is well-documented that abnormal gastrointestinal motility in individuals with diabetes occurs panenteric, and symptoms are not attributed to one particular gastrointestinal region.[5–8] Gastrointestinal dysmotility may even exist without accompanying symptoms.[39] One study found small bowel dysmotility in 80% of individuals referred with symptoms of gastroparesis, while only 28% had delayed gastric emptying time, questioning gastroparesis as the only underlying pathophysiology.[40] Applying gastrointestinal MRI scans, we recently found panenteric volume changes and an adynamic postprandial small bowel in individuals with diabetes and gastrointestinal symptoms.[12] In another study, the combined information on multi-segmental transit times and contractile activity led to treatment change in three-quarters of the patients.[7] Thus, investigation of the entire gastrointestinal tract is essential for accurate diagnostics and management in individuals with diabetes and gastrointestinal symptoms.

Several studies among individuals with diabetes have examined the association between gastric emptying time and symptoms of gastroparesis. Results have been inconsistent, and correlations are generally poor, possibly due to symptomatic overlap with other gastrointestinal diseases and symptoms arising from other gastrointestinal segments.[3,41–43] This aligns with our data, which only showed an association between prolonged gastric emptying time and increased satiety score, suggesting poor accommodation to drive symptom generation. Nevertheless, we observed a positive association between most gastrointestinal symptoms and gastric motility index. However, the bloating, satiety, and indigestion sub-scores did not reach statistical significance, and no association was seen for the constipation sub-score. This association was not previously observed in individuals with type 1 diabetes.[19,44] The divergent results may be explained by the questionable presence of diabetic gastroenteropathy in previous studies. The pathophysiology of gastric motor dysfunction in diabetes includes impaired gastric accommodation, contractile dyscoordination, increased pyloric tone, and antral hypomotility.[45–47] During normal digestion, solids accumulate in the proximal stomach before moving more distally for trituration.[46] As the indigestible motility capsule is not triturated, it may be positioned proximally in the stomach until emptied by the arrival of the fasting high-amplitude contractions.[48] Thus, an increased contractile activity (supposedly representing loss of inhibitory neurons) with symptoms does not necessarily contradict the characteristic antral hypomotility in diabetic gastroenteropathy.

Within the small bowel, the severity of diarrhea was associated with rapid small intestinal transit time, while the remaining symptom scores did not correlate. No symptom associations were observed for the small bowel motility index. In the previously mentioned wireless motility capsule studies investigating individuals with questionable diabetic gastroenteropathy, no correlations were observed between symptoms and either small bowel motility index or transit times.[19,44] We found a correlation between constipation and prolonged colonic transit time within the colon, aligning with findings from previous studies.[19,49]

Abnormal signaling in the afferent gut-brain neuronal pathways and changes in the brainstem and brain cause impaired visceral sensitivity in diabetic gastroenteropathy.[45] This complicates the interpretation of gastrointestinal symptoms and may explain varying associations between gastrointestinal symptoms and motility measures across studies.

### 4.2 | Associations between gastrointestinal symptoms and extraintestinal autonomic measures

We observed that symptoms from the proximal gastrointestinal tract were positively associated with the severity of the cardiovascular autonomic neuropathy score. As in our study, gastrointestinal symptoms have previously been positively associated with diabetic cardiovascular autonomic neuropathy.[18] Abnormal cardiovascular autonomic reflex tests signify parasympathetic vagal withdrawal, and the association with proximal gastrointestinal symptoms seems reasonable from a pathophysiological perspective as the stomach is densely vagally innervated, while vagal innervation decreases significantly towards the descending colon.[50] Ambiguous reports on the integrative neuronal communication between the enteric and autonomic nervous systems seem reasonable because we frequently and erroneously assume that neurodegenerative changes occur concurrently.[51] However, although the interplay of autonomic dysfunction across organ systems remains incompletely understood, our results suggest that cardiovascular reflex tests may help qualify whether symptoms from the proximal gastrointestinal tract are caused by diabetic gastroenteropathy. This point may be supported by the

observed association between abnormal cardiovascular reflex tests and glycemic dysregulation, as indicated by HbA1c, alongside the lack of associations between HbA1c and gastrointestinal measures. Diabetic dysregulation is a well-established risk factor for cardiovascular autonomic neuropathy.[13] Thus, these findings suggest that cardiovascular reflex tests are likely a more precise indicator of cardiac autonomic neuropathy than gastrointestinal measures are for gastrointestinal autonomic neuropathy. This distinction arises from the multiple pathophysiological factors contributing to diabetic gastrointestinal dysfunction, with autonomic neuropathy being only one of them.[52]

In contrast, neither gastrointestinal symptoms nor HbA1c were associated with cardiac vagal tone, which was comparable to previous studies.[19,39] In one study, cardiac vagal tone was closely associated with traditional heart rate variability measures in individuals with type 1 diabetes and peripheral neuropathy, and it performed slightly better in recognizing borderline but not manifest cardiovascular autonomic neuropathy in another cohort of individuals with type 1 diabetes.[35,36] Consequently, we expected similar associations with gastrointestinal measurements for both cardiac-derived measurements assessing the parasympathetic function. However, the cardiovascular autonomic reflex tests represent the response to physiological provocative maneuvers, while the cardiac vagal tone represents the autonomic function when resting, which could influence the observed associations.

### 4.3 | Association between gastrointestinal motility and extraintestinal autonomic measures

Previous studies have mainly investigated the association between gastric emptying time and cardiovascular autonomic reflex tests when addressing autonomic dysfunction in the gut. However, the results have been contradictory, with some studies supporting an association[18,42,53,54] while others do not.[55,56] We observed a non-significant increase in gastric emptying time across the cardiovascular autonomic neuropathy categories, while no associations were observed with the remaining segmental transit times. In diabetes, gastrointestinal symptoms develop depending on the underlying motor disturbances, which may lead to transit time changes.[30] One previous study showed increased gastric motility indices with decreased parasympathetic tone,[19] while another observed an association between manometrically assessed gastric dysmotility and diabetic cardiovascular autonomic neuropathy.[57] Although the gastric motility index increased slightly with the severity of cardiovascular autonomic neuropathy, we did not demonstrate any significant difference across the autonomic categories using the segmental motility indices.

We found no association between cardiac vagal tone and motility measures, except for a minor non-significant increase in gastric emptying and small bowel transit times with an abnormal decrease in cardiac vagal tone. Similarly, in two previous studies of individuals with diabetes, cardiac vagal tone was unrelated to gastrointestinal transit times.[19,39] In contrast, a higher gastric motility index in the group with low cardiac vagal tone was seen in one of these studies, which we could not confirm in our population.[19]

The sudomotor sweat responses, estimating the sympathetic autonomic innervation of the peripheral sweat glands, were not associated with gastrointestinal motility markers.[37,38] Previous studies have only sparsely investigated these associations. The SUDOSCAN device has been proposed as a quick and feasible screening tool for detecting cardiovascular autonomic neuropathy, but the sensitivity of the device is still questioned.[58] Furthermore, the SUDOCAN device underperformed in detecting manifest cardiovascular autonomic neuropathy compared to cardiac vagal tone.[36] Thus, it cannot replace established cardiovascular autonomic reflex tests or markers of diabetic gastroenteropathy.[59,60]

### 4.4 | The motility index in a pathophysiological context

The wireless motility capsule cannot distinguish propagating from non-propagating contractions, as it is a free-floating device registering each pressure independently. Hence, the obtained motility index is a composite summary measure combining contraction frequency and amplitudes across a given gastrointestinal segment.[30] Combined usage of antroduodenal manometry and wireless motility capsule measurements showed comparable pressure patterns.[48] Furthermore, individuals with diabetic gastroparesis had lower motility indices in the distal stomach and proximal small bowel compared to healthy, signifying the use of the contractile activity measured by the capsule despite the lack of peristalsis details.[48]

In our study, the proximal gastrointestinal tract symptoms were positively associated with the gastric motility index and the cardiovascular autonomic neuropathy score. This may indicate symptom-generating dyscoordinated gastric contractile and sphincter activity in diabetic gastroenteropathy potentially driven by autonomic neuropathy. Inhibitory enteric neurons and inhibitory efferent parasympathetic vagal nerve fibers are especially susceptible to diabetes-related damage.[50,61] These inhibitory neurons are essential for sufficient intragastric and gastroduodenal inhibitory reflexes promoting normal peristalsis, as they relax the gastric smooth muscle cells ahead of contractions, provide pyloric relaxation, and coordinate the passage of ingested content into the small bowel.[10,45,50] Theoretically, dysfunction of inhibitory neurons, leading to a dominance of vagal excitatory neurons, would increase the contractile activity and the motility index, but this increase would not necessarily represent propagation. Likewise, abnormally enhanced motility patterns can be caused by neuropathy-induced decreased sympathetic activity.[45] A previous study showed parasympathetic dysfunction to correlate with gastrointestinal symptom severity in individuals with gastroparesis, and both sympathetic and parasympathetic hypofunction were frequently seen in the diabetic subgroup.[18] Furthermore, specialized positron emission tomography scans have confirmed a reduced parasympathetic enteric innervation in individuals with

diabetes and gastrointestinal symptoms.[9] These gastrointestinal autonomic alterations comply with the cardiovascular parasympathetic dysfunction represented by an abnormal cardiovascular autonomic neuropathy score, which may explain the observed correlations with gastrointestinal symptoms.

### 4.5 | Limitations

The present study has limitations. It is cross-sectional and cannot address whether cardiovascular and gastrointestinal autonomic neuropathy develop in parallel. Individuals had either type 1 or type 2 diabetes, making the study cohort less homogeneous. However, studies have indicated a similar prevalence of diabetic autonomic neuropathy for both diabetes types, and the pathophysiological mechanisms for neuropathy are thought to be similar.[43] Moreover, several previous studies have assessed gastrointestinal measures in mixed diabetes cohorts.[7,49,62] The investigational setting was standardized and conducted after an overnight fast, but blood glucose levels were not controlled during the wireless motility capsule investigation. Additionally, the SmartBar consumed with the wireless motility capsule has a high carbohydrate content. It is well-known that glycemic levels and gastric emptying have an interdependent relationship, with acute hyperglycemia known to slow gastric emptying and enhance gastrointestinal symptoms.[63] However, we found no association between diminished glycemic control, indicated by higher levels of Hba1c, and gastrointestinal symptoms or motility measures. Still, fluctuations in blood glucose may have impacted gastrointestinal measures to some extent.[4]

External confounding factors may have affected the gastrointestinal measures. Participants were not tested for small intestinal bacterial overgrowth, pancreatic insufficiency, or lactose intolerance. However, those using prokinetic drugs or GLP1 receptor agonists were excluded due to the direct motility-changing effect of these drugs, and supplementary analysis without those taking laxatives did not change the results. Moreover, distal gastrointestinal symptoms are not extensively covered by the questionnaires used. The choice of questionnaires reflects the aim of the randomized study, where symptoms from the proximal gastrointestinal tract are most relevant, as the vagal nerve predominantly innervates the proximal gastrointestinal tract.

To determine the presence of cardiovascular autonomic neuropathy sufficiently, it is recommended to evaluate orthostatic hypotension (sympathetic dysfunction) as part of the cardiovascular autonomic reflex tests. As we used the VAGUS™, this was not part of the standard test panel. Furthermore, the presence of peripheral neuropathy was not verified objectively or historically, and a pelvic floor disorder induced by somatic nerve neuropathy could contribute to symptom generation. We observed a low prevalence of nephropathy, as reflected by median creatinine levels within normal ranges and an estimated glomerular filtration rate below 60 mL/min in only 10% of the cohort. These findings may suggest a relatively mild degree of gastroenteropathy in the cohort, but while end-organ damage can occur concurrently, the severity does not necessarily run in parallel.

The exploratory nature of the study requires several statistical tests, increasing the risk of mass significance. Moreover, the study constituted a secondary analysis of our randomized trial, whereas no power calculations were performed. Lastly, the cardiovascular tests used are surrogate measures of cardiovascular autonomic innervation. In contrast, the gastrointestinal measurements represent dysfunction throughout the entire brain-gut axis, including neuropathy in the enteric nervous system. Furthermore, diabetic gastrointestinal myopathy, depletion of the interstitial cells of Cajal, dysfunctional microbiota, and other structural changes also contribute to the findings.[64] In particular, the microbiota has an important role in symptom generation and gastrointestinal motility regulation by acting as a key component in the neurohormonal communication between the brain and the gut.[65] Hence, the results do not directly compare the autonomic tone between the heart and the gut, potentially explaining discrepancies between organ systems.

## 5 | CONCLUSION

In conclusion, proximal gastrointestinal tract symptoms were associated with the gastric motility index and cardiovascular autonomic reflex tests. This may support using cardiovascular autonomic reflex tests to qualify whether gastrointestinal symptoms are related to diabetic gastroenteropathy. However, methods assessing extraintestinal autonomic neuropathy cannot replace the objective evaluation of gastrointestinal transit times and contractility in research and clinical practice.

### AUTHOR CONTRIBUTIONS

A.M.D., C.B., K.K., F.K.K., C.S.H., and B.B. conceptualized and designed the study. All authors contributed to the protocol and logistical planning. D.S.K., D.B., T.O., and H.K. recruited participants, and D.S.K., D.B., H.K., K.L.H., A-M.W., and T.O. conducted trial days. D.S.K. and E.B.M. conducted statistical analyses. D.S.K. drafted the manuscript, which was reviewed and approved by all authors. Figures were produced in licensed versions of GraphPad Prism version 10.2.1 and www.biorender.com.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data set generated during and analyzed in the study is available upon reasonable request from the corresponding author.

## USE OF ARTIFICIAL INTELLIGENCE

While preparing this work, the authors used Grammarly only to correct spelling and grammatical errors. The authors take full responsibility for all the content of this publication.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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