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Associations of PYY, GLP-1 and LEAP2 with changes in feeding-related cognition, body weight and glucose homeostasis after bariatric surgery in non-diabetic women

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Abstract

Roux-en-Y gastric bypass (RYGB) is an effective surgical intervention for severe obesity, but the role of gastrointestinal hormones in its benefits remains unclear. We examined longitudinal pre-to-post-meal gastrointestinal hormone changes and their relationships with glucose homeostasis and feeding-related cognitive responses in women undergoing RYGB. Seventeen non-diabetic women were evaluated pre-RYGB (Visit 1, V1), 1-month post-RYGB (Visit 2, V2), and 1-year post-RYGB (Visit 3, V3). Plasma glucose, insulin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), ghrelin, and liver-expressed antimicrobial peptide 2 (LEAP2) were measured before and after a breakfast in all visits. Appetite ratings and feeding-related cognitive performance were evaluated using visual analog scales, Ideal Portion Size, and Food Stroop tasks. At V3, RYGB induced weight loss (30.8%) and improved glucose homeostasis ($p = .020$), accompanied by reduced hunger ($p = .042$), smaller self-reported ideal portion size ($p < .001$), and improved cognitive control toward food-cues ($p = .002$). Fasting GLP-1 and PYY levels remained stable across visits but showed enhanced post-meal responses at V2 and V3 (GLP-1: $p < .001$; PYY: $p = .013$). Ghrelin levels increased post-RYGB ($p = .010$) without post-meal variation. LEAP2 concentrations

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remained stable. Fasting LEAP2 correlated positively with BMI at V1 ($p < .001$). Fasting PYY correlated inversely with BMI at V3 ($p = .005$), and its post-meal rise inversely correlated with ideal portion size at V1 ($p = .022$). GLP-1 increments negatively correlated with ideal portion size ($p = .007$) at all visits and glycemia ($p = .017$) at V1. In non-diabetic women, RYGB improves feeding-related cognitive processes. BMI is associated with LEAP2 only pre-surgery, and with PYY 1-year post-RYGB. Restoration of GLP-1 and PYY post-meal increments contributes to metabolic and behavioral improvements.

Clinical Trial Registry: This study was registered at clinicaltrials.gov as NCT01815216. https://clinicaltrials.gov/study/NCT01815216.

KEYWORDS
bariatric surgery, gastrointestinal hormones, LEAP2, Roux-en-Y gastric bypass

1 | INTRODUCTION

Bariatric surgery is considered the most effective treatment for obesity, particularly in severe cases.[1,2] Among these procedures, Roux-en-Y gastric bypass (RYGB) stands out as one of the most widely performed techniques due to its ability to induce substantial and sustained weight loss while improving obesity-related comorbidities, including type 2 diabetes (T2D).[3] Understanding its underlying mechanisms could guide the development of safer, less invasive therapies for obesity.

RYGB markedly reduces energy intake and appetite,[4,5] but the underlying mechanisms remain unclear. Few studies have assessed appetite sensations via visual-analog scales (VAS), with inconsistent results.[6] Similarly, feeding-related cognitive processes remain poorly characterized post-RYGB. Inhibitory cognitive control over food-related cues is typically assessed with the Stroop Food Task, an adaptation of the classic Stroop Task,[7] which measures an individual's ability to maintain cognitive control and inhibit automatic responses (i.e., reading words instead of naming the ink colors) in a food-related context.[8] Individuals with obesity show altered Stroop Food Task performance,[8–10] suggesting that reduced cognitive control contributes to maladaptive eating. To our knowledge, only two studies have assessed RYGB effects on the classic Stroop Color–Word Task, showing cognitive improvement[11] and no association with weight loss,[12] while a study found poorer inhibitory control on the Stroop Food Task in patients who failed to maintain weight loss.[13] Meal size control is also crucial for long-term surgical success.[14] The ideal self-selected portion can be quantified using a validated computer-based portion-size task that reliably predicts intake,[15,16] but this task has not yet been tested in patients post-RYGB.

RYGB alters basal and post-meal levels of some gastrointestinal (GI) hormones.[17] Several studies have shown that RYGB amplifies post-meal glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) responses,[6] which have been proposed to reduce food intake and improve glycemia in patients with T2D.[18,19] However, links between these hormones and appetite remain inconsistent, with some studies associating reduced hunger with GLP-1 and others with PYY.[20,21] Notably, the GI hormone liver-expressed antimicrobial peptide 2 (LEAP2) was recently proposed as a non-surgical 'bypass mimetic,' as its expression increases in mice after sleeve gastrectomy.[22] LEAP2 is an endogenous antagonist and inverse agonist of the ghrelin receptor (GHSR), thereby functionally opposing ghrelin signaling.[23] In line with this, LEAP2 administration reduces food intake and glycemia in healthy individuals.[24] In line with this, fasting plasma LEAP2 levels are inversely associated with hunger,[25] and its post-meal increases are linked to appetite suppression.[26] Also, plasma LEAP2 levels increase in obesity and are associated not only with BMI but also with motor impulsivity and inhibitory control toward low-calorie food cues in individuals with obesity.[27,28] Despite its relevance in obesity, few studies have examined LEAP2 post-RYGB, with mixed results.[29–31] LEAP2 levels after RYGB may be informative not only due to their role in energy balance, but also for calculating the ghrelin/LEAP2 ratio, which has been suggested as a valuable proxy for estimating effective GHSR tone.[25,30] Together, these observations support the relevance of LEAP2 as a physiological modulator of GHSR signaling and provide a rationale to investigate its role in the metabolic and behavioral adaptations following RYGB.

The primary aim was to investigate plasma concentrations of GLP-1, PYY, ghrelin, and LEAP2 in a cohort of non-diabetic women with obesity undergoing RYGB, and to examine their associations with appetite sensations, feeding-related cognitive responses, and markers of glucose homeostasis. These measures were obtained before and after a standardized test meal at three time points: 1-month pre-RYGB, 1-month, and 1-year post-RYGB.

2 | MATERIALS AND METHODS

2.1 | Participants

Data and plasma samples originate from a study conducted at Uppsala University regarding resting-state fMRI before and after RYGB.[32–34] Inclusion and exclusion criteria and surgical procedure are described in Appendix S1. Participants were recruited from Uppsala University Hospital and signed written informed consent. The study was

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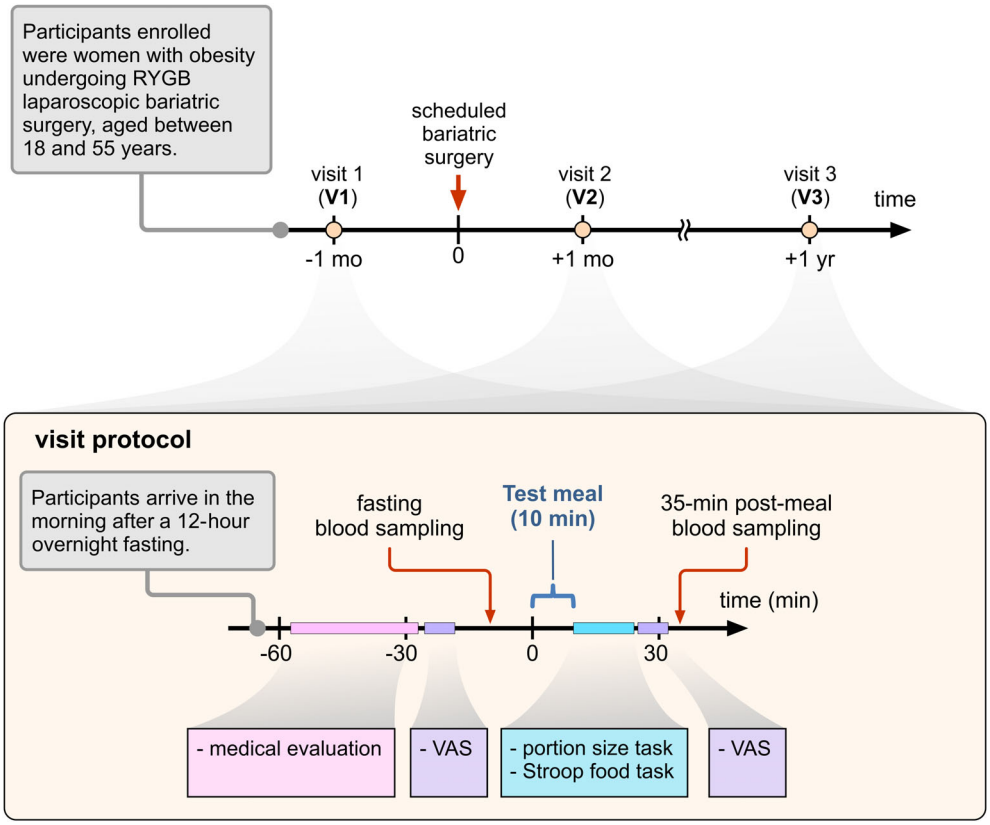

FIGURE 1 Overview of study design.

approved by the Regional Ethical Review Board in Uppsala, in accordance with the Helsinki Declaration. This study was registered at clinicaltrials.gov as NCT01815216.

2.2 | Study protocol

Participants were studied in a breakfast test meal at three time points (Figure 1): 1-month pre-RYGB (Visit 1, V1, baseline), 1-month post-RYGB (Visit 2, V2), and 1-year post-RYGB (Visit 3, V3). During each visit, participants arrived at the designated location after a 12-h fast and underwent a medical evaluation including height and weight measurements,[35] hunger and fullness rating on a 100-mm VAS,[36] and a fasting blood sampling. Participants then consumed a 260-kcal liquid meal (carbohydrates/protein/fat = 64/32/4 energy%) within 10 min (Gainomax Recovery Vanilla; Sweden). Immediately after meal consumption, participants performed a Portion Size Task and the Stroop Food Task (Appendix S1). Appetite sensations were assessed again 25 min after meal consumption, and a post-meal blood sample was collected 10 min later (i.e., 35 min after the meal). Blood samples were collected using a DPP-IV inhibitor (Millipore, USA). Plasma was obtained and stored at −80°C until analysis.

2.2.1 | Biochemical analyses

Assessment of plasma glucose, insulin, LEAP2, active GLP-1, total PYY, and total ghrelin is described in Appendix S1. Insulin resistance was estimated by the homeostasis model assessment for insulin resistance (HOMA-IR index).[37] Ghrelin/LEAP2 ratio was computed on a molar basis as ghrelin concentration divided by LEAP2 concentration.[25]

2.3 | Statistical analyses

The study was conducted using SPSS software (version 28). Variables with a normal distribution are presented as mean and standard deviation (SD), non-normally distributed variables are reported as median and interquartile range (IQR). Linear mixed-effects models were used to assess longitudinal changes across visits and their modification by hormone and glucose concentrations. Effect sizes were reported as partial eta squared (η^2_p) for fixed effects and interactions in the linear mixed-effects models (Appendix S1).

3 | RESULTS

3.1 | Characteristics of the participants

The study started with 17 women (V1, mean age = 38 years, range 19–55). All participants completed the 1-month post-RYGB visit (V2), and 14 (82%) remained at 1 year (V3). As shown in Table 1, body weight decreased by ~12% at V2 and ~31% at V3. Pre-prandial levels of glucose, insulin, and HOMA-IR declined at V2, with HOMA-IR

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TABLE 1 Anthropometric characteristics, pre-prandial metabolic profile, and feeding-related cognitive responses.

	Visit 1, baseline ($n = 17$)	Visit 2, 1-month post-surgery ($n = 17$)	Visit 3, 1-year post-surgery ($n = 14$)	*p*-value	η^2_p
Body weight[1] (kg)	119.9 (19.3)[a]	105.5 (17.1)[b]	79.5 (11.0)[c]	**<.001**	0.90
BMI[1] (kg/m^2)	44.0 (6.4)[a]	38.7 (5.86)[b]	29.3 (3.9)[c]	**.010**	0.91
Weight loss[1] (kg)	0[a]	14.3 (5.08)[b]	36.0 (11.88)[c]	**.010**	0.89
Weight loss[1] (%)	0[a]	11.9 (3.37)[b]	30.7 (8.00)[c]	**.002**	0.92
Glucose[1] (mmol/L)	5.43 (0.54)[a]	5.27 (0.39)[a,b]	4.93 (0.39)[b]	**.020**	0.25
Insulin[2] (μU/mL)	17.70 (12.90, 23.00)[a]	9.85 (5.80, 12.08)[b]	4.95 (4.07, 6.77)[b]	**.001**	0.65
HOMA-IR index[3]	4.36 (3.21, 5.94)[a]	2.07 (1.43, 3.01)[b]	1.25 (0.75, 2.04)[c]	**.001**	0.68
GLP-1[3] (pM)	0.55 (0.32, 0.92)	0.42 (0.17, 1.02)	0.48 (0.27, 0.84)	.744	0.03
PYY[3] (ng/mL)	23.84 (11.60, 49.03)	16.48 (8.43, 32.25)	15.25 (8.28, 28.10)	.389	0.08
Ghrelin[3] (pg/mL)	49.35 (33.18, 73.41)	51.15 (36.74, 71.21)	69.04 (43.56, 109.43)	**.045**	0.24
LEAP2[3] (ng/mL)	11.17 (8.48, 14.70)	8.99 (6.33, 12.76)	10.75 (8.70, 13.28)	.607	0.07
Ghrelin/LEAP2 ratio[1] ($\times 10^{-3}$)	7.57 (4.99)	8.93 (5.29)	9.43 (5.55)	.629	0.03
Hunger score[1] (mm)	59.41 (17.08)[a]	40.57 (25.64)[b]	52.50 (27.87)[a,b]	**.042**	0.19
Fullness score[1] (mm)	18.82 (17.14)	23.93 (22.25)	30.86 (23.57)	.058	0.18
Ideal portion size (kcal)					
All food items[1]	211 (69)[a]	112 (22)[b]	134 (40)[b]	**<.001**	0.67
Meal items[1]	204 (66)[a]	102 (13)[b]	122 (24)[b]	**<.001**	0.71
Snack items[1]	219 (102)[a]	123 (37)[b]	147 (61)[b]	**<.001**	0.48
Stroop Food Task					
No. of correct neutral words[1]	74.43 (12)	78.20 (11)	79.00 (15)	.159	0.14
No. of correct food words[1]	70.68 (14)[a]	75.86 (13)[a,b]	80.00 (16)[b]	**.002**	0.38

Note: Data presented as mean (SD) (1), median (Q1, Q3) (2), or geometric mean (CI) (3). *p*-value testing for differences in participant characteristics throughout the visits using linear mixed-effects models, including visit and age as fixed effects. Different superscript letters denote statistically significant differences based on Bonferroni-adjusted pairwise comparisons. Values of 0.01, 0.06, and 0.14 should be interpreted as small, medium, and large effects, respectively.

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; $\eta^2 p$, partial eta squared values for effect sizes for Visit in the linear mixed-effects models.

further reduced at V3. Pre-prandial ghrelin levels increased slightly while GLP-1, PYY, and LEAP2 levels and the ghrelin/LEAP2 ratio remained unchanged across visits. Subjective hunger decreased at V2 and partially rebounded at V3, with values not significantly different from V1 or V2. Subjective fullness showed a trend to rise across visits. Self-selected portion sizes decreased post-surgery across all food types. Stroop Food Task performance improved at V3 for food words but not for neutral words.

3.2 | Associations of BMI, markers of glucose homeostasis, and feeding-related cognitive responses with fasting hormone levels

We tested whether changes in BMI, glucose homeostasis, appetite, and feeding-related cognition across visits were associated with fasting LEAP2, ghrelin, PYY, GLP-1, insulin, and glucose levels, including a Visit × hormone interaction term (Table 2). A significant Visit × LEAP2 interaction was found for BMI ($\eta^2_p = 0.19$), indicating that the association between LEAP2 and BMI differed across visits. While the average main effect of LEAP2 was significant ($p = .015$, $\eta^2_p = 0.09$), the positive association was primarily evident at V1. Also, a significant Visit × lnLEAP2 interaction was observed for Stroop Food Task performance ($\eta^2_p = 0.30$), indicating a large effect and substantial effect modification across visits, although associations at each visit were nonsignificant. Pre-prandial ghrelin levels were not significantly associated with BMI, glucose-related measures, or feeding-related cognitive responses. No significant Visit × ghrelin/LEAP2 ratio was observed for BMI but the average main effect of the ghrelin/LEAP2 ratio was significant ($p = .005$, $\eta^2_p = 0.21$), with a negative association primarily evident at V1. A significant Visit × PYY interaction was found for BMI ($\eta^2_p = 0.44$), shifting from no association at V1 and V2 to a negative association at V3 ($p = .005$); and ideal snack portion size ($\eta^2_p = 0.27$), with a significant main effect ($p = .027$, $\eta^2_p = 0.21$) and a transient inverse association at V2. No associations were observed between LEAP2 or PYY and subjective appetite ratings. A significant Visit × GLP-1 interaction was detected for subjective hunger rating ($\eta^2_p = 0.28$). No significant Visit × insulin interactions were found, but insulin positively associated with self-reported portion size for all food and snack items (main effect

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TABLE 2 Associations of pre-prandial hormone and glucose concentrations with BMI, markers of glucose homeostasis, and feeding-related cognitive responses across visits.

	LEAP2			PYY			Ghrelin			GLP-1		
Outcome variable	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]
BMI (kg/m^2)	**0.003**			**0.002**			0.738	−1.00 (−3.70, 1.70)	.455	0.371	−1.18 (−3.02; 0.66)	.199
V1		5.13 (2.80, 7.46)	**<.001**		−0.72 (−1.88; 0.44)	.210						
V2		0.80 (−2.7, 4.3)	.660		1.56 (−0.39; 3.52)	.450						
V3		1.04 (−2.6, 4.7)	.580		−2.92 (−3.77; −0.61)	**.005**						
Glucose (mmol/L)[b]	0.114	−0.39 (−0.92, 0.13)	.134	0.750	−0.26 (−0.55; 0.02)	.065	0.927	−0.33 (−0.71, 0.05)	.086	0.085	−0.24 (−0.52; 0.04)	.089
Insulin (μU/mL)[b]	0.807	−0.04 (−0.57; −0.11)	.862	0.400	−0.16 (−0.38; 0.06)	.147	0.770	−0.29 (−0.64; 0.05)	.093	0.663	0.07 (−0.02; 0.37)	.593
HOMA-IR index[b]	0.796	−0.19 (−0.77; 0.37)	.487	0.348	−0.18 (−0.49; 0.12)	.224	0.734	−0.28 (−0.66; 0.11)	.152	0.857	0.02 (−0.30; 0.34)	.891
Hunger score (mm)[b]	0.137	4.31 (−18.19; 26.82)	.698	0.419	2.56 (−7.92; 13.04)	.620	0.926	4.24 (−13.54; 22.03)	.631	0.050	−0.21 (−11.91; 11.48)	.971
Fullness score (mm)[b]	0.321	10.10 (−10.74; 30.95)	.331	0.662	2.37 (−6.65; 11.39)	.596	0.811	10.08 (−4.85; 25.01)	.179	0.451	−0.06 (−10.99; 10.87)	.991
Ideal portion size (kcal)												
All food items[b]	0.417	−34.1 (−93.2; 25.0)	.248	0.303	−11.59 (−31.21; 8.01)	.235	0.764	−10.4 (−52.9; 32.0)	.620	0.811	14.22 (−18.67; 47.13)	.383
Meal items[b]	0.927	−21.9 (−74.1; 30.3)	.398	0.405	−16.66 (−34.62; 1.30)	.068	0.933	8.47 (−28.33; 45.26)	.642	0.368	19.73 (−7.16; 46.62)	.144
Snack items	0.437	−46.9 (−131.1; 37.2)	.264	**0.046**			0.753	−27.7 (−87.2; 31.8)	.349	0.981	6.45 (−40.65; 53.55)	.781
V1					−0.07 (−29.15; 29.00)	.996						
V2					−61.9 (−109.8; −13.9)	**.033**						
V3					−23.9 (−80.5; 32.6)	.440						
Stroop Food Task												
No. correct neutral words[b]	0.235	7.38 (−0.86; 15.63)	.077	0.816	−0.62 (−4.26; 3.01)	.727	0.296	−1.25 (−6.87; 4.38)	.652	0.332	−0.14, (−5.94; 5.65)	.960
No. correct food words	**0.022**			0.703	−1.27 (−5.99; 3.44)	.582	0.717	−1.39 (−9.18; 6.39)	.214	0.616	4.35 (−2.23, 10.93)	.186
V1		−6.11 (−15.95; 3.73)	.214									
V2		−6.47 (−20.5, 7.6)	.380									
V3		10.91 (−4.6, 26.4)	.180									

	Ghrelin/LEAP2 ratio			Insulin			Glucose		
Outcome variable	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]
BMI (kg/m^2)[b]	0.196	−0.61 (−1.02; 0.20)	**.005**	0.811	1.06 (−3.75, 5.88)	.657	0.194	−1.88 (−5.66; 1.88)	.317
V1									
V2									
V3									
Glucose (mmol/L)[b]	0.654	−0.015 (−0.065; 0.034)	.529						
Insulin (μU/mL)[b]	0.905	−0.016 (−0.067; 0.034)	.524						

(Continues)

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TABLE 2 (Continued)

Outcome variable	Ghrelin/LEAP2 ratio			Insulin			Glucose		
	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]	V × H p	Beta (95% CI)	p[a]
HOMA-IR index[b]	0.667	−0.009 (−0.066; 0.046)	.730						
Hunger score (mm)[b]	0.900	−0.16 (−2.80; 2.48)	.903	0.775	−12.97 (−42.79; 16.84)	.383	0.335	−6.89 (−31.75; 17.96)	.577
Fullness score (mm)[b]	0.763	1.09 (−1.02; 3.22)	.300	0.594	−9.61 (−34.00; 14.77)	.429	0.237	−0.73 (−1.38; −0.78)	**.029**
Ideal portion size (kcal)									
All food items[b]	0.682	−0.18 (−6.22; 5.86)	.952	0.118	73.29 (16.92; 129.65)	**.012**	0.109	80.23 (30.38; 130.08)	**.002**
Meal items[b]	0.780	1.18 (−3.94; 6.30)	.641	0.475	34.94 (−19.38; 89.26)	.200	0.589	30.80 (−14.51; 76.12)	.176
Snack items	0.584	−1.77 (−10.27; 6.73)	.674	0.089	118.03 (38.22; 197.84)	**.005**	**0.041**		
V1								137.90 (69.80; 206.01)	**<.001**
V2								−113.7 (−240.2; 1.6)	.450
V3								−127.9 (−240.1; −15.7)	.900
Stroop Food Task									
No. correct neutral words[b]	0.592	−0.08 (−1.31; 1.15)	.900	0.896	11.53 (−1.36; 24.43)	.078	0.464	0.73 (−11.66; 13.13)	.905
No. correct food words	0.423	0.58 (−0.90; 2.06)	.434	0.215	20.34 (5.33; 35.34)	**.009**	0.347	2.16 (−13.37, 17.69)	.780
V1									
V2									
V3									

Note: Data are presented as the coefficient beta (95% confidence interval) from linear mixed effects models. Fixed factors: age, V, fasting LEAP2/GLP-1/PYY/insulin/glucose concentrations, V × fasting LEAP2/GLP-1/PYY concentrations.

Abbreviations: BMI, body mass index; H, hormone; V, Visit.

[a]Estimate of fixed effect of hormones. Pre-surgical visit (V1) set as reference.

[b]Beta (95% CI) and *p*-value of fixed effect of hormones correspond to V1 (reference).

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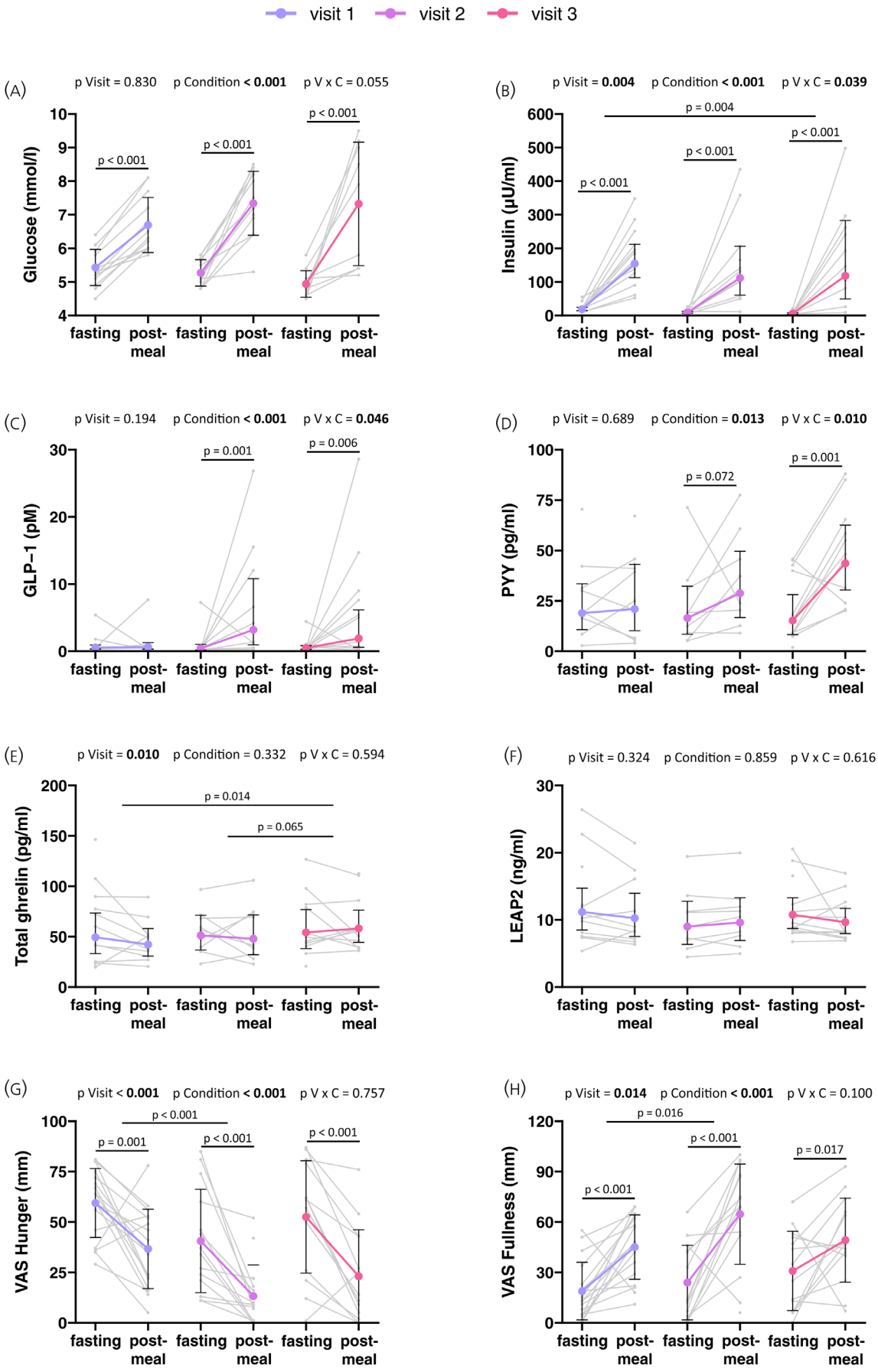

FIGURE 2 Legend on next page.

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$p = .040$, $\eta^2_p = 0.12$), and with the number of correct food words in the Stroop Food Task (main effect $p = .006$, $\eta^2_p = 0.19$). A significant Visit × glucose interaction was detected for snack portion size ($\eta^2 p = 0.17$), with a significant main effect ($p = .021$, $\eta^2_p = 0.15$), shifting from a positive association at V1 to no associations at V2 and V3. Also, glucose was inversely associated with fullness (main effect $p = .045$, $\eta^2_p = 0.11$) and ideal portion size of all food items.

3.3 | Post-meal changes across visits

Post-meal hormone and glucose changes were analyzed including a Visit × Condition (pre- vs. post-meal) interaction term (Figure 2). Post-meal glycemia was higher vs. fasting levels at all visits (Figure 2A). Insulin exhibited a significant Visit × Condition interaction, as fasting insulin declined over time and post-meal levels remained stable; the difference between pre- and post-meal levels increased progressively from V1 to V3 (Figure 2B). GLP-1 levels showed a significant Visit × Condition interaction, with post-meal GLP-1 elevated at V2 and V3, but not at V1 (Figure 2C). Similarly, PYY exhibited a significant Visit × Condition interaction, with post-meal PYY levels higher at V3 (Figure 2D). Ghrelin was unaffected by Condition but increased across visits (Figure 2E). LEAP2 levels remained unchanged (Figure 2F). Subjective hunger ratings varied by visit, being higher at V1 vs. V2 (Figure 2G). Subjective hunger was higher in fasting vs. post-meal states. Subjective fullness was greater in post-meal vs. fasting states and higher at V2 vs. V1 (Figure 2H).

3.4 | Associations of post-meal hormone changes with BMI, markers of glucose homeostasis, appetite ratings and feeding-related cognitive responses across visits

We next assessed associations between insulin, GLP1 and PYY post-meal changes (Δ) and BMI, markers of glucose homeostasis, appetite ratings, and feeding-related cognitive responses (Table 3). A Visit × Δinsulin interaction was found for BMI ($p = .037$, $\eta^2_p = 0.27$), with a positive association at V3 only. Also, ΔInsulin was inversely associated with self-reported portion size for all foods (main effect, $p = .047$, $\eta^2_p = 0.13$) and snack items. A Visit × ΔGLP-1 interaction was found for glucose ($\eta^2_p = 0.30$), with a significant main effect ($p = .017$, $\eta^2_p = 0.19$), showing a negative association at V1 only. ΔGLP-1 was inversely related to snack self-reported portion size across visits (main effect $p = .007$, $\eta^2_p = 0.26$). ΔPYY was inversely associated with self-reported portion size for all food items (main effect $p = .026$, $\eta^2_p = 0.25$), with a Visit × ΔPYY interaction ($\eta^2_p = 0.29$) and a negative association at V1 only. ΔPYY was inversely associated with self-reported portion size for meal items at V1 and showed a main effect for snack items ($p = .033$, $\eta^2_p = 0.23$). A Visit × ΔPYY interaction was found for Stroop neutral word accuracy ($\eta^2_p = 0.42$), with a positive association at V1 only. Appetite ratings were not associated with post-meal changes.

4 | DISCUSSION

Our results show for the first time that RYGB in non-diabetic women is associated with changes in feeding-related cognition, with smaller selected ideal portions and enhanced cognitive control over food cues 1 year after surgery. Some of these changes were associated with changes in key GI hormones (Figure S1). LEAP2 levels remained stable across visits and showed no response to the meal. However, fasting LEAP2 levels positively correlated with BMI only pre-RYGB, suggesting that LEAP2 may be relevant in obesity. Conversely, fasting PYY levels negatively correlated with BMI 1-year post-RYGB, suggesting that PYY gains relevance after weight loss. GLP-1 increments were inversely linked to selected portion size and glycemia, underscoring its dual metabolic and appetitive functions. Plasma insulin and glucose levels were associated with appetite sensations and feeding-related cognition, supporting a coordinated relationship between glucose metabolism and feeding regulation post-RYGB.

Certain feeding-related cognitive processes are known to be altered in obesity.[8,38,39] Here, we report that feeding-related cognitive processes are improved post-RYGB. Specifically, subjective hunger transiently decreased at 1 month, fullness tended to increase—with considerable inter-individual variability—and smaller ideal portions were selected for all food items post-RYGB. Previous studies have reported that hunger tends to decline and fullness to rise post-RYGB, but few have detected statistically significant effects.[21,40] We also found that accuracy for food-related, but not neutral, words improved in the Stroop Food Task post-RYGB, indicating enhanced cognitive control and reduced bias toward food cues.[8] As appetite sensations and feeding-related cognition strongly influence intake and food choice,[8,15,41] these changes likely contribute to reduced energy intake, the primary driver of RYGB-induced weight loss.[6,41]

We found that fasting LEAP2 levels are not affected post-RYGB, consistent with prior studies at 3 or 6 months post-RYGB.[29,31] Since LEAP2 is altered in T2D,[42] the inclusion of mixed-sex cohorts and T2D subjects in a study reporting reduced fasting LEAP2

FIGURE 2 Pre- and post-meal concentrations of glucose (A), insulin (B), GLP-1 (C), PYY (D), total ghrelin (E), LEAP2 (F), hunger (G) and fullness sensation (H) according to visit (V1: pre-RYGB; V2: 1-month post-RYBP; V3: 1-year post-RYBP). Data were analyzed using linear mixed-effects models controlling for visit, condition (pre-post-meal), and age, followed by pairwise comparisons with Bonferroni adjustment. Colored points and lines show the geometric mean and 95% CI (insulin, GLP-1, PYY, total ghrelin, and LEAP2) or mean and SD (glucose, hunger, and fullness). Significant *p*-values for the main effects and the interaction between visit and condition are shown. (B–D) The significant V × C interactions reflect a progressive increase in the pre-post-meal difference from V1 to V3.

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TABLE 3 Associations between pre-to post-meal insulin, GLP1, and PYY concentration changes (Δ) and BMI, markers of glucose homeostasis, and feeding-related cognitive responses across visits.

	Δ Insulin			Δ GLP1			Δ PYY		
Outcome variable	V × Δ *p*-value	Beta (95% CI)	*p*-value[a]	V × Δ *p*-value	Beta (95% CI)	*p*-value[a]	V × Δ *p*-value	Beta (95% CI)	*p*-value[a]
BMI (kg/m^2)	**0.037**			0.263	−0.46 (−1.06; 0.13)	.122	0.179	0.09 (−0.05; 0.24)	.195
V1		−0.008 (−0.026; 0.009)	.327						
V2		0.006 (−0.010; 0.023)	.850						
V3		0.020 (0.004; 0.038)	**.019**						
Glucose (mmol/L)	0.067	−0.002 (−0.005, 0.000)	.109	**0.023**			0.052	−0.002 (−0.026; 0.021)	.814
V1					−0.13 (−0.22; −0.04)	**.006**			
V2					0.010 (−0.118; 0.139)	.940			
V3					−0.002 (−0.129; 0.126)	.990			
Insulin (μU/mL)[b]	0.067	−0.002 (−0.005; 0.000)	.109	0.354	−0.03 (−0.12; 0.06)	.496	0.152	0.002 (−0.017; 0.022)	.818
HOMA-IR index[b]				0.291	−0.05 (−0.15; 0.05)	.312	0.188	0.002 (−0.019; 0.024)	.826
Hunger score (mm)[b]	0.195	−0.03 (−0.18; 0.11)	.627	0.107	0.82 (−2.95; 4.60)	.656	0.331	0.227 (−0.782; 1.237)	.643
Fullness score (mm)[b]	0.608	−0.036 (−0.165; 0.093)	.576	0.611	−1.61 (−2.22; 5.44)	.396	0.959	−0.28 (−1.26; 0.71)	.565
Ideal portion size (kcal)									
All food items	0.145	−0.35 (−0.65; −0.053)	**.023**	0.557	−6.26 (−14.80; 2.27)	.142	**0.040**		
V1								−2.21 (−4.06; −0.36)	**.022**
V2								−0.47 (−3.23, 2.30)	.640
V3								0.32 (−2.37, 3.02)	.790
Meal items[b]	0.406	−0.25 (−0.55; 0.04)	.090	0.650	2.46 (−5.50; 10.43)	.529	0.077	−1.83 (−3.63; −0.39)	**.046**
Snack items[b]	0.207	−0.471 (−0.933; −0.008)	**.046**	0.058	−16.66 (−28.68; −4.64)	**.009**	0.163	−2.84 (−6.02; 0.33)	.076
Stroop Food Task									
Number of correct neutral words	0.867	0.024 (−0.017; 0.066)	.234	0.581	0.18, (−1.10; 1.46)	.771	**0.013**		
V1								0.37 (0.11; 0.61)	**.006**
V2								0.177 (−0.353, 0.345)	.980
V3								0.181 (−0.451, 0.259)	.570
Number of correct food words[b]	0.647	−0.006 (−0.065; 0.053)	.839	0.725	−0.32 (−1.89, 1.25)	.679	0.308	−0.14 (−0.52; 0.24)	.443

Note: Data are presented as the coefficient beta (95% confidence interval) from linear mixed effects models. Fixed factors: age, V, pre- to post-meal insulin/GLP-1/PYY concentration changes (delta, Δ), V × Δ.
Abbreviations: BMI, body mass index; V, visit.

[a]Estimate of fixed effect of delta, pre-surgery.

[b]Beta (95% CI) and *p*-value of fixed effect of hormones correspond to V1 (reference).

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post-RYGB[30] likely explains the divergent results. Similarly, we detected no post-meal changes in LEAP2, possibly due to a short sampling window, as this peptide is not stored but secreted constitutively upon biosynthesis.[23] Fasting LEAP2 levels are higher in women with obesity,[25,27,30] and post-meal LEAP2 levels in obesity have been reported to increase or decrease, depending on the test meal.[27,30] The lack of decrease in pre-prandial LEAP2 levels post-RYGB may reflect that BMI remained in the overweight range after surgery, sustaining a high LEAP2 tone. Interestingly, pre-prandial LEAP2 levels were positively associated with BMI only pre-RYGB, suggesting that LEAP2 mitigates the orexigenic and hyperglycemic effects of GHSR signaling in severe obesity.[22,23,30,43] The absence of a LEAP2–BMI association post-RYGB suggests that this relationship is BMI status-dependent, as previously reported,[27] and that LEAP2 alone plays a minor role in post-RYGB improvements. Notably, plasma ghrelin levels increased with weight loss, consistent with previous findings,[44] presumably reflecting a reduction in energy stores, but were not associated with BMI. However, the ghrelin/LEAP2 ratio, which may reflect GHSR tone,[25,30] was inversely associated with BMI independent of the visit, suggesting that the balance between these GHSR ligands, rather than their individual levels, captures the relationship with body weight status more accurately.

We found that pre-prandial LEAP2 levels were not associated with appetite ratings or outcomes of the portion size task post-RYGB. Previous reports show an inverse association between fasting LEAP2 and hunger[25] and a negative relationship of post-meal LEAP2 increase with appetite suppression in healthy subjects.[26] However, we have shown that the link between LEAP2 and appetite is BMI-dependent, and that stratifying individuals by BMI reveals that pre-prandial LEAP2 levels are positively associated with fullness exclusively in lean subjects.[27] Thus, LEAP2 seems to be unrelated to appetite in obesity, and weight loss post-RYGB may be insufficient to restore this link. Despite the absence of specific associations at each visit, the relationship between plasma LEAP2 concentration and Stroop Food Task performance changed across visits, suggesting that the link between LEAP2 and feeding-related cognition varies post-RYGB. Notably, ghrelin levels and the ghrelin/LEAP2 ratio were not associated with feeding-related cognitive responses. Thus, plasma LEAP2 appears more linked to altered feeding-related cognition than ghrelin, particularly in obesity; however, its contribution to food intake reduction post-RYGB seems limited.

Our study revealed an inverse association of fasting PYY with BMI 1-year post-RYGB, when the association of LEAP2 with BMI disappears, highlighting a shift in GI hormones-BMI relationship post-RYGB. Fasting PYY levels remained stable post-RYGB, consistent with previous reports,[21,40] and were related to ideal snack portion size in a visit-dependent manner, but this link was only significant at 1 month post-RYGB. Post-meal PYY levels increased post-RYGB, as previously shown,[45,46] confirming post-surgical restoration of enteroendocrine adaptations.[17] Here, greater post-meal increases in PYY were inversely associated with self-reported portion size, and this relationship was more evident pre-RYGB—when PYY responses were small. Enhanced post-meal PYY responses have been linked to increased satiety, reduced food intake, and weight loss post-RYGB[17,18]; however, our findings suggest that portion-size selection is not one of the underlying mechanisms. Thus, the post-RYGB association between PYY and BMI may reflect a restored satiety hormone profile, with PYY contributing more prominently to long-term weight maintenance.

Fasting GLP-1 levels remained stable post-RYGB, but post-meal responses were enhanced, as observed for PYY and in line with previous reports.[40,45] GLP-1 likely acts in concert with PYY to sustain food intake reduction post-RYGB; however, its independent contribution remains uncertain.[18] Here, GLP-1 levels were marginally associated ($p = .050$) with subjective hunger, and post-meal GLP-1 increments were inversely related to self-reported portion size for snack items only. These relationships were visit-independent, suggesting that enhanced post-meal GLP-1 secretion may play a role in limiting meal size and food intake post-RYGB. Although liraglutide enhanced performance in the classical Stroop Task in individuals with mood disorders,[47] we did not observe a relationship between endogenous GLP-1 and feeding-related cognitive control. Notably, GLP-1 was the only assessed GI hormone related to glucose metabolism: fasting levels tended to be inversely associated with glycemia ($p = .085$), and post-meal increments were inversely associated with glycemia pre-RYGB. This aligns with the notion that GLP-1 strongly contributes to improved glucose homeostasis post-RYGB.[19,48] However, GLP-1 levels were not associated with reduction in plasma insulin or improvements in insulin sensitivity post-RYGB, confirming that multifactorial metabolic adaptations occur post-RYGB.[49] Thus, GLP-1 appears to play a dual role in post-RYGB improvements, through its effects on appetite and modulating glucose metabolism.

The improvements in appetite sensations and feeding-related cognition post-RYGB were concomitant with improved glucose metabolism. As previously reported,[19,50] we observed reductions in fasting glucose, insulin, and HOMA-IR post-RYGB. Fasting insulin was positively associated with selected portion size and inhibitory control toward food cues across visits, suggesting that post-RYGB insulin decrease may contribute to reducing portion size and intake. Post-meal insulin increments were positively associated with BMI 1-year post-RYGB, possibly reflecting persistence of insulin resistance to maintain glucose homeostasis. Consistent with evidence linking hypoglycemia to increased hunger and poorer Stroop Food task performance,[51] fasting glycemia was inversely associated with fullness and directly with preferred portion size, independent of BMI and visit, suggesting that higher glycemia relates to weaker satiety and preference for larger portions. Pre-prandial glycemia also depicted a visit-dependent association with snack portion size, shifting from a positive association pre-RYGB to no association thereafter, suggesting that RYGB disrupts the preexisting coupling between glycemic status and feeding-related decision-making. Thus, metabolic and feeding-related cognitive mechanisms appear to be linked and jointly reshaped post-RYGB.

This study presents several strengths. One-month and 1-year follow-up visits provide valuable information on short and long-term changes post-RYGB. Moreover, combining plasma assessments under pre- and post-meal conditions with appetite ratings and

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feeding-related cognitive tasks offers an integrated view of systemic and cognitive adaptations. Nonetheless, some limitations should be acknowledged. The relatively small sample size may limit sensitivity to subtle effects; however, the medium and large effect sizes observed reinforce the reliability of the associations detected. We have shown that RYGB in these patients alters brain functional connectivity in regions involved in cognitive control over eating[34]; however, it remains unclear whether the observed changes in appetite ratings and performance in feeding-related cognitive tasks are related to these central adaptations or to other RYGB-related constraints, such as reduced gastric capacity or discomfort. The study design included only one post-meal time point, which might not capture the full dynamics of systemic responses. Additionally, we measured active GLP-1, the physiologically relevant form, but total ghrelin and total PYY, which include both bioactive and inactive forms; the extent to which this difference influenced the observed associations remains uncertain, as the precise balance among the various forms of these GI hormones in the context of RYGB is not well established. Finally, the use of a standardized liquid meal may not fully reflect responses to solid or mixed meals.[52]

In summary, this study provides an integrative view of how RYGB reshapes the interplay between key GI hormones, glucose homeostasis, and feeding-related cognition in non-diabetic women with obesity. We identified several specific associations that likely contribute to recalibrating appetite and feeding behavior, underpinning both the metabolic benefits and long-term weight loss post-RYGB. Future studies combining longitudinal and interventional approaches, such as pharmacological modulation of GI hormone receptors, will be important to establish causality. In addition, integrating detailed temporal hormone profiling with neuroimaging or circuit-level assessments could help clarify the mechanisms linking peripheral signals to behavior.

AUTHOR CONTRIBUTIONS

Pablo N. De Francesco: Formal analysis; visualization; writing – review and editing. **María F. Andreoli:** Investigation; data curation; writing – review and editing; writing – original draft; methodology; formal analysis; conceptualization. **Magnus Sundbom:** Investigation; writing – review and editing. **Robert Fredriksson:** Investigation; writing – review and editing; resources. **Helgi B. Schiöth:** Funding acquisition; writing – review and editing; supervision; conceptualization; project administration. **Olga E. Titova:** Investigation; writing – review and editing. **Wei Zhou:** Investigation; writing – review and editing. **Ahmed Alsehli:** Investigation; writing – review and editing. **Mario Perello:** Investigation; funding acquisition; writing – original draft; writing – review and editing; supervision; conceptualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to Swedish regulations on personal data and health information. However, the described data, codebook, and analytic code used in the study are available from the corresponding author upon reasonable request.

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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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