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REVIEW

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Gut peptides before and following Roux-En-Y gastric bypass: A systematic review and meta-analysis

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Summary

A systematic search was conducted in Medline Ovid, Embase, Scopus, and Cochrane Central Register of Controlled Trials up until March 2021 following PRISMA guidelines. Studies included evaluated ghrelin, GLP-1, PYY or appetite sensation via visual analogue scales (VASs) before and after Roux-en-Y gastric bypass (RYGB) in adults. A multilevel model with random effects for study and follow-up time points nested in study was fit to the data. The model included kcal consumption as a covariate and time points as moderators. Among the 2559 articles identified, $k = 47$ were included, among which $k = 19$ evaluated ghrelin, $k = 40$ GLP-1, $k = 22$ PYY, and $k = 8$ appetite sensation. Our results indicate that fasting ghrelin levels are decreased 2 weeks post-RYGB ($p = 0.005$) but do not differ from baseline from 6 weeks to 1-year post-RYGB. Postprandial ghrelin and fasting GLP-1 levels were not different from pre-surgical values. Postprandial levels of GLP-1 increased significantly from 1 week ($p < 0.001$) to 2 years post-RYGB ($p < 0.01$) compared with pre-RYGB. Fasting PYY increased at 6 months ($p = 0.034$) and 1 year ($p = 0.029$) post-surgery; also, postprandial levels increased up to 1 year ($p < 0.01$). Insufficient data on appetite sensation were available to be meta-analyzed.

KEYWORDS
appetite, ghrelin, glucagon-like peptide-1, meta-analysis, peptide YY, Roux-en-Y gastric bypass, systematic review

1 | INTRODUCTION

Obesity prevalence rose globally from 11% in 2010 to 15% in 2020 and is projected to reach 18% by 2030.[1] Health risks are high for people living with severe obesity, and after multiple failed attempts to lose weight with traditional strategies, surgical approaches are currently the most robust solution for long-term weight loss.[2,3] Roux-en-Y gastric bypass (RYGB) is one of the most performed types of bariatric surgery.[3,4] From 2014 to 2018, 38% of bariatric surgeries worldwide were a RYGB surgery, totalling 72,645 RYGB surgeries reported in the registry.[5] RYGB benefits are numerous, including large weight losses, reduced medication use, remission of type 2 diabetes (T2D), dyslipidemia and hypertension, lowered risk of coronary heart disease, reduced obstructive sleep apnea, and improved quality of life.[2,6–11] For example, the CROSSROADS randomized controlled trial results showed a 25.8% body weight loss and 60% T2D remission in participants at 1-year post-op RYGB compared with only 6.4% and 5.9% for the intensive lifestyle and medical interventions, respectively.[12] When compared with the sleeve gastrectomy, which is the

List of abbreviations: AUC, area under the curve; BA, before and after study design; ECLIA, electrochemiluminescence-based immunoassays; ELISA, enzyme-linked immunosorbent assay; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; kcal, kilocalorie; NGT, normal glucose tolerance; NR, not reported; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO, International Prospective Register of Systematic Reviews; PYY, peptide YY; QE, quasi-experimental study design; RCT, randomized control trial; RIA, radioimmunoassay; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; T2D, type 2 diabetes; USA, United States of America; VAS, visual analogue scale.

most performed bariatric intervention, RYGB has also shown to procure stronger results for weight loss, both short and long term, as well as for comorbidity remission rates.[5,10,13] However, inadequate weight loss, which is classified as weight loss ≤50% of excess body weight,[4] can occur in patients following bariatric surgery. A recent study identified that at 5 years post-RYGB, 23% of 5936 participants met at least 1 of the 3 common definitions of unsuccessful weight loss.[14] Thus, it is crucial to have a better understanding of the contribution of the main mechanisms involved in successful weight loss following RYGB. Patients who undergo RYGB have permanent anatomical changes to their digestive system, creating a much smaller pouch and bypassing the duodenum.[15,16] Intuitively, it may be assumed that the restrictive nature of the intervention is the chief reason for the subsequent lower energy intake; however, changes in appetite regulating hormones are thought to play an instrumental role in the decrease and maintenance of reduced energy intake.[17] Although RYGB has been repeatedly shown to profoundly impact gut peptides and appetite, a demonstration of the causal relationship between these parameters under such conditions has yet to be demonstrated. Of note, there is evidence of increased energy intake and appetite when ghrelin is injected to human participants.[18] Similarly, both PYY[19] and GLP-1[20] are also known to decrease appetite and energy intake when injected peripherally in humans. Thus, it is also important to consider perceived appetite when investigating gut peptides.[21,22] This review will focus on key episodic appetite hormones, namely, ghrelin, glucagon-like peptide-1 (GLP-1), and peptide YY (PYY), that have been demonstrated to influence appetite and food intake.[23]

RYGB surgery substantially amplifies the postprandial response of gastrointestinal (GI) hormones. An increase in GLP-1 and PYY and a decrease in ghrelin levels are all associated with the reduced appetite demonstrated post-surgery.[24] The fluctuation of these hormones is thought to have an important role in food intake control and decreasing motivation to eat for RYGB patients.[17,25] The changes in ghrelin levels noted early after RYGB are substantial and are a common feature of RYGB surgery,[15] although this change has been reported to be only transient.[26] The variation in GLP-1 and PYY levels seems to be among outcomes leading to successful weight loss in RYGB patients. Bypassing the duodenum and proximal jejunum results in the accelerated passage of undigested nutrients to the distal part of the intestine, which is more densely populated with L-cells.[15] This results in an exaggerated GLP-1 and PYY response to food intake in RYGB patients.[15] Increased levels of GLP-1 and PYY appear to be longer lasting, although a clearer depiction of their variation with time is needed.

Although there have been narrative reviews on the topic of gut peptides following RYGB, and systematic reviews and meta-analyses on vertical sleeve gastrectomy,[27,28] it is important to note that, to our knowledge, no systematic review and meta-analysis have been performed to document how post-RYGB gut peptide responses evolve with time. While narrative reviews can be useful, they do not include the calculation of effect sizes, which can be used to examine the strength of the effectiveness of an intervention and document the magnitude of the effect, which was the primary intent of the work presented herein. In short, systematic reviews and meta-analyses provide a more objective and informative portrayal of available data than do narrative reviews. As such, the aim of this systematic review and meta-analysis is to provide detailed information on the time course of changes in key appetite-related hormones (ghrelin, GLP-1, PYY) as well as appetite sensation following RYGB.

2 | METHODOLOGY

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[29] and is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42021253743), thereby following the gold standard steps for systematic reviews and meta-analysis to ensure quality of reported results.

2.1 | Eligibility criteria

Studies were eligible if they (I) included adults who underwent RYGB; (II) evaluated participants before and after RYGB surgery; (III) evaluated the meal induced response of ghrelin, GLP-1, PYY, and/or appetite sensation with a visual analogue scale (VAS); and (IV) published their results in a peer reviewed journal in English or French. Animal studies, case studies, and cross-sectional studies were excluded. Studies were also excluded if they did not provide the macronutrient composition of meals, did not require a minimum of 8 h of fast before the evaluation, collected or reported only fasted appetite-related hormones data, reported postprandial data collection limited to less than 120 min postprandial, or did not provide a minimum of 3 time points to calculate the area under the curve (AUC). Appetite sensations consist of measures of hunger, fullness, satiety, prospective food consumption, and/or satisfaction. If multiple articles from the same study were initially included, only the articles with the longest follow-up period were included.

2.2 | Information sources and search strategy

Four electronic databases were searched in March 2021: Medline Ovid, Embase, Scopus, and Cochrane Central Register of Controlled Trials with no restriction for the date of publication. Databases were searched using a combination of MeSH terms and keywords. A search strategy was elaborated based on our research question, population, intervention, and outcomes of interest with the support of a university librarian. Search terms included variations of gastric bypass, ghrelin, GLP-1, PYY, hunger, and appetite (Table S1). For the databases Medline and Embase, animal studies were excluded within the search strategy. The search strategy was validated by confirming it identified key articles recognized prior as being eligible.[30,31] An identical electronic search strategy was performed in March 2022 with a restriction for the date of publication from 2021 to 2022. The search strategy was set to retrieve articles with leptin as one of our outcomes of

interest. Subsequently, articles that measured only leptin were excluded. The reasoning for this is that a large number of studies solely evaluating leptin were retrieved and could, by themselves, be studied in a future meta-analysis. Because leptin signaling does not appear to be necessary for appetite suppression and weight loss after RYGB,[25,32,33] members of the research group decided not to have leptin as a main outcome in this paper. If data from multiple reports corresponded to the same study, only the study with the most information of the outcomes of interest was included.

2.3 | Article selection

Articles identified with the search strategy from all four databases were imported into Covidence.[34] Covidence is an online platform to manage systematic reviews and was used to track, manage progress, and identify conflicts during the progress of screening articles by the authors. Once imported, the duplicates were automatically removed by the platform and manually verified by one author (MS). Two authors independently screened all records by titles and abstracts for potentially eligible studies (MS, EB). They then independently evaluated the full text of relevant studies to identify eligible articles. A third author resolved any conflicts that arose from each step of the screening process (AB).

2.4 | Data extraction

The data were manually extracted into Microsoft Excel by a single reviewer (MS) and verified by a second reviewer (EB). Fasting and AUC values of ghrelin, GLP-1, PYY, and VAS appetite sensation were extracted from included studies. If key information such as total caloric intake of the meal, macronutrient content of the meal, AUC or incremental AUC for ghrelin, GLP-1, PYY, or VAS appetite sensation scores were not presented in the article, the authors were contacted by email on up to two occasions. For each outcome of interest, fasting, AUC, or incremental-AUC values were extracted with their standard deviation (SD) at baseline and at each time point evaluated.

Additional data extracted regarding the study details were the article title, journal, year of publication, country of publication, and design. Regarding the study population, the following data were extracted: number of participants, average and/or age range, ethnicity, number and/or percentage of women included, number of women menopaused, number of participants initially with T2D, and comorbidities. The following data regarding the study intervention were extracted: description of any pre-surgery mandatory weight loss, surgery details such as pouch size, biliopancreatic and alimentary limb length, fasting duration, consistency of meal (liquid or solid with description when solid or semi-solid), quantity of test meal (ml), duration of test meal, total caloric intake (kcal), and macronutrient composition (%). Weight and/or body mass index (BMI) and weight loss and/or BMI loss before and after the surgery were also extracted. The following information regarding the outcome measurements were extracted: type of hormone analysis (total/active), type of kit and company for each hormone measures, and the description of time points evaluated postprandially. For studies with a randomized control trial (RCT) design, the control group data were not extracted. Some assumptions were made when information in the included studies was unclear, such as the test meal was entirely consumed by participants at all time points evaluated and that overnight fasting was assumed to be of a minimum of 8 h. When not mentioned, AUC was assumed to be calculated with the trapezoid method and to be total AUC unless authors indicated that they calculated incremental AUC.

2.5 | Risk of bias assessment

The quality of included articles was assessed with a standardized tool for before after (pre-post) studies with no control group developed by the National Heart, Lung and Blood Institute (NHLBI, USA).[35] The tool is composed of 12 items designed to evaluate the internal validity of the studies. Three of the 12 criteria were defined as "fatal flaws" when not met or identified: (I) participants representative of clinical population of interest; (II) outcome measures clearly described, valid, and reliable (duplicate essays for hormone analysis); and (III) follow-up rate of ≥80%. Study quality was defined as good, fair, and poor when 0, 1, and ≥2 fatal flaws were identified, respectively. The remaining criteria targeted the study question, eligibility criteria, study population, enrollment of eligible participants, sample size, clear intervention description blinding of outcome assessors, statistical analysis, multiple outcome measures, and group-level interventions and individual level outcome efforts. Two authors independently assessed study quality of included studies (MS, EB), and a third author resolved any conflicts that arose through discussion (AB).

2.6 | Statistical analysis

The effect measure used for ghrelin, GLP-1, and PYY was mean AUC and fasting mean. Mean weight was meta-analyzed to determine if the weight of the population of included studies was decreasing following the RYGB surgery. Multilevel models with cluster robust variance estimation were performed.

Forest plots were used to visually display results of individual studies and syntheses. When a study contributed multiple arms, each arm was treated as an independent study within the meta-analysis. Forest plots present studies ordered based on the size of their outcome estimate within each time point to facilitate appraisal of outcome distributions. Analyses were performed using R version 4.2.1. Metafor, 3.4.0.[36] For each measure of interest, outcomes were weighted by inverse-variance and analyzed in a multilevel model with random effects for (a) study and (b) time points nested within studies.[37] The model adjusted for kcal consumption of the test meal. Dependency from repeated measurement was addressed by calculating cluster robust standard errors. Cluster-robust standard errors were calculated when there was sufficient data; otherwise, regular standard errors were

reported. When cluster robust methods were incorporated, the moderator was tested with an *F* test. When standard multilevel methods were applied, the moderator was tested with a Qm test. Because the included studies did not randomly sample participants and did not randomly assign treatment, inferences in this meta-analysis are restricted to the population of participants included in these studies. Statistical heterogeneity was evaluated with Cochrane's *Q* and was separated into between-study and between-time point components. Heterogeneity variance was calculated as sigma-squared for each component. Prediction intervals were calculated based on the between-subject heterogeneity and sampling error. The 95% prediction intervals in forest plots illustrate the range of mean values expected from a random study from the same population as our sample. Between-study heterogeneity was estimated with restricted maximum likelihood (REML).

There were syntheses that could not be conducted due to insufficient data. Only time points with at least two data points were aggregated in each meta-analysis. If a study presented data with a type of outcome (active, total), time AUC (incremental, total, 120–300 min postprandial), or time point post-RYGB that no other included studies presented, the data point could not be analyzed in the meta-analysis. There were no statistical methods used to explore causes of heterogeneity because of insufficient power. When large heterogeneity was observed, methodological differences between studies and possible errors in data extraction or original articles were explored. Sensitivity analyses were not conducted.

3 | RESULTS

3.1 | Study selection

The database search initially identified 4437 articles that were imported into Covidence. Covidence automatically removed 1878 duplicates (17 more duplicates were excluded manually). Of the 2559 articles remaining, 2211 were deemed irrelevant after titles and abstract screening. The full text was retrieved for 228 studies, and of those, 181 studies were excluded. Out of the excluded full texts, 13% ($k = 23$) were the wrong study design, 12% ($k = 22$) did not have a meal test, 11% ($k = 20$) did not measure the postprandial response up to 120 min, and 40% ($k = 72$) only measured leptin (Figure 1). Eight studies would have met the inclusion criteria but were excluded because key information (i.e., meal test kcal, measure of outcomes of interest fasting, and AUC) were not presented in the article and the missing information could not be obtained from corresponding

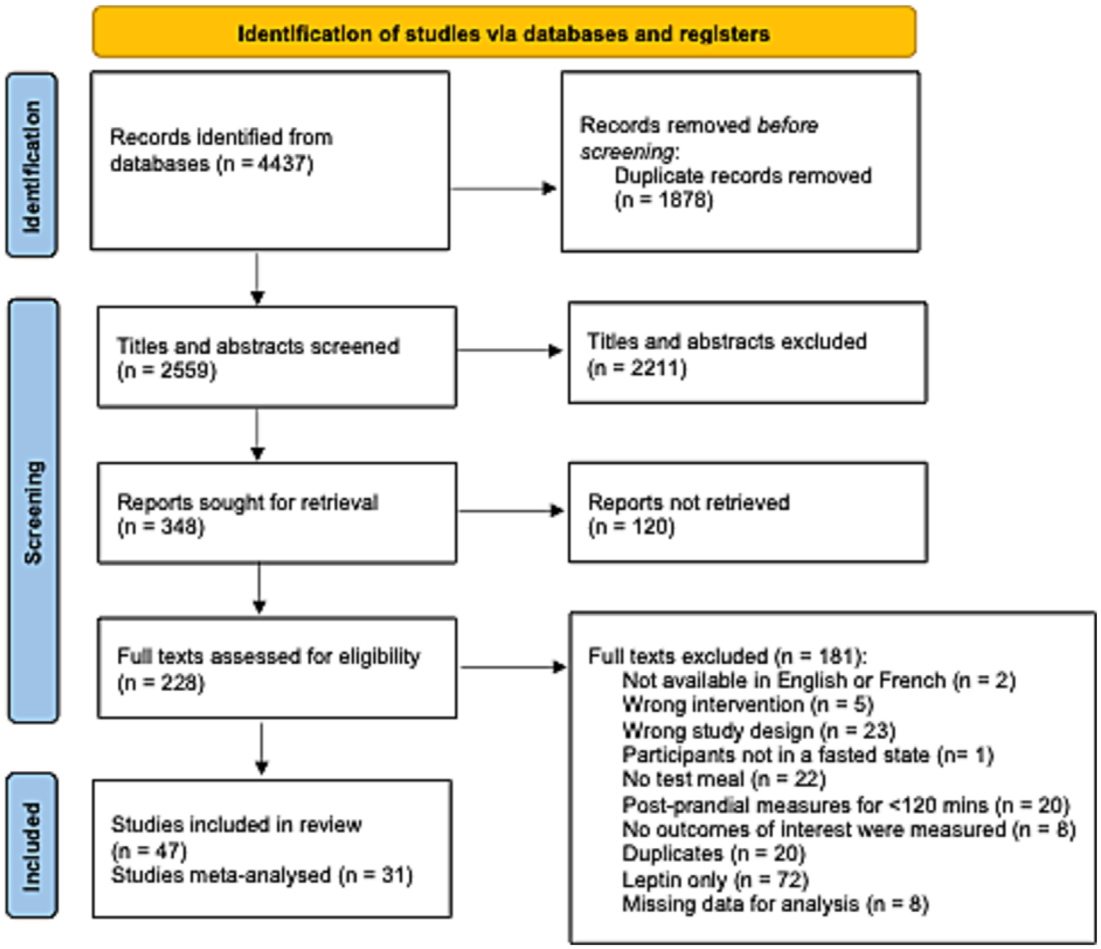

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 flow chart for identification of studies.

authors.[38–45] Therefore, a total of 47 studies were included, of which 31 presented sufficient information to be included in the meta-analysis for at least one outcome of interest, and 27 were meta-analyzed for weight (Figure 1).

3.2 | Study characteristics

Study characteristics and main findings are presented in Table 1. Included studies were published between 2004 and 2021, with 40% ($k = 19$) published between 2016 and 2021.[29,30,45,48,52,53,55,63,65,72,74–82] The median (range) total sample size was $n = 12$ (5–60) with a total of $n = 904$. The median of women evaluated was 75% (24–100%) across included studies, and 15% ($k = 7$) of studies evaluated women only.[46,54,63,80,85,86,88] The median (range) follow-up time post-RYGB was 6 months (1 week–48 months), where 51% ($k = 24$) of studies evaluated their participants up to at least 12 months post-RYGB.[30,31,46–50,53,56,60–62,66,69,70,72,73,76,81,87,89,90] A pre-surgery weight loss or diet was mandatory in 23% ($k = 11$) of studies.[47,56–58,60,63,69,74,77,82,89] For 13% ($k = 6$) of these studies, an 8% weight loss was mandatory.[58,59,62,65,83,90] In these studies, all pre-RYGB weight, BMI, and hormone analyses were done after the pre-surgical weight loss. Most studies did not report weight stabilization before the surgery. Pre-RYGB BMI was reported by all except 3 studies,[56,58,79] and in 94% ($k = 43$) of studies, the median BMI was 44.8 kg/m^2 (32.1–53.3) kg/m^2. All surgery details were reported by 62% ($k = 29$) of the studies. Pouch size averaged 26 ml (15–40 ml), biliopancreatic limb length averaged 73 cm (25–150 cm), and alimentary limb length averaged 124 cm (100–150 cm) (Table S2). Most studies (85%, $k = 40$) reported giving a liquid meal tests to their participants,[29,30,45–47,49–53,55–62,64–69,71–77,82–87,89] and 11% ($k = 5$) of studies reported semi-solid or solid meal tests (44,51–53,82). A further 2% ($k = 1$) of the studies provided both liquid and solid meal tests on different days[81] (Table S2). Meal duration was standardized across participants in 57% ($k = 27$) of studies,[29,30,45,47,49–51,53,54,56–58,60,61,64,71,72,74,76,79–82,86–89] ranging from 3 to 30 min. The median caloric intake (range) of the meal test was 304 kcal (75–600 kcal) (Table S2). Regarding the outcomes of interest, 40% ($k = 19$) of studies evaluated ghrelin,[30,31,46,47,50,52,54,55,58,61,63,67,71,74,75,78,87,88] 85% ($k = 40$) GLP-1,[31,46–51,53–66,68,69,71–76,78–82,84,86,88–90] 47% ($k = 22$) PYY,[30,31,46,50,54,58,61–63,66,68,70,71,74,75,77,78,80,83,85,86,88] and a VAS was used to measure appetite sensation AUC in 17% ($k = 8$) of studies.[47,51,54,68,78,80,83,85,88]

3.3 | Risk of bias

The NHLBI quality assessment tool for pre-post studies with no control group revealed a total of 13% ($k = 6$) of studies with an overall good quality rating, 62% ($k = 29$) of studies with a fair rating, and 26% ($k = 12$) of studies with a poor rating (Table 1). The complete summary of risk of bias assessment can be found in the Table S3. Most fatal flaws recorded arose from the same flaw, which related to the quality of the study outcome measures, more precisely in this case, reliability by verifying if assays were performed in duplicates for the measurement of Ghrelin, GLP-1, and PYY. All 12 of the poor-quality studies and a total of 41 out of the 47 studies did not assay the peptides in duplicates.

3.4 | Ghrelin

Only total ghrelin concentrations were analyzed and presented as we had insufficient data points to analyze active ghrelin. Pre-RYGB, $k = 10$ eligible studies (11 arms) reported fasting total ghrelin ($n = 194$). The estimated fasting total ghrelin concentration was 554 pg/ml (95% CI: 437–670). At 2 weeks post-RYGB, 2 studies (3 arms) ($n = 39$) showed an estimated fasting total ghrelin level of 432 pg/ml (95% CI: 301–562). At 6 weeks post-RYGB, 2 studies ($n = 17$) showed an estimated fasting total ghrelin level of 448 pg/ml (95% CI: 290–605). At 26 weeks post-RYGB, 4 studies ($n = 118$) showed an estimated fasting total ghrelin level of 541 pg/ml (95% CI: 421–661). Lastly, at 52 weeks post-RYGB, 5 studies ($n = 132$) revealed an estimated fasting total ghrelin level of 553 pg/ml (95% CI: 434–673) for fasting total ghrelin (Figure 2). These analyses demonstrated that fasting total ghrelin 2 weeks post-surgery was significantly lower compared with pre-surgery levels (Q_m [df = 4] = 14.82, $p = 0.005$). At 6 weeks post-RYGB, concentrations increased to pre-surgical levels, at which time values were no longer significantly different from pre-RYGB values. This was sustained from 6 to 52 weeks post-RYGB. The between-study heterogeneity was $\sigma^2 = 35{,}956$, QE (df = 20) = 293.530, $p < 0.001$.

Pre-RYGB, and at 26 and 52 weeks post-RYGB, 3 eligible studies reported AUC for total ghrelin ($n = 90$). The estimates were 51,875 pg/ml/min (95% CI: 37,471–66,279), 51,389 pg/ml/min (95% CI: 36,968–65,810), and 51,517 pg/ml/min (95% CI: 37,003–66,030), respectively (Figure 3). No significant difference between follow-up measurements of postprandial levels of total ghrelin was found, (Q_m [df = 3] = 2.3, $p = 0.51$). The between-study heterogeneity was $\sigma^2 = 151924752.4$, QE (df = 5) = 55.283, $p < 0.001$.

3.5 | GLP-1

Total GLP-1 fasting concentrations were analyzed pre-RYGB in 11 studies (15 arms; $n = 301$) and revealed an estimated 9 pmol/L (95% CI: 6–13) pre-RYGB. At 1 week post-*RYGB*, 2 studies (5 arms; $n = 55$) reported fasting GLP-1 concentration (9 pmol/L; 95% CI: 5–13). At 2 weeks post-RYGB, the estimated fasting concentration from 2 studies ($n = 35$) was 10 pmol/L (95% CI: 4–16). Fasting level was 9 pmol/L (95% CI: 5–13) at 12 weeks post-RYGB for the 4 studies that were analyzed (7 arms; $n = 92$). At 52 weeks post-RYGB, 5 studies were analyzed (6 arms; $n = 174$), and the resulting estimated fasting total GLP-1 was 10 pmol/L (95% CI: 6–13). Finally, at 104 weeks, 2 studies were analyzed (3 arms; $n = 100$) revealing an estimated 8 pmol/L (95% CI: 6–13) (Figure 4). However, there was no difference between any time point in population estimates. The heterogeneity was significant ($\sigma^2 = 24.4$, QE [df = 32] = 359.94, $p < 0.001$).

TABLE 1 Summary of study characteristics, main findings, and quality assessment rating of included studies.

Author, year of publication (country) *Design*	*n* (% W)	Average age ± SD (range) [25th, 75th percentile]	Initial BMI kg/m^2 ± SD (range)	Test meal (kcal)	Post-prandial AUC time (minutes)	Type of assay (provider)
Alamuddin et al., 2017[46] (USA) *QE*	23 (100)	35.5 ± 2	44.6 ± 0.9	240	180	ELISA (Millipore)
Arakawa et al., 2020[30] (USA) *BA*	40 (80)	43.6 ± 1.6 (22–64)	46.4 ± 0.9 [w]	320	120	RIA (Millipore)
Bryant et al., 2013[47] (England) *BA*	12 (75)	36 ± 2	30.3 ± 1.8	300	180	RIA (NR)
Campos et al., 2010[48] (USA) *QE*	12 (75)	47.4 ± 8.7	48.4 ± 6.8	300	180	ELISA (Millipore)
Cazzo et al., 2017[49] (Brazil) *BA*	11 (55)	36.7 ± 8.2	46.3 ± 3.1 [w]	515	180	ELISA (Millipore)
Chronaiou et al., 2012[50] (Greece) *RCT*	12 (67)	NR	46.1 ± 2.2 [w]	300	120	RIA (Millipore)
Evans et al., 2012[51] (USA) *QE*	20 (70)	49.6 ± 11.2	45.6 ± 7.6	262	120	Multiplex immunoassay (Millipore)
Fellici et al., 2015[89] (Brazil) *BA*	36 (47)	47.4 ± 8.4 (31–54)	32.1 ± 0.3 [w]	515	180	ELISA (Linco)
Foschi et al., 2008[52] (Italy) *BA*	10 (90)	43.1 ± 4.1	32.1 ± 0.3	504	180	RIA (DRG diagnostics)
Griffo et al., 2016[53] (Italy) *BA*	9 (56)	46 ± 7	42 ± 6 [w]	304	180	ELISA (Millipore)
Halliday et al., 2019[54] (USA) *QE*	6 (100)	37.6 ± 4.6	41.4 ± 1.4	200	180	ELISA (Alpco diagnostics)
Hansen et al., 2011[55] (USA) *BA*	9 (67)	41 ± 11	51.9 ± 6 [w]	250	240	RIA (Millipore)

TABLE 1 (Continued)

Author, year of publication (country) *Design*	*n* (% W)	Average age ± SD (range) [25th, 75th percentile]	Initial BMI kg/m^2 ± SD (range)	Test meal (kcal)	Post-prandial AUC time (minutes)	Type of assay (provider)
Ilesanmi et al., 2021[56] (United Kingdom) *BA*	10 (80)	50.2 ± 13.2	NR [w]	330	180	Milliplex magnetic bead-based multi-analyte (Millipore)
Jørgensen et al., 2013[57] (Denmark) *BA*	9 (33)	50 ± 3	39.5 ± 2.5	300	240	RIA (NR)
Jacobsen et al., 2012[58] (Denmark) *BA*	8 (75)	35.5 ± 8.8 (26-55)	*NR [w]	300	210	RIA (Linco)
Jacobsen et al., 2013[59] (Denmark) *BA*	12 (75)	NR	*39.2 ± 1.8	300	240	RIA (NR)
Jiménez et al., 2012[60] (Spain) *BA*	6 (NR)	43 ± 13	44.8 ± 4.6	398	120	RIA (Millipore)
Jørgensen et al., 2012[90] (Denmark) *BA*	25 (75)	52 ± 9	NGT (a) *41.5 ± 4.8 [w] T2D (b) *43.1 ± 5.1 [w]	300	240	RIA (NR)
Korner et al., 2009[61] (USA) *BA*	28(86)	45 ± 2	48 ± 1	320	120	RIA (Linco)
Lindegaard et al., 2015[62] (Denmark) *BA*	25 (NR)	NR	NGT (a) *41.5 ± 4.8 [w] T2D (b) *43.2 ± 5.3 [w]	300	240	RIA (NR)
Lips et al., 2014[63] (The Netherlands) *QE*	31 (100)	NGT (a) 18.6 ± 1.6 T2D (b) 51.3 ± 1.9	NGT (a) 44.2 ± 0.8 [w] T2D (b) 43.5 ± 1.1 [w]	400	180	ELISA (Millipore)
Magro et al., 2018[64] (Brazil) *BA*	11 (55)	36.7 ± 8.2	46.3 ± 3.1 [w]	515	180	ELISA (Millipore)
Martinussen et al., 2015[65]	30 (67)	NGT (a)	NTG (a)	300	180	RIA

(Continues)

TABLE 1 (Continued)

Author, year of publication (country) *Design*	*n* (% W)	Average age ± SD (range) [25th, 75th percentile]	Initial BMI kg/m^2 ± SD (range)	Test meal (kcal)	Post-prandial AUC time (minutes)	Type of assay (provider)
(Denmark) *BA*		*41 ± 2.8 IGT (b) *42 ± 3.3 T2D (c) *46 ± 2.8	*43.2 ± 1.3 [w] IGT (b) *40.4 ± 1.4 [w] T2D (c) *41.2 ± 1.3 [w]			(NR)
Miras et al., 2021[66] (United Kingdom) *Mechanistic study*	53 (59)	49 ± 10 Long (b) 48 ± 9	42 ± 6 Long (b) 43 ± 8	300	120	Multiplexed Magpix immunoassay (NR)
Morínigo et al., 2004[67] (Spain) *QE*	8 (63)	46 ± 3.1	49.5 ± 1.8	398	120	RIA (Linco)
Morínigo et al., 2006[68] (Spain) *QE*	9 (78)	39.4 ± 10.7	47.4 ± 6.1	398	120	RIA (Linco)
Morínigo et al., 2006[69] (Spain) *BA*	NGT (a) 12 (75) IGT (b) 12 (75) T2D (c) 10 (50)	NGT (a) 41.8 ± 2.7 IGT (b) 46.8 ± 3.2 T2D (c) 50.05 ± 3	NGT (a) 49.7 ± 1.7 IGT (b) 48.6 ± 1.8 T2D (c) 49 ± 2.1	398	120	RIA (Linco)
Morínigo et al., 2008[70] (Spain) *QE*	25 (24)	43.6 ± 2.1	48.8 ± 1.2	398	120	RIA (Linco)
Nannipieri et al., 2013[71] (Italy) *BA*	23 (NR)	NR	41.8 ± 5.4 [w]	350	300	ELISA (Millipore)
Nguyen et al., 2015[72] (USA) *RCT*	60 (63)	49 ± 9	35.8 ± 0.5	250	120	ELISA (Millipore)
Nosso et al., 2016[73] (Italy) *BA*	14 (57)	49 ± 7	42 ± 6 [w]	304	180	ELISA Merck-(Millipore)
Peterli et al., 2009[74] (Switzerland) *Randomized parallel group study*	13 (NR)	41.8 ± 10.4 (23.6–53.9)	47 ± 6.4 [w]	400	180	ELISA (Linco)
Pop et al., 2018[75] (USA) *BA*	10 (NR)	53.2 (48–58.4)	51.14 (45.96–56.32)	360	360	ECLIA (Meso Scale Discovery)

TABLE 1 (Continued)

Author, year of publication (country) *Design*	*n* (% W)	Average age ± SD (range) [25th, 75th percentile]	Initial BMI kg/m^2 ± SD (range)	Test meal (kcal)	Post-prandial AUC time (minutes)	Type of assay (provider)
Purnell et al., 2018[76] (USA) *BA*	62 (77)	NGT (a) 52 [45, 54] T2D (b) 52 [47, 57]	NGT (a) 45.7 [43.6, 50.7] T2D (b) 47.9 [43.1, 54.8]	360	240	Single-plex immunoassays (Meso Scale Discovery)
Rao et al., 2017[77] (USA) *QE*	21 (81)	43.1 ± 2.4	47.8 ± 1.7 [w]	320	120	Single-plex immunoassays (Meso Scale Discovery)
Schmidt et al., 2016[78] (Denmark) *QE*	14 (71)	37.7 ± 10.4	45.4 ± 5.1	310	180	Milliplex (Linco)
Shah et al., 2019[79] (USA) *BA*	5 (80)	51 ± 6	NR [w]	220	180	C-terminal assay (Millipore)
Shankar et al., 2017[80] (USA) *QE*	17 (100)	45 ± 10	53.3 ± 3.5	389	120	RIA (Millipore)
Stano et al., 2017[81] (USA) *BA*	21 (92)	L-group (a)35.3 ± 10.5 S-group (b)34.8 ± 9.2	L-group (a) 47.4 ± 6.62 [w] S-group (b) 48.02 ± 9.28	600	360	RIA (Millipore)
Steven et al., 2016[82] (United Kingdom) *QE*	9 (NR)	NR	43 ± 1.1	100	120	ELISA (AlpcoDiagnositics)
Svane et al., 2016[83] (Denmark) *BA*	9 (33)	50 ± 3	*39.2 ± 2.5	301	240	RIA (Millipore)
Tsouristakis et al., 2019[31] (USA) *BA*	38 (NR)	43.8 ± 2.5	47.2 ± 0.7 [w]	320	120	RIA (Millipore)
Umeda et al., 2011[84] (Brazil) *BA*	10 (NR)	NR	39.7 ± 1.9 [w]	353	120	ELISA (Linco)
Valderas et al., 2010[85] (Chile) *QE*	8 (100)	38.7 ± 4.5	37.8 ± 0.8	355	180	RIA (Linco)

TABLE 1 (Continued)

Author, year of publication (country) *Design*	*n* (% W)	Average age ± SD (range) [25th, 75th percentile]	Initial BMI kg/m^2 ± SD (range)	Test meal (kcal)	Post-prandial AUC time (minutes)	Type of assay (provider)
Yan et al., 2014[86] (USA) *QE*	20 (100)	NGT (a) 36.7 ± 2.4 T2D (b) 49.1 ± 2.0	NGT (a) 44.3 ± 1.1 [w] T2D (b) 46.6 ± 2.3 [w]	75, 150 and 300	120	ELISA (Millipore)
Yang et al., 2014[87] (China) *BA*	16 (56)	35.2 ± 11.8 (20–55)	38.6 ± 6.4 [w]	300	120	ELISA (Novatein)
Yousseif et al., 2014[88] (United Kingdom) *BA*	10 (100)	46.8 ± 1.5	45 ± 1.5	500	180	ELISA (Millipore)

Note: [f] = fasting data were meta-analyzed; [a] = AUC data were meta-analyzed; [w] = weight was meta-analyzed; * = Initial BMI pre-RYGB after 8% mandatory weight loss. All significant ($p < 0.05$) differences compared with pre-RYGB (unless stated otherwise) are represented by arrows in the direction of the change (↓ or ↑), and non-significant change is represented by =.
Abbreviations: AUC, area under the curve; BMI, body mass index; ECLIA, electrochemiluminescence-based immunoassays; ELISA, enzyme-linked immunosorbent assay; F, fasting; GLP-1, glucagon-like peptide-1; m, months; NGT, normal glucose tolerance; NR, not reported; PFC, prospective food consumption; PYY, peptide YY; RIA, radioimmunoassay; RYGB, Roux-en-Y gastric bypass; T2D, type 2 diabetes; VAS, visual analogue scale.

TABLE 1 (Continued)

Author, year of publication (country) *Design*	Time post-RYGB of outcome measures					Outcomes of interest	Main findings	Quality assessment rating
	Total (m)	0–3 m.	4–6 m.	7–12 m.	12+ m.			
Alamuddin et al., 2017[46] (USA) *QE*	18		✓		✓	Ghrelin GLP-1 PYY	F and AUC ghrelin: =6 m, =12 m (control) F GLP-1: =6 m, =12 m AUC GLP-1: ↓ 6 m, =12 m F and AUC active PYY: ↓ 6 m, ↓ 12 m	2
Arakawa et al., 2020[30] (USA) *BA*	12		✓	✓		Ghrelin [f, a] PYY [f, a]	F and AUC ghrelin: =6 m, =12 m F PYY: ↑ 6 m, =12 m AUC PYY: ↑ 6 m, ↑ 12 m	3
Bryant et al., 2013[47] (England) *BA*	12	✓		✓		Ghrelin GLP-1 VAS	AUC ghrelin: =3 days, =2 m, =12 m AUC GLP-1: =3 days, ↑ 2 m, ↑ 12 m AUC VAS hunger: =3 days, =2 m, =12 m AUC VAS fullness: ↑ 3 days, ↑ 2 m, =12 m	1
Campos et al., 2010[48] (USA)	6	✓	✓			GLP-1	AUC GLP-1: ↑ 6 m	2

TABLE 1 (Continued)

Author, year of publication (country) *Design*	Time post-RYGB of outcome measures					Outcomes of interest	Main findings	Quality assessment rating
	Total (m)	0–3 m.	4–6 m.	7–12 m.	12+ m.			
QE								
Cazzo et al., 2017[49] (Brazil) *BA*	12			✓		GLP-1 VAS	AUC GLP-1: =12 m °VAS hunger: ↑ 12 m °VAS fullness: ↑ 12 m °VAS satisfaction: ↑ 12 m °VAS PFC: ↓ 12 m °VAS one point post-prandial only	1
Chronaiou et al., 2012[50] (Greece) *RCT*	12	✓	✓	✓		Ghrelin [f, a] GLP-1 PYY [f, a]	F ghrelin: ↓ 3 m, =6 m, ↑12 m F GLP-1: =3 m, =6 m, =12 m F PYY: =3 m, ↑ 6 m, ↑ 12 m *P* values for AUC NR	3
Evans et al., 2012[51] (USA) *QE*	0.5	✓				GLP-1 PYY [f, a] VAS	F GLP-1: =2 weeks AUC GLP-1: ↑ 2 weeks F PYY: =2 weeks AUC PYY: =2 weeks AUC VAS hunger: ↓ 2 weeks	2
Fellici et al., 2015[89] (Brazil) *BA*	12	✓	✓	✓		GLP-1	AUC GLP-1: ↑ 3 m. ↑ 6 m, ↑ 12 m	1
Foschi et al., 2008[52] (Italy) *BA*	6		✓			Ghrelin	*P* values for comparison pre-RYGB NR	2
Griffo et al., 2016[53] (Italy) *BA*	24				✓	GLP-1	AUC GLP-1: ↑ 24 m	1
Halliday et al., 2019[54] (USA) *QE*	1	✓				Ghrelin [f] GLP-1 [f] PYY [f] VAS	F ghrelin: ↓ 1 m F GLP-1: =1 m F PYY: =1 m F VAS hunger, satiety, and PFC: =1 m AUC ghrelin: ↓ 1 m AUC GLP-1: =1 m AUC PYY: =1 m AUC VAS hunger: ↓ 1 m AUC VAS satiety and PFC: ↑ 1 m	2
Hansen et al., 2011[55] (USA) *BA*	1.5	✓				Ghrelin [f] GLP-1	*P* values for comparison with pre-RYGB NR	2
Ilesanmi et al., 2021[56] (United Kingdom) *BA*	12	✓		✓		GLP-1 [f]	F GLP-1: =1 m, ↑ 12 m AUC GLP-1: ↑ 1 m, ↑ 12 m	1

TABLE 1 (Continued)

Author, year of publication (country) *Design*	Time post-RYGB of outcome measures					Outcomes of interest	Main findings	Quality assessment rating
	Total (m)	0–3 m.	4–6 m.	7–12 m.	12+ m.			
Jørgensen et al., 2013[57] (Denmark) *BA*	3	✓				GLP-1 [a]	F GLP-1: ↓ 1 week, ↓ 3 m	2
Jacobsen et al., 2012[58] (Denmark) *BA*	0.5	✓				Ghrelin [f] GLP-1 [f] PYY	F and AUC ghrelin: ↓ 2 weeks F GLP-1: =2 weeks AUC GLP-1: ↓ 2 weeks F and AUC PYY: ↓ 2 weeks	1
Jacobsen et al., 2013[59] (Denmark) *BA*	3	✓				GLP-1 [f]	F and AUC GLP-1: ↑ 3 m	2
Jiménez et al., 2012[60] (Spain) *BA*	47				✓	GLP-1	*P* values for comparison with pre-RYGB NR	2
Jørgensen et al., 2012[90] (Denmark) *BA*	12	✓		✓		GLP-1 [f, a]	F GLP-1 NGT: =1 week, =3 m, =12 m F GLP-1 T2D: =1 week, =3 m, ↑12 m AUC GLP-1 NGT and T2D: ↑ 1 week, ↑ 3 m, ↑ 12 m	2
Korner et al., 2009[61] (USA) *BA*	12		✓	✓		Ghrelin [f] GLP-1 [f] PYY [f]	F ghrelin: =2 weeks, =3 m, =6 m, =12 m F GLP-1: =6 m, ↑ 12 m F PYY: =2 weeks, =3 m, =6 m, ↑ 12 m	3
Lindegaard et al., 2015[62] (Denmark) *BA*	12	✓		✓		GLP-1 [a]	AUC GLP-1: ↑ 1 week, ↑ 3 m, ↑12 m	2
Lips et al., 2014[63] (The Netherlands) *QE*	0.75	✓				Ghrelin [f] GLP-1 [f] PYY	F and AUC ghrelin NGT and T2D: ↓ 3 weeks F GLP-1 NGT and T2D: =3 weeks AUC GLP-1 NGT and T2D: ↑ 3 weeks F PYY NGT: =3 weeks F PYY T2D: ↓ 3 weeks AUC PYY NGT and T2D: ↑ 3 weeks	2
Magro et al., 2018[64] (Brazil) *BA*	12			✓		GLP-1	AUC GLP-1: =12 m	2
Martinussen et al., 2015[65] (Denmark) *BA*	3	✓				GLP-1 [f, a]	F GLP-1 NGT, IGT and T2D: =1 week, =3 m AUC GLP-1 NGT, IGT, and T2D: ↑ 1 week. ↑ 3 m	2
Miras et al., 2021[66] (United Kingdom) *Mechanistic study*	12	✓	✓	✓		GLP-1 PYY	AUC GLP-1: =2 weeks, other time points NR AUC PYY: =2 weeks, other time points NR Compared with pre-RYGB	2

TABLE 1 (Continued)

Author, year of publication (country) *Design*	Time post-RYGB of outcome measures					Outcomes of interest	Main findings	Quality assessment rating
	Total (m)	0–3 m.	4–6 m.	7–12 m.	12+ m.			
Morínigo et al., 2004[67] (Spain) *QE*	1.5	✓				Ghrelin [f]	F ghrelin: ↓ 6 weeks AUC ghrelin: =6 weeks	2
Morínigo et al., 2006[68] (Spain) *QE*	1.5	✓				GLP-1 PYY VAS	AUC GLP-1: ↑ 6 weeks AUC PYY: ↑ 6 weeks AUC VAS hunger: =6 weeks AUC VAS satiety: ↑ 6 weeks	2
Morínigo et al., 2006[69] (Spain) *BA*	12	✓		✓		GLP-1 [f]	F GLP-1 NGT, IGT, and T2D: =6 weeks AUC GLP-1 NGT, IGT: ↑ 6 weeks, ↑ 12 m AUC GLP-1 T2DL = 6 weeks, ↑ 12 m	1
Morínigo et al., 2008[70] (Spain) *QE*	12	✓		✓		PYY	F PYY NGT and T2D: =6 weeks, =12 m AUC PYY NGT and T2D: ↑ 6 weeks, ↑ 12 m	2
Nannipieri et al., 2013[71] (Italy) *BA*	12	✓		✓		Ghrelin GLP-1 [f] PYY	F and AUC ghrelin: =2 weeks, ↓ 12 m F GLP-1: ↑ 2 weeks, ↓ 12 m AUC GLP-1: ↑ 2 weeks, =12 m F and AUC PYY: =2 weeks, ↑ 12 m	2
Nguyen et al., 2015[72] (USA) *RCT*	12			✓		GLP-1 [f]	F GLP-1: ↓ 12 m	1
Nosso et al., 2016[73] (Italy) *BA*	12			✓		Ghrelin GLP-1 [f]	F ghrelin: =12 m F GLP-1: =12 m AUC GLP-1: ↑ 12 m	2
Peterli et al., 2009[74] (Switzerland) *Randomized parallel group study*	3	✓				Ghrelin GLP-1 [f] PYY	AUC ghrelin: ↑ 1 week, ↑ 3 m AUC GLP-1: ↑ 1 week, ↑ 3 m AUC PYY: ↑ 1 week, ↑ 3 m F *P* values NR	2
Pop et al., 2018[75] (USA) *BA*	0.3	✓				Ghrelin GLP-1 PYY	F and AUC acyl ghrelin: ↓ 10 days F and AUC GLP-1: ↑ 10 days F PYY: =10 days AUC PYY: ↑ 10 days	2
Purnell et al., 2018[76] (USA) *BA*	24		✓		✓	GLP-1 [f, a]	F GLP-1 NGT and T2D: ↓ 6 m, ↓ 24 m AUC GLP-1 NGT and T2D: ↑ 6 m, ↑ 24 m	2
Rao et al., 2017[77] (USA) *QE*	6		✓			PYY [f]	F PPY: =6 m AUC PYY: ↑ 6 m	3

TABLE 1 (Continued)

Author, year of publication (country) *Design*	Time post-RYGB of outcome measures					Outcomes of interest	Main findings	Quality assessment rating
	Total (m)	0–3 m.	4–6 m.	7–12 m.	12+ m.			
Schmidt et al., 2016[78] (Denmark) *QE*	1	✓				Ghrelin GLP-1 PYY VAS	*P* values for comparison with pre-RYGB NR	2
Shah et al., 2019[79] (USA) *BA*	1	✓				GLP-1 [a]	F GLP-1: =1 m	1
Shankar et al., 2017[80] (USA) *QE*	1	✓				GLP-1 PYY VAS	AUC GLP-1: ↑ 2 weeks, ↑1 m AUC PYY: ↑ 2 weeks, ↑1 m AUC VAS hunger: ↓ 2 weeks, ↓ 1 m AUC VAS fullness, meal satisfaction, and PFC: ↑ 2 weeks, ↑ 1 m	2
Stano et al., 2017[81] (USA) *BA*	12			✓		GLP-1	L-group AUC GLP-1: ↑ 12 m S-group AUC GLP-1: =12 m	1
Steven et al., 2016[82] (United Kingdom) *QE*	0.25	✓				GLP-1	AUC GLP-1: ↑ 1 week	2
Svane et al., 2016[83] (Denmark) *BA*	3	✓				GLP-1 [f, a] PYY VAS	F GLP-1: =3 m AUC GLP-1: ↑ 3 m F PYY: =3 m AUC PYY: ↑ 3 m AUC VAS hunger and satiety: =3 m	2
Tsouristakis et al., 2019[31] (USA) *BA*	48		✓	✓	✓	Ghrelin [f, a] GLP-1 PYY [f, a]	F and AUC ghrelin: =6 m, =12 m, ↑ 24 m, ↑ 36 m, ↑ 48 m F GLP-1: =6 m, =12 m, =24 m, =36 m, =48 m AUC GLP-1: ↑ 6 m, ↑ 12 m, ↑ 24 m, ↑ 36 m, ↑ 48 m F and AUC PYY: ↑ 6 m, ↑ 12 m, ↑ 24 m, ↑ 36 m, ↑ 48 m	3
Umeda et al., 2011[84] (Brazil) *BA*	3	✓				GLP-1 [f]	F GLP-1: =1 week, ↓ 1 m, =3 m AUC GLP-1: =1 week, ↑ 1 m, ↑ 3 m	1
Valderas et al., 2010[85] (Chile) *QE*	2	✓				PYY [f] VAS	F PYY: =2 m AUC PYY: ↑ 2 m AUC VAS hunger: ↓ 2 m AUC VAS satiety: ↑ 2 m	2

TABLE 1 (Continued)

Author, year of publication (country) *Design*	Time post-RYGB of outcome measures					Outcomes of interest	Main findings	Quality assessment rating
	Total (m)	0–3 m.	4–6 m.	7–12 m.	12+ m.			
Yan et al., 2014[86] (USA) *QE*	3	✓				GLP-1 PYY	75 kcal NGT and T2D AUC GLP-1: =1 week, =3 m 150-kcal NGT AUC GLP-1: ↑ 1 week, ↑ 3 m 150-kcal T2D AUC GLP-1: ↑ 1 week, =3 m 300-kcal NGT and T2D AUC GLP-1: ↑ 1 week, ↑ 3 m 75-kcal NGT and T2D AUC PYY: =1 week, =3 m 150-kcal NGT and T2D AUC PYY: ↑ 1 week, ↑ 3 m 300-kcal NGT and T2D AUC PYY: ↑ 1 week, ↑ 3 m	1
Yang et al., 2014[87] (China) *BA*	12			✓		Ghrelin	F ghrelin: ↑ 12 m	3
Yousseif et al., 2014[88] (United Kingdom) *BA*	3	✓				Ghrelin GLP-1 [f] PYY VAS	F and AUC ghrelin: =6 weeks, =3 m F GLP-1: =6 weeks, =3 m AUC GLP-1: ↑ 6 weeks, ↑ 3 m F PYY: =6 weeks, =3 m AUC PYY: ↑ 6 weeks, ↑ 3 m F VAS hunger: ↓ 6 weeks, ↓ 3 m AUC VAS hunger: ↓ 6 weeks, =3 m F VAS fullness: =6 weeks, =3 m AUC VAS fullness: ↓ 6 weeks, ↓ 3 m	1

Note: [f] = fasting data were meta-analyzed; [a] = AUC data were meta-analyzed; [w] = weight was meta-analyzed; * = Initial BMI pre-RYGB after 8% mandatory weight loss. All significant ($p < 0.05$) differences compared with pre-RYGB (unless stated otherwise) are represented by arrows in the direction of the change (↓ or ↑), and non-significant change is represented by =.

Abbreviations: AUC, area under the curve; BMI, body mass index; ECLIA, electrochemiluminescence-based immunoassays; ELISA, enzyme-linked immunosorbent assay; F, fasting; GLP-1, glucagon-like peptide-1; m, months; NGT, normal glucose tolerance; NR, not reported; PFC, prospective food consumption; PYY, peptide YY; RIA, radioimmunoassay; RYGB, Roux-en-Y gastric bypass; T2D, type 2 diabetes; VAS, visual analogue scale.

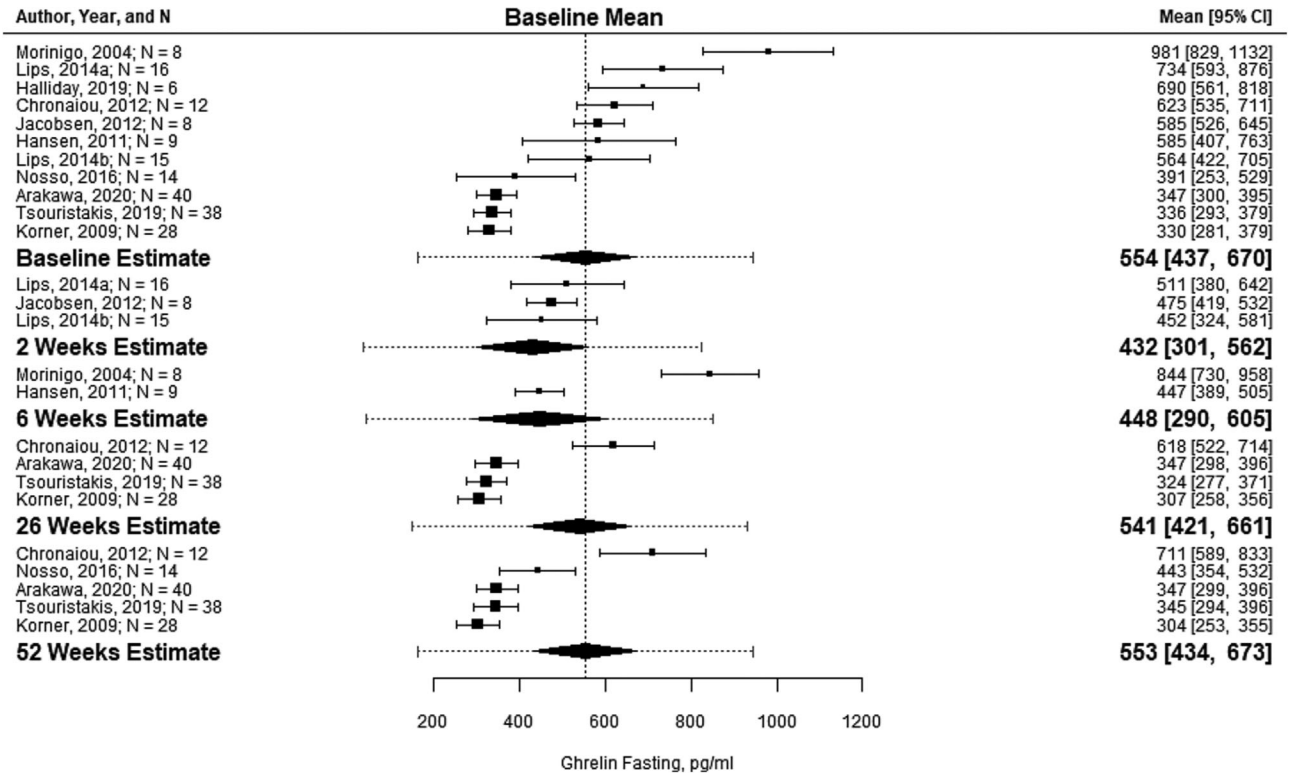

FIGURE 2 Fasting total ghrelin levels and estimates (pg/ml) of included studies before and 2, 6, 26, and 52 weeks post-Roux-en-Y gastric bypass (RYGB).

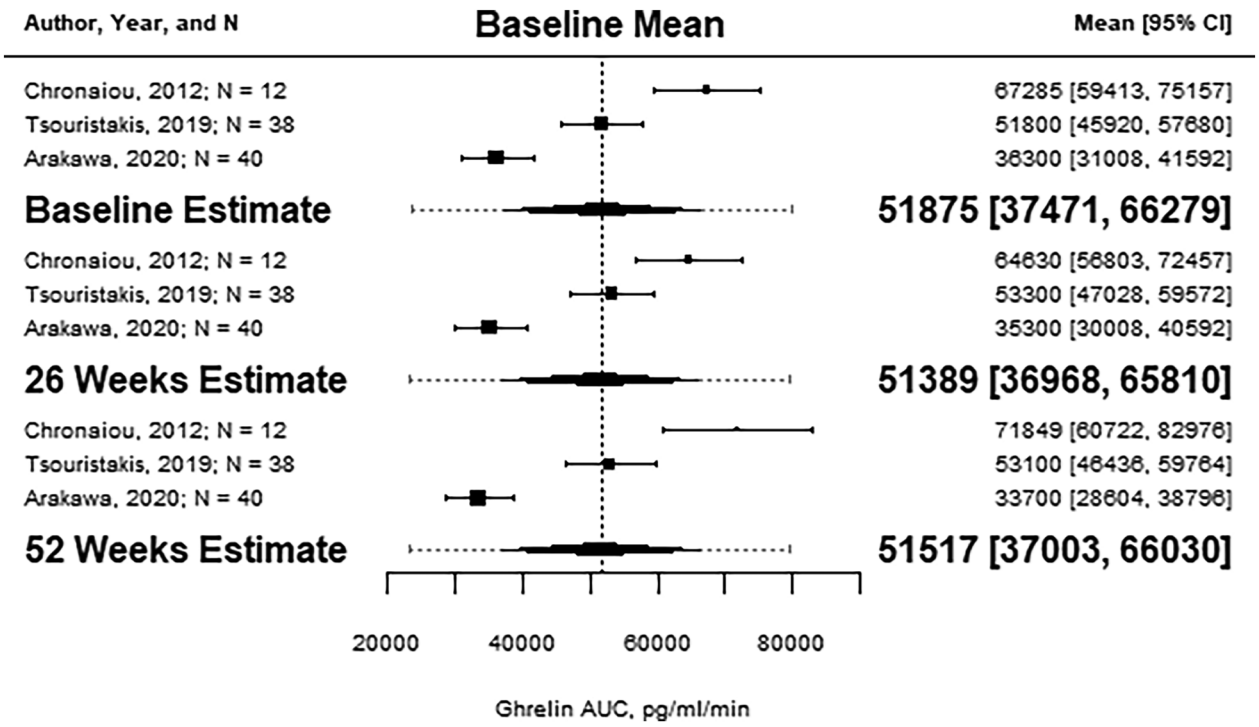

FIGURE 3 Postprandial response (120 min; total area under the curve [AUC]) of total ghrelin levels and estimates (pg/ml/min) of included studies before Roux-en-Y gastric bypass (RYGB), 26 and 52 weeks post-RYGB.

The estimated active GLP-1 fasting concentration pre-RYGB across 7 studies (10 arms; $n = 122$) was 5 pmol/L (95% CI: 2–9), 5 pmol/L (95% CI: 1–8) at 2 weeks post-RYGB for 1 study (2 arms; $n = 31$), 5 pmol/L (95% CI: 2–9) at 12 weeks post-RYGB for 3 studies ($n = 33$), and 6 pmol/L (95% CI: 2–10) at 52 weeks post-RYGB for 2 studies ($n = 24$). Forest plots for active fasting GLP-1 can be found in Figure S1. However, there was no significant difference among time points estimated for GLP-1 in the population. The heterogeneity was significant ($\sigma^2 = 11.3$, QE [df = 13] = 130.7990, $p < 0.001$).

For the analysis of total GLP-1 Incremental-AUC (180 min postprandial), 2 studies were analyzed pre-RYGB (4 arms; n = 35) and other time points 1 study (3 arms; $n = 30$). Pre-RYGB the estimate for total GLP-1 Incremental-AUC (180 min) was 694 pmol/L/min (95% CI: 300–1089), at 1 week post-RYGB the estimate was 5360 pmol/L/min (95% CI: 4530–6190) and at 12 weeks 4366 pmol/L/min (95% CI: 3740–4993) (Figure 5). Postprandial levels of GLP-1 increased significantly at Weeks 1 and 12 compared with pre-RYGB, Q_m (df = 3) = 274.77, $p < 0.001$. The between-study heterogeneity was $\sigma^2 = 106{,}560.87$, but the residual heterogeneity was not significant, QE (df = 6) = 6.922, $p = 0.328$.

The analysis of GLP-1 Incremental-AUC (240 min postprandial) pre-RYGB included 3 studies (4 arms; $n = 43$), and the estimate was 1385 pmol/L/min (95% CI: 144–2625). At Week 1 post-RYGB, 2 studies were analyzed (3 arms; $n = 34$), and the estimate was 6427 pmol/L/min (95% CI: 4627–8227); at 12 weeks, values of 3 studies were analyzed (4 arms; $n = 43$), and the estimate was 5398 pmol/L/min (95% CI: 3871–6926). At 52 weeks, post-RYGB 1 study was analyzed (2 arms; $n = 25$) with an estimate of 7802 pmol/L/min (95% CI: 5060–10,543) (Figure 6). Differences in postprandial GLP-1 levels among all time points post-RYGB are significantly higher compared with pre-RYGB, Q_m (df = 4) = 35.69, $p < 0.01$. There was significant residual heterogeneity, QE (df = 8) = 33.27, $p < 0.01$. Profile analysis showed the model was unable to estimate σ^2 between-studies.

For the analysis of GLP-1 AUC over 240 min postprandially, 2 studies were analyzed at baseline (3 arms; $n = 74$) and 1 study (2 arms) at 26 weeks and 104 weeks post-RYGB ($n = 62$). The estimates were 1872 pmol/L/min (95% CI: 1740–2003), 4805 pmol/L/min (95% CI: 4406–5204) and 4449 pmol/L/min (95% CI: 4088–4810), respectively (Figure 7). Again, the postprandial response of GLP-1 was significantly higher at 26 and 104 weeks post-RYGB compared with pre-RYGB (Q_m

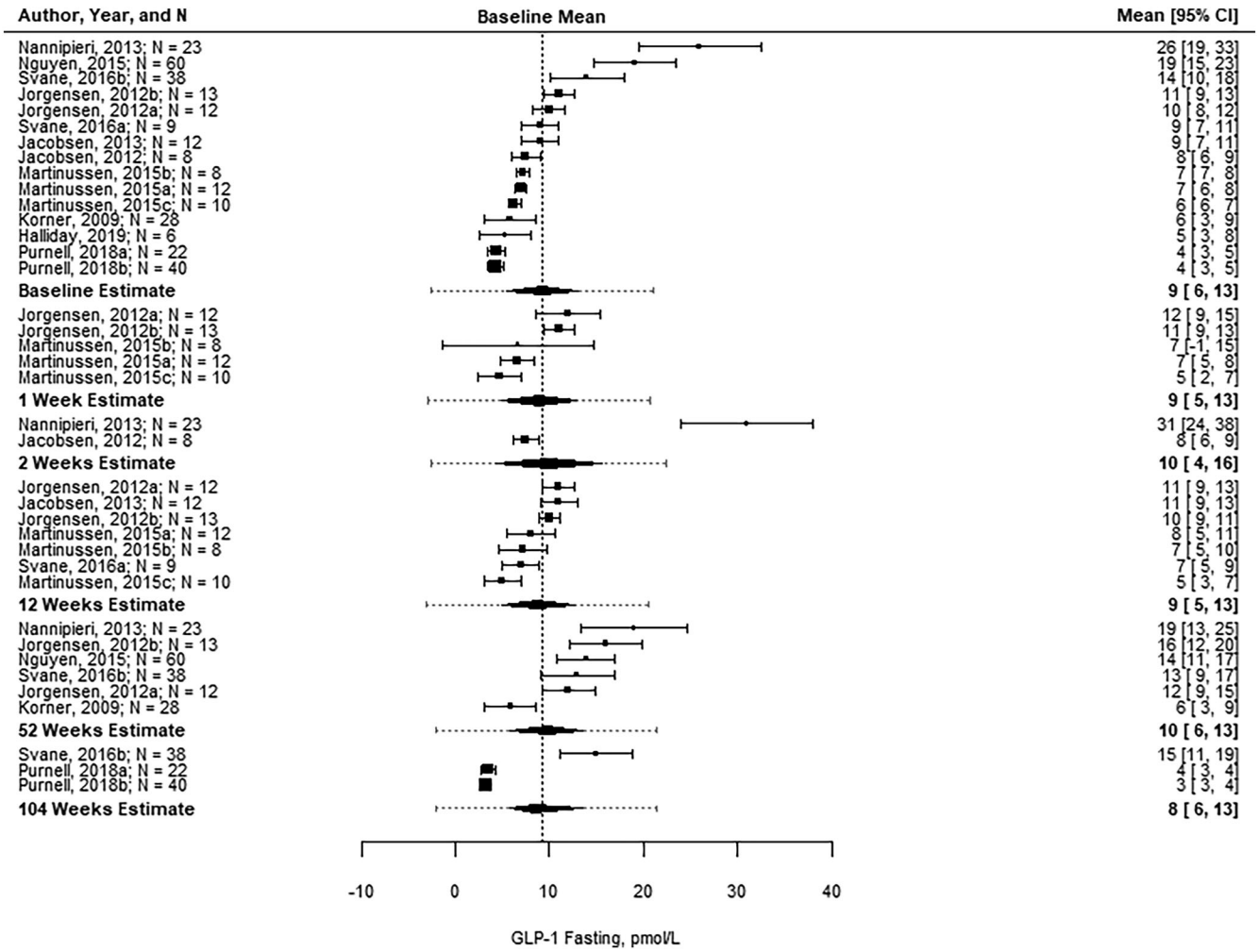

FIGURE 4 Fasting glucagon-like peptide-1 (GLP-1) levels and estimates (pmol/L) of included studies before and 1, 2, 12, 52, and 104 weeks post-Roux-en-Y gastric bypass (RYGB).

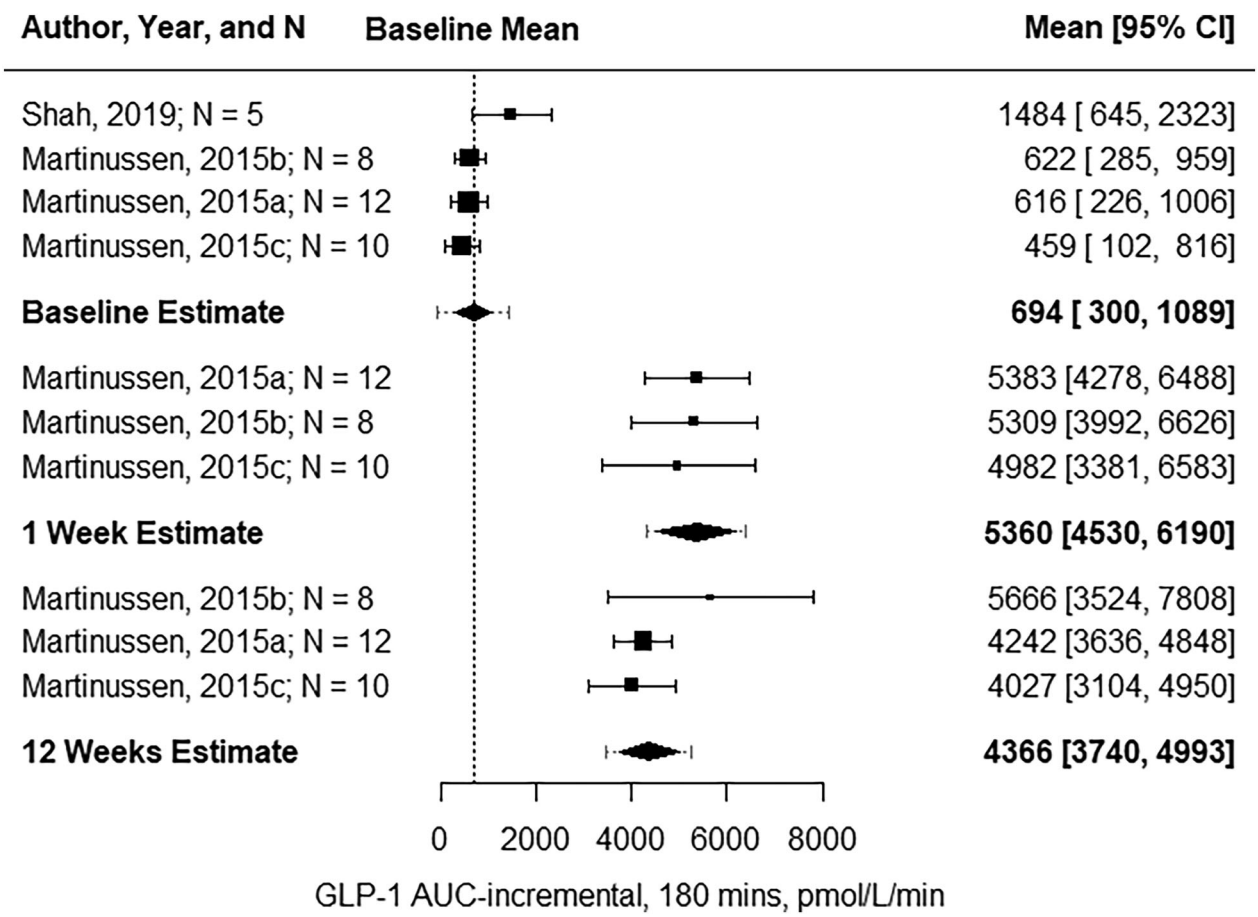

FIGURE 5 Postprandial response (180 min; incremental-area under the curve [AUC]) of glucagon-like peptide-1 (GLP-1) levels and estimates (pmol/L/min) of included studies before Roux-en-Y gastric bypass (RYGB), 1, 12, and 52 weeks post-RYGB.

(df = 3) = 366.09, $p < 0.01$, when compared with pre-RYGB estimates. Residual heterogeneity was not significant, QE (df = 3) = 0.57, $p = 0.90$. The model could not estimate sigma squared.

3.6 | PYY

Pre-RYGB, fasting levels of total PYY values were presented by 8 studies (9 arms; $n = 187$), and the analysis revealed an estimate of 96 pg/ml (95% CI: 80–112). At 2 weeks post-RYGB, 1 study (2 arms) was analyzed ($n = 20$) with an estimate of 98 pg/ml (95% CI: 64–133), whereas at 12 weeks (2 studies; $n = 33$), the estimate was 120 pg/ml (95% CI: 102–137). For the analyses at 26 and 52 weeks post-RYGB (4 studies; $n = 89$), the estimates were 116 pg/ml (95% CI: 107–125) and 123 pg/ml (95% CI: 104–142), respectively (Figure 8). Fasting levels of PYY increased significantly compared to pre-RYGB at 26 and 52 weeks post-RYGB, $p = 0.034$ and 0.030, respectively. Nevertheless, the omnibus test of the time point moderator failed to reach significance, $F(1, 4) = 4.829$, $p = 0.078$. There was no significant residual heterogeneity QE (df = 16) = 8.84, $p = 0.92$, $\sigma^2 = 0.001$.

Pre-RYGB, total PYY AUC values over 120 min in response to the test meal were presented by 4 studies (5 arms; $n = 81$), and the estimate was 18,314 pg/ml/min (95% CI: 10,725–25,903). At 2 weeks post-RYGB, 1 study (2 arms) was analyzed ($n = 20$), and the estimate was 23,362 pg/ml/min (95% CI: 12,785–33,939). At 26 and 52 weeks post-RYGB, 3 studies were analyzed ($n = 61$), and the estimate were 36,647 pg/ml/min (95% CI: 27,982–45,313) and 37,453 pg/ml/min (95% CI: 28,795–46,112), respectively (Figure 9). Post-prandial levels of PYY were significantly increased at 26 and 52 weeks post-RYGB compared with pre-RYGB values (Q_m [df = 4] = 45.23, $p < 0.01$). There was significant heterogeneity, QE (df = 8) = 52.45, $p < 0.01$, $\sigma^2 = 54{,}348{,}043.35$.

3.7 | Appetite sensation with VAS

Appetite sensation AUC was reported in a low number of studies and could not be meta-analyzed (Table S4). Hunger AUC was reported in 11% ($k = 5$) of studies[54,80,83,85,88] ($n = 50$) at pre-RYGB and up to 12 weeks post-RYGB. Although AUC varied pre-RYGB and was not reported in all studies that measured hunger, data available of post-RYGB hunger values were lower than pre-surgical values but not significantly different in 4 studies[47,54,68,83] and significantly lower in 3 studies.[51,80,85] One study found significant lower hunger score at 6 weeks post-RYGB, but values were no longer different from pre-RYGB at

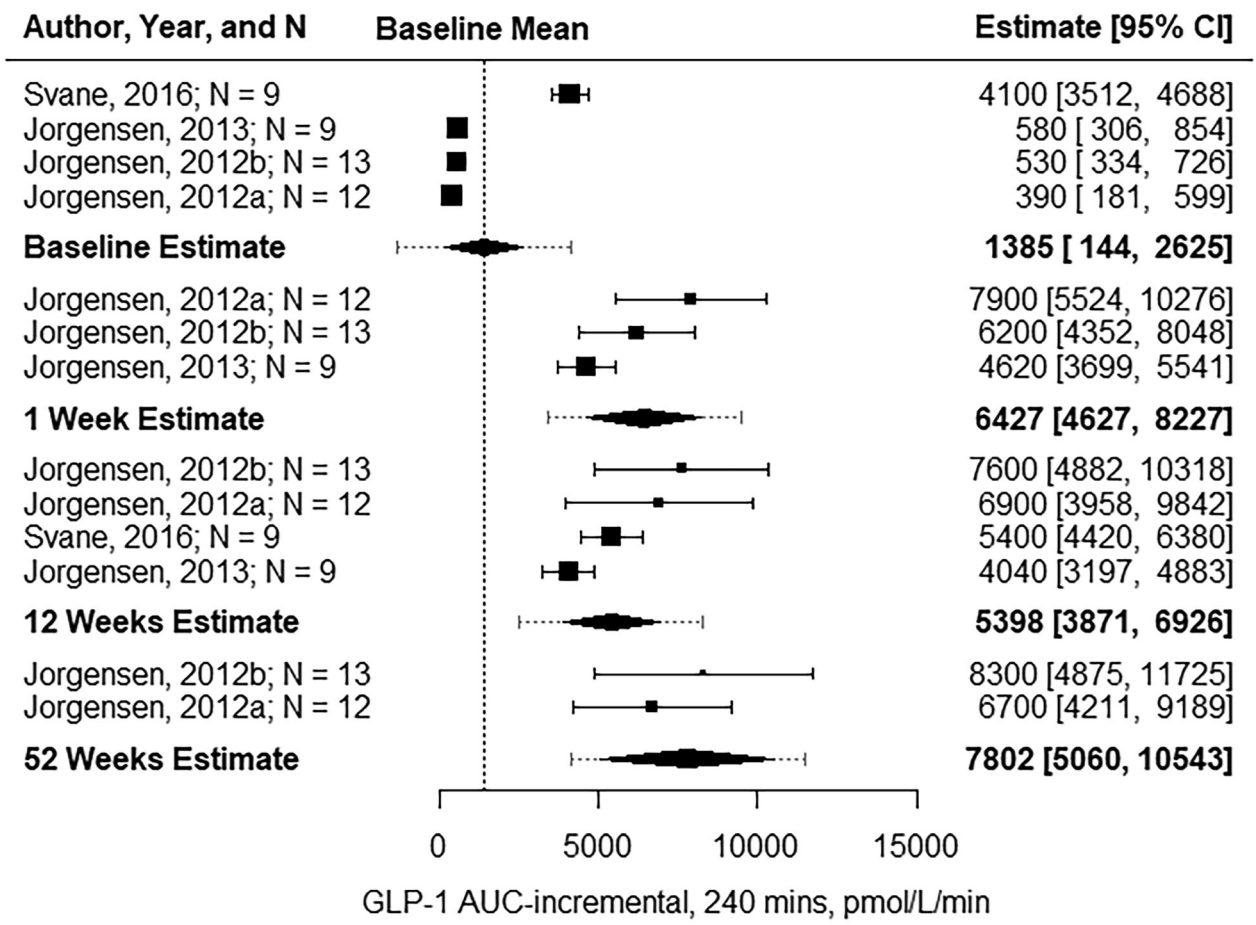

FIGURE 6 Postprandial response (240 min; incremental-area under the curve [AUC]) of glucagon-like peptide-1 (GLP-1) levels and estimates (pmol/L/min) of included studies before Roux-en-Y gastric bypass (RYGB), 1, 12, and 52 weeks post-RYGB.

3 months post-surgery.[88] Fullness AUC was reported in 4% of studies ($k = 2$; $n = 27$)[80,88] pre-RYGB and up to 12 weeks post-RYGB, when compared with pre-surgical values fullness increased after RYGB in both studies but only significantly in one.[80] Bryant et al. reported increased fullness at 3 days and 2 months post-RYGB but no significant differences at 1 year.[47] Satiety was reported by 6% of studies ($k = 3$; $n = 23$)[54,83,85] at baseline and increased post-RYGB in all studies; increase was significant in 2 of the studies.[54,85] The prospective food consumption was reported in 4% of studies ($k = 2$; $n = 33$)[54,80] pre-RYGB and up to 12 weeks post-RYGB and when compared with pre-surgical values of prospective food consumption was significantly lower post-RYGB in both studies. Satisfaction of the test meal was reported in only 4% of studies ($k = 2$; $n = 23$)[80] and was significantly higher 1 month post-RYGB compared with pre-RYGB.

3.8 | Weight

Pre-RYGB, 24 eligible studies (31 arms) reported mean weight after an overnight fast ($n = 446$), and the calculated estimate was 124 kg (95% CI: 118–129). The estimates were 119 kg (95% CI: 21–39) at 1 week (6 studies; 11 arms; $n = 199$), 115 kg (95% CI: 112–119) at 2 weeks (2 studies; 3 arms; $n = 54$), 113 kg (95% CI: 105–122) at 4 weeks (4 studies; $n = 33$), 101 kg (95% CI: 95–107) at 12 weeks (7 studies; 12 arms; $n = 154$), 94 kg (95% CI: 91–97) at 26 weeks (5 studies; $n = 143$), 87 kg (95% CI: 83–92) at 52 weeks (14 studies; 17 arms; $n = 290$), and 90 kg (95% CI: 83–96) at 104 weeks (4 studies; $n = 93$) (Figure 10). Mean weight was significantly lower at all time points after RYGB compared with pre-RYGB weight, $F(df1 = 7, df2 = 23) = 198.76$, $p < 0.0001$. Significant heterogeneity, QE ($df = 79$) $= 4619.62$ $p < 0.001$, $\sigma^2 = 78.36$.

4 | DISCUSSION

4.1 | Summary of evidence

To our knowledge, this is the first meta-analysis to investigate and determine the time-course of changes of gut peptides following RYGB. Indeed, previous meta-analyses and systematic reviews on bariatric interventions collapsed studies with varying follow-up times in their analyses, whereas we only analyzed similar follow-up times. In our view, this provides a much clearer depiction of the time-course of changes of gut peptides post RYGB. As such, this meta-analysis

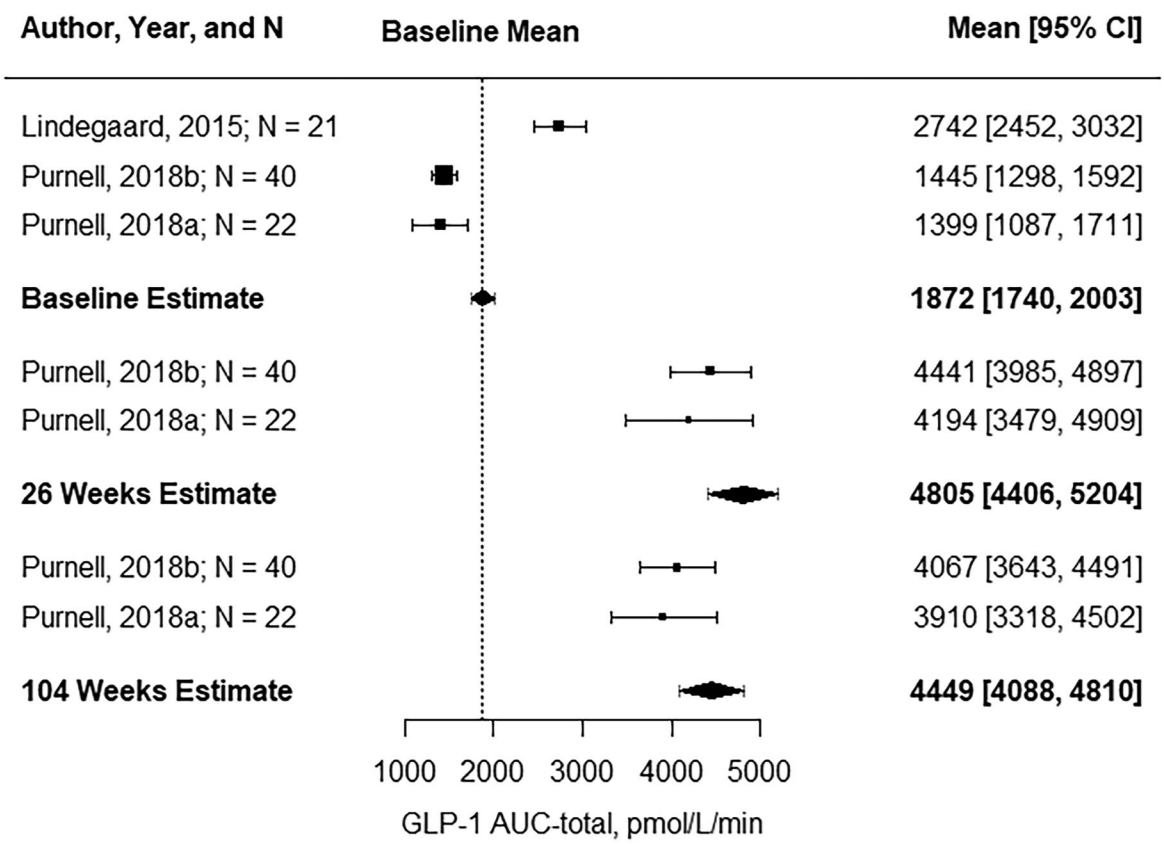

FIGURE 7 Postprandial response (240 min; total area under the curve [AUC]) of glucagon-like peptide-1 (GLP-1) levels and estimates (pmol/L/min) of included studies before Roux-en-Y gastric bypass (RYGB), 26 and 104 weeks post-RYGB.

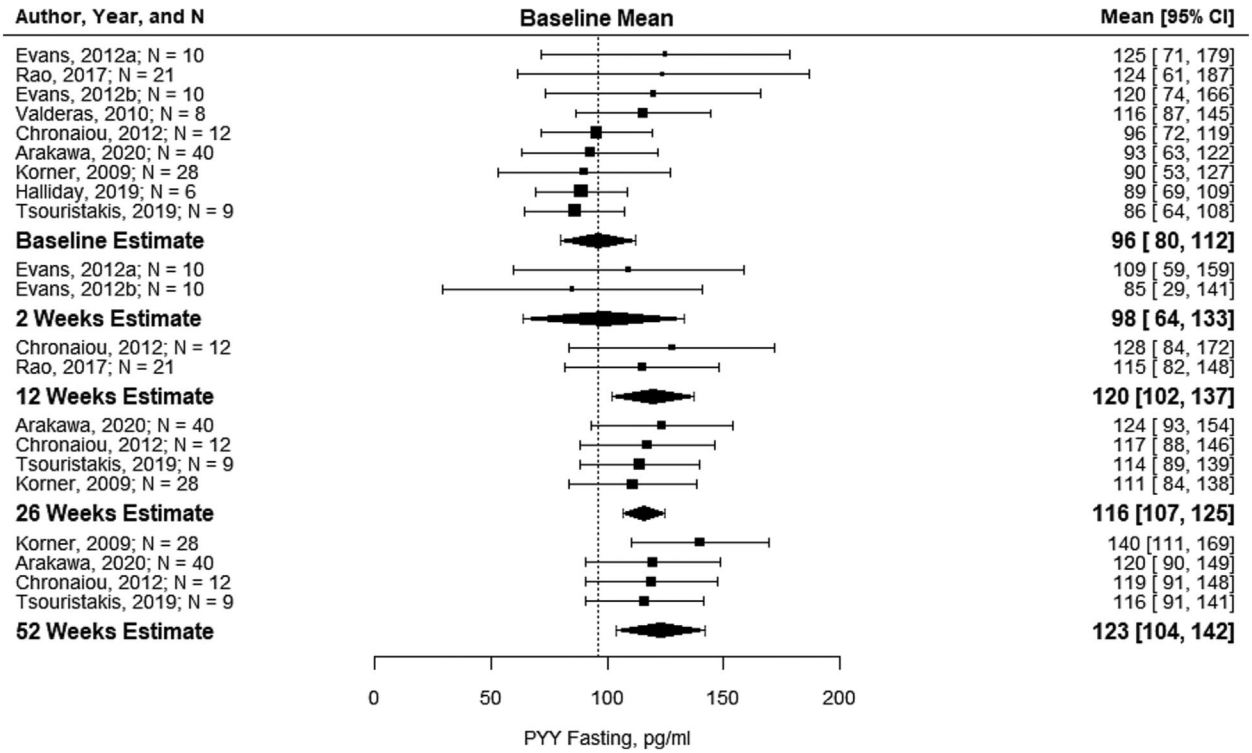

FIGURE 8 Fasting peptide YY (PYY) levels and estimates (pg/ml) of included studies before and 2, 12, 26, and 52 weeks post-Roux-en-Y gastric bypass (RYGB).

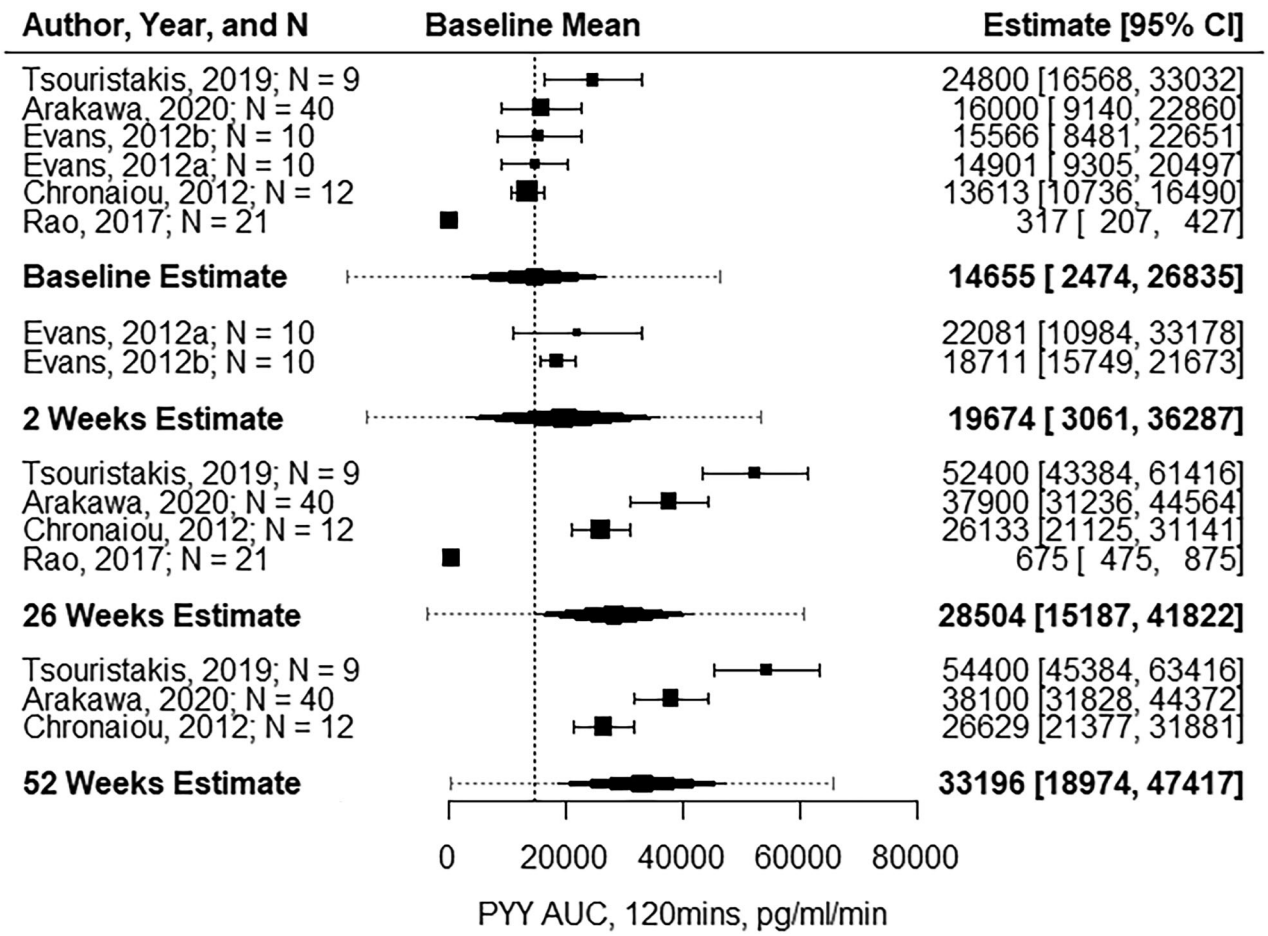

FIGURE 9 Postprandial response (120 min; total area under the curve [AUC]) of peptide YY (PYY) levels and estimates (pg/ml/min) of included studies before Roux-en-Y gastric bypass (RYGB), 2, 26, and 52 weeks post-RYGB.

was conducted for fasting and postprandial response of total ghrelin, GLP-1, and PYY, as well as for weight before and at different time points after RYGB surgery.

Our results show that after an initial decrease in fasting total ghrelin levels at 2 weeks post-RYGB, levels at other time points analyzed up to 12 months post-RYGB were not significantly different from pre-surgical values (Figure 2). In light of the observed heterogeneity, it is unclear if the decrease in fasting total ghrelin at 2 week post-RYGB is robust. The postprandial levels of total ghrelin following RYGB were not different from pre-surgical levels at 6 months and 1 year post-surgery (mean pre-RYGB: 51875 pg/ml/min, 6 months post: 51,389 pg/ml/min and 1 year post: 51517 pg/ml/min). Although available data are limited, Figure 3 illustrates that following RYGB postprandial levels of total ghrelin in the included studies did not change. Our results are in accordance with another previously published meta-analysis that investigated standard mean differences of fasting levels of ghrelin only before and after RYGB, where results were divided into short-term (<3 months) and long-term (>3 months) change post-RYGB.[26] They found a significant decrease in fasting ghrelin levels in the short-term and a contrasting increase in the long-term.[26] Our analysis also points to a short-term slight but significant decrease in fasting ghrelin levels at 2 weeks post-RYGB, yet levels appear to return to pre-RYGB levels from 6 weeks to 1 year as opposed to the increase described by Xu et al.[26] Potential sources for the different findings could include the lower number of participants post-RYGB in our study because we performed a multilevel analysis while they combined all data >3 months post-RYGB together. A recent non-systematic review described that most studies found no changes in fasting and postprandial ghrelin levels after RYGB, whereas still a few reported a decrease or increase.[91]

Although fasting levels of total and active GLP-1 could not be combined for the analyses, the outcome for the individual analyses was congruent. Indeed, fasting GLP-1 was not different between pre-RYGB and up to 2 years post-surgery for total GLP-1 and up to 1 year post-RYGB for active GLP-1 (Figure 4). For both active and total fasting GLP-1, heterogeneity was significant ($p < 0.001$). The wide variability in pre-RYGB data points indicates a confounder most likely influenced the sample of included studies before the intervention. The source of this confounder could be derived from participant or measurement variability, though the exact cause cannot be identified with the given information in the included studies. Fasting GLP-1 levels are higher compared with other similar studies at all time points measured, including at baseline in the Nannipieri et al.'s study.[71] Notably, this study did not provide the number of women evaluated or

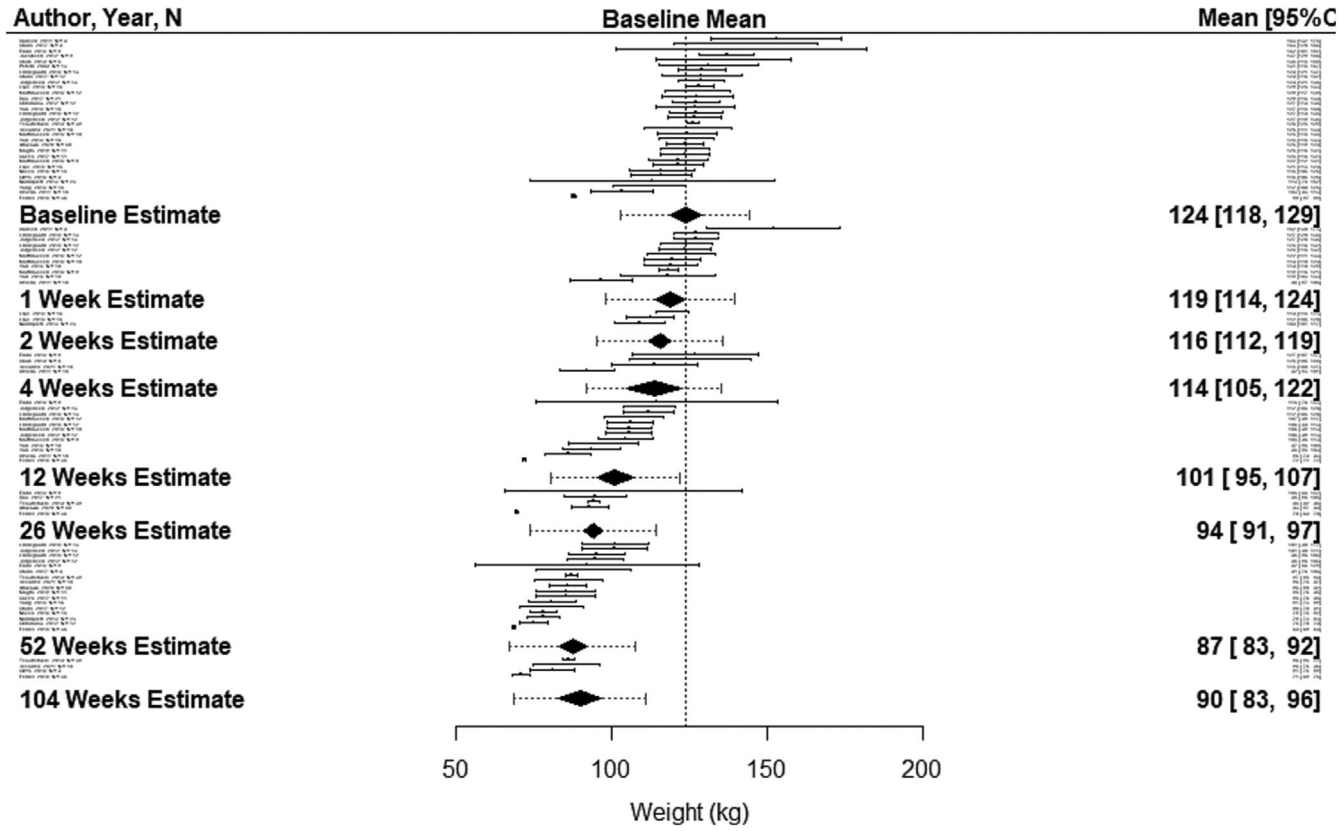

FIGURE 10 Mean weight (kg) of included studies before Roux-en-Y gastric bypass (RYGB) and 1, 2, 4, 12, 26, 52, and 104 weeks post-RYGB.

average age of the participants. They also provided a semi-solid test meal, whereas some studies in our analysis offered a liquid meal test. These characteristics along with assay kit variability could be potential confounders; however, the provided information was not sufficient to consider the study an outlier.

Postprandial responses of GLP-1 were computed in 3 different analyses. There were methodological differences in blood sampling times and appraisal of both incremental and total data in the included studies, thus preventing synthesis of all postprandial GLP-1 in one analysis. Although only a small number of studies were included in each separate analysis, all 3 analyses trended towards similar results. GLP-1 incremental-AUC at 180 min increased significantly at 1 week post-RYGB, as well as 3 months post-RYGB, compared with pre-surgical values. The 3-month estimate represented approximately a 6.3-fold increase from pre-RYGB. Results were similar for incremental-AUC at 240 min with a significant increase at 1 year post-RYGB. The 1-year estimate represented a 5.6-fold increase compared with pre-RYGB. The third analysis, total GLP-1 at 240 min, combined data at time points of 6 months and 2 years post-RYGB where differences compared with pre-RYGB were significantly higher. In this analysis at 6 months and 2 years post-RYGB, the estimate represented a 2.6-fold and 2.4-fold increase, respectively, compared with the pre-RYGB mean. Figures 5–7 together illustrate the clear increase in GLP-1 levels starting at 1 week extending up to 2 years post-RYGB in our population. Because heterogeneity could not be estimated due to the small study sample size, the results should be interpreted with caution and limited to our population. Nevertheless, consistent with our results are in agreement with the central role of GLP-1 as a modulator of appetite in humans. The results are also in agreement with earlier studies showing an appetite-suppressing role of GLP-1,[20] as well as more recent trials using GLP-1 agonists for weight loss.[92] In 2018, Jirapinyo et al published a meta-analysis on fasting and post-prandial GLP-1 changes after RYGB.[93] Consistent with our findings, they also concluded that fasting GLP-1 was unchanged after RYGB and that postprandial GLP-1 increased following RYGB.[93] While direction of changes is consistent with the previous meta-analysis, our analysis provides additional information on the extent of these changes at different time points post-RYGB and expected ranges of GLP-1 in our study population.

Fasting PYY levels were significantly higher than pre-surgical values at both 6 months and 1 year post-RYGB. The 1-year estimate represented approximately a 1.3-fold increase from pre-RYGB (Figure 8). However, because the omnibus test of the time point moderator did not reach significance, the fasting PYY results cannot be considered robust. However, it is relevant to note that this increase in fasting PYY has also been reported in both rodents[94] and humans.[63] Postprandial values of PYY increased significantly at 6 months (two-fold increase) and 1 year post-surgery (twofold increase) compared with pre-RYGB. As only a very small number of studies could be analyzed for AUC of PYY ($k = 4$), caution is warranted in interpreting these findings. Our results are in agreement with the appetite-suppressing role of PYY, similarly to GLP-1 as they both exert similar

effects on the central nervous system.[95,96] Fasting PYY remaining unchanged post-RYGB and higher levels of PYY post-surgery were also reported in a recently published review where no statistical synthesis was performed.[91]

Results regarding appetite sensations remain unclear because the data presented in the included studies could not be compared due to the presence of subcategories of appetite sensations (e.g., hunger and satiety) and time points post-RYGB and/or time of AUC that did not match between studies, thus hindering further analyses. In addition, values of AUC over 3 months post-RYGB were unavailable, giving a very small window in time to compare values with pre-surgical scores or further even compare appetite sensation scores with appetite-related hormone changes over time. What is more, the relationship between post-surgery levels of circulating gut peptides and appetite suppression may be clouded by other compounding factors. Indeed, it was recently reported that defective weight loss post-surgery is more likely to stem from a central defect in the anorectic response to these peptides rather than to a suboptimal peripheral secretion.[97] These results are also supported by some of our own work where we were not able to show differences between individuals who were weight stable and weight regainers when comparing their gut profile responses with a meal test.[98] Although it could be argued that meta-analyses and systematic reviews are hardly the venue the discuss mechanistic perspectives, these previous results warrant some caution when trying to ascertain whether the increased peripheral production of these hormones per se could be used as a proxy of intervention success or lack thereof.

Evaluating the changes of weight following RYGB was not a main objective of this review. However, it shows that the RYGB intervention led to significant weight loss in the studies that were included in the systematic review/meta-analysis. As such, these results should not be taken as a reflection of the effects of RYGB on weight loss but rather to show that the peptide profiles analyzed and presented herein were drawn from a population of individuals with obesity who underwent significant weight losses. As can be expected, participants of the included studies did experience a significant weight loss and reached weight nadir at or after 12 months post-RYGB.

4.2 | Strength and limitations

This systematic review/meta-analysis is the first of its kind as it includes multilevel models that allowed for the illustration of the time course of changes in ghrelin, GLP-1, and PYY at distinct time points post-RYGB compared with pre-surgical values. As mentioned earlier, previous meta-analyses and systematic reviews on bariatric interventions collapsed studies with varying follow-up times, whereas we only compared similar follow-up times in our statistical approach to obtain a post-surgery time course of the changes in gut peptides. This study is not without significant limitations. Firstly, only articles available in English or French were assessed. Moreover, the included studies show high levels of heterogeneity. Plausible explanations for this could be the variability in type of assay kit, providers, time span between included studies, meal macronutrient composition, lack of duplicate assays, and even inter-study lot-to-lot variability in longitudinal studies. Assay kit variability cannot be neglected as a source of variability, as pre-RYGB values of main outcomes in this meta-analysis vary greatly, even when corrected for meal test caloric intake. Only a very limited number of included studies ($k = 6$) performed duplicate assays of main outcomes, which is necessary because it leads to higher reliability of results and facilitates the identification of outliers within and between studies.[99] In addition, it should also be noted that several of the studies that were included in the analyses were conducted by the same research group. Lastly, only a small number of studies could be compared in the analyses. Variability in protocol of main outcome measurements was high, which further added to the complexity for study comparison. Sub-analyses were required, and multiple data points could not be included in the meta-analysis when comparable data were not available. This combined with high heterogeneity between studies at baseline limits our interpretation of results. Although the conclusions should be interpreted with caution, this study sheds light on the current state of the literature. Higher quality measurements of appetite hormones and standardized protocols of post-prandial response measurements could provide more consistent results for future meta-analyses for these outcomes. Because bariatric surgery and appetite hormone agonists are gaining popularity and availability due to the growing population in need of effective long-term weight loss interventions, pooling data of more studies to solidify knowledge and comprehension of these mechanisms of weight loss following RYGB is required.

4.3 | Implication of findings and future research

This review provided new information regarding the time course of changes of appetite-related hormones following RYGB surgery. Although significant changes compared with pre-surgical levels of gut peptides were found, methodological inconsistencies and large heterogeneity between studies prevent strong conclusions regarding the effect of the RYGB surgery on appetite-related hormones. Future research should consider evaluating longer term effects of RYGB on appetite-related hormones and investigate whether fluctuations are present with weight regain over time. Additional studies measuring appetite sensations are required and should be considered when assessing gut peptides. Measuring appetite sensation via VAS provides additional information on appetite perception of the participants and is highly accessible and reproducible.[100] Other considerations for prospective studies include thorough descriptions of participant characteristics, sample collection, process, and storage, assay kits, intra and inter-kit variability, surgery details, and meal duration. These additions would improve transparency and potentially lower between-study heterogeneity. Standardization of postprandial response measurements, including units and time of the AUC for each outcome (i.e., ghrelin, GLP-1, and PYY) would be beneficial for future synthesis of results. Additionally, disclosure of mean fasting and AUC levels of peptides in all future published studies is prompted for

effective analysis of the literature. Finally, it would be relevant for future systematic reviews to provide detailed information on the expected ranges and changes over time of other gut hormones (e.g., CCK, secretin, and neurotensin) following RYGB and other bariatric surgery (e.g., vertical sleeve gastrectomy and biliopancreatic diversion with duodenal switch).

5 | CONCLUSION

In conclusion, this meta-analysis provides insight on the current state of the literature regarding changes in fasting and postprandial gut peptides before and following RYGB surgery. While heterogeneity between studies limits our findings to the population of included studies, our data show that following RYGB, fasting total ghrelin levels were lower than pre-RYGB only at 2 weeks post-surgery. While postprandial levels were unchanged. GLP-1 fasting levels were unchanged after RYGB, although for the postprandial response of GLP-1, an important increase was present early after surgery and up to 2 years post-RYGB. PYY levels were increased at both the fasted state and postprandially after the surgery. More standardized research with longer follow-up periods is needed to confidently understand changes in gut peptides following RYGB surgery.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest statement.

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