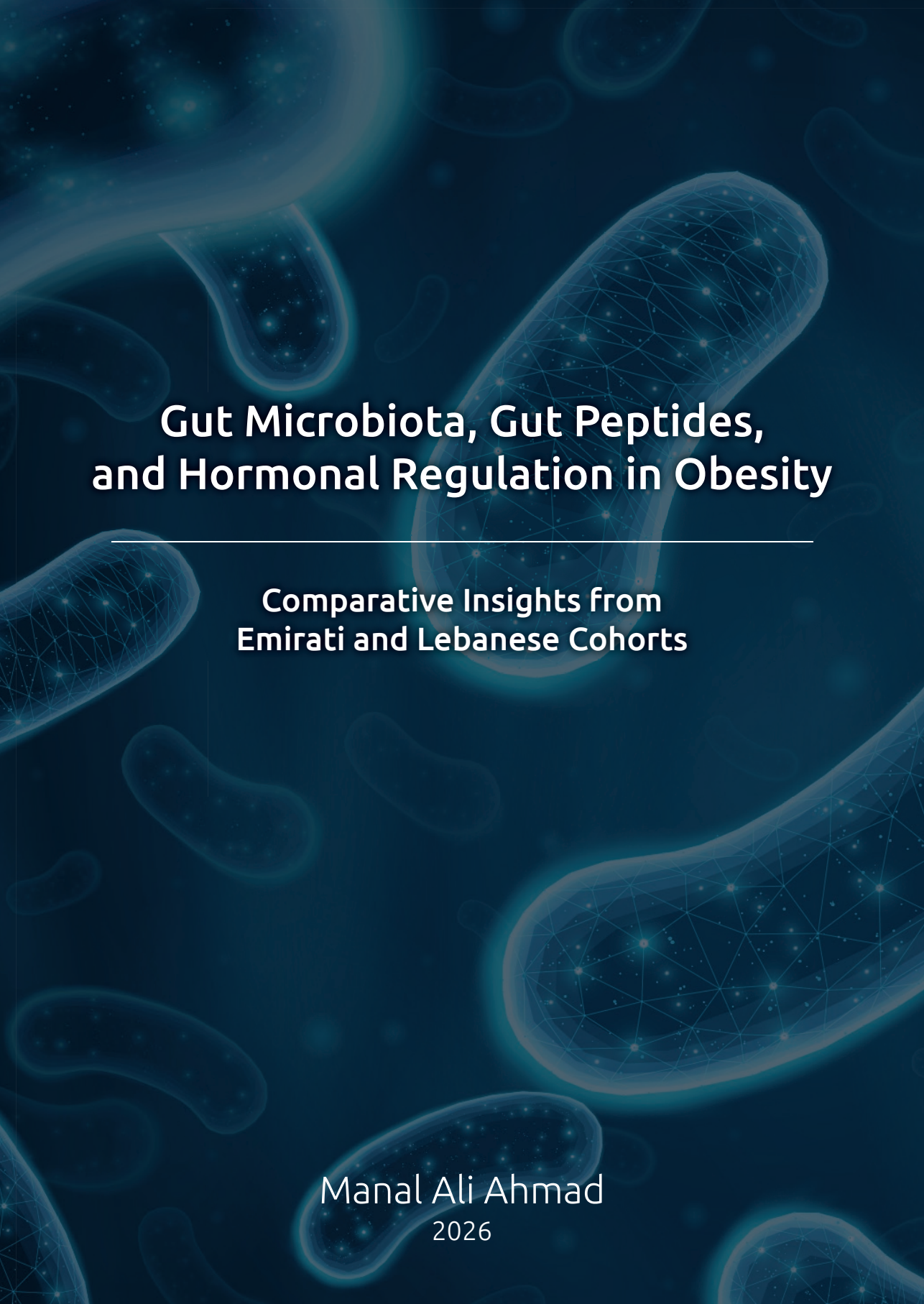


Gut Microbiota, Gut Peptides, and Hormonal Regulation in Obesity

Comparative Insights from Emirati and Lebanese Cohorts

Manal Ali Ahmad

2026

Gut Microbiota, Gut Peptides, and Hormonal Regulation in Obesity: Comparative Insights from Emirati and Lebanese Cohorts

by Manal Ali Ahmad

Propositions

1. Distinct differences in circulating gut-derived peptide hormone profiles between lean individuals and individuals with obesity indicate altered hormonal regulation in obesity. Understanding these alterations may provide leads for population-relevant therapeutic strategies, particularly in regions with a high obesity burden such as the UAE.
(This thesis)

2. Circulating fasting GLP-1 concentrations are associated with obesity and insulin resistance, supporting a role for gut-derived peptides in metabolic regulation; however, their clinical or diagnostic relevance cannot be inferred from the present data.
(This thesis)

3. Alterations in the gut microbiota observed in individuals with obesity should be interpreted as associative rather than causal, underscoring the need for longitudinal and intervention studies to clarify their role
(This thesis)

4. The absence of significant differences in the Firmicutes/Bacteroidetes ratio between lean Emirati and those adults with obesity supports evidence that this ratio is not a consistent marker of obesity.
(This thesis)

5. Bariatric surgery is associated with alterations in gut peptide profiles and concurrent shifts in gut microbiota composition alongside metabolic improvement.
(This thesis)

6. Gut microbiota profiles differ between Emirati and Lebanese adults with obesity, indicating population-related variation in obesity-associated microbiota patterns.
(This thesis)

7. Microbiota-targeted dietary strategies represent a potential avenue for future research in obesity management.
(Impact)

8. Integrating knowledge of gut peptides and gut microbiota with information on diet, lifestyle factors, and detailed metabolic and behavioral phenotyping may contribute to a more comprehensive understanding of obesity pathophysiology.
(Impact)

9. Pursuing scientific work within diverse cultural contexts requires resilience and adaptability.
(Personal reflection)

10. In the middle of difficulty lies opportunity (Albert Einstein)

11. The real voyage of discovery consists not in seeking new landscapes, but in having new eyes (Marcel Proust)

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This thesis is based on research carried out at Al Qassimi Hospital in Sharjah and Dr. Sulaiman Al Habib Hospital in Dubai, both located in the United Arab Emirates. This study was performed as part of a PhD thesis with the School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands.

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Comparative Insights from Emirati and Lebanese Cohorts

Dissertation

to obtain the degree of Doctor at Maastricht University,
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In accordance with the decision of the Board of Deans,
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Chapter 1

General Introduction

1. Global and UAE Perspectives on Obesity: Prevalence, Burden, and Drivers

Obesity has become a major public health concern in recent years, characterised by excessive fat accumulation and impaired adipose tissue function. The increased fat mass and, in particular, body fat distribution and adipose dysfunction can adversely affect health by increasing the risk of comorbidities such as type 2 diabetes, cardiovascular diseases (CVDs), dyslipidaemia, and impaired mental health, among others (Blüher, 2025; Lim et al., 2024; World Health Organization, 2022). The World Health Organization (WHO) reported that in 2022, 2.5 billion adults were overweight, with more than 890 million living with obesity (World Health Organization, 2022). By 2025, it is projected that approximately one in five adults worldwide (≈20%) will be living with obesity, according to estimates from the World Obesity Federation (World Obesity Federation, 2019). Obesity prevalence has also increased markedly in Gulf countries over recent decades, rising from approximately 6.5% in 1975 to 20% in 2016 (Ritchie, 2017). In the United Arab Emirates (UAE), obesity prevalence is notably high, with estimates indicating that approximately 28% of males and 41% of females are affected (World Obesity Federation, 2023). The most recent nationally representative UAE obesity prevalence data available at the time of writing are derived from World Health Organization estimates reported in 2016. This increasing burden of obesity places substantial pressure on healthcare systems, contributing to increased healthcare costs and utilization (Razzak et al., 2017).

High intake of energy-dense foods combined with sedentary lifestyles are key contributors to positive energy balance and the development of obesity (Ahmed & Mohammed, 2025; Hall et al., 2022). However, obesity is increasingly recognised as a complex multifactorial disease influenced by factors beyond diet and physical inactivity, including genetic susceptibility, gut microbiota composition and function, sleep deprivation, endocrine disruptors, pharmaceutical exposures, and epigenetic mechanisms (Almazan et al., 2023; Chaput et al., 2023; Hinte et al., 2024; Jaskulak et al., 2025; Rubino et al., 2025; Van Hul & Cani, 2023). Against this multifactorial framework, this thesis focuses on two interconnected biological systems increasingly implicated in obesity pathophysiology—the gut microbiota and gut-derived peptide hormones—with specific attention to underrepresented Arab populations.

2. Gut Microbiota in Obesity: Composition and Functional Role

The gut microbiota has emerged as a pivotal factor influencing the pathogenesis of various non-communicable diseases, including obesity, type 2 diabetes mellitus, and metabolic syndrome (Rinninella et al., 2019). The intricate microbial ecosystem is composed of a vast array of microorganisms—bacteria, fungi, viruses, and archaea—that collectively modulate host metabolic processes, immune responses, and energy homeostasis (Lynch & Pedersen, 2016). Importantly, the gut microbiota exhibits a highly individualised composition, shaped by host genetics, diet, environmental exposures, and lifestyle factors, which highlights the necessity for personalised approaches in metabolic health management and the prevention of non-communicable diseases (Vatanen et al., 2018).

Quantitative reassessments estimate that an average adult harbours a microbial population comparable in magnitude to human cells, with a vast microbial gene repertoire supporting extensive functional diversity that may contribute to inter-individual and population-specific metabolic differences (Almeida et al., 2021; Li et al., 2014; Pasolli et al., 2019; Qin et al., 2010; Sender et al., 2016).

The gut microbial community comprises several hundred bacterial species, dominated by the phyla Bacteroidota (Bacteroidetes) and Bacillota (Firmicutes), alongside Actinomycetota (Actinobacteria), Pseudomonadota (Proteobacteria), and Verrucomicrobiota (Lynch & Pedersen, 2016; Rinninella et al., 2019). Both updated and traditional phylum nomenclature are provided at first mention for clarity, as subsequent chapters use conventional terminology. The colonisation of the gastrointestinal tract begins shortly after birth and undergoes dynamic alterations during early life, eventually stabilising into a relatively consistent adult microbiota profile (Milani et al., 2017; Robertson et al., 2019). The gut microbiome ferments indigestible food components, like dietary fibres, thereby forming products such as short-chain fatty acids (SCFAs), which can influence host energy and substrate metabolism, gut barrier function, inflammation, and overall metabolic health (Rowland et al., 2018; Vinelli et al., 2022).

Mechanisms Linking the Gut Microbiota to Obesity

The gut microbiota interacts closely with the host to regulate energy metabolism through diverse mechanisms, including dietary energy harvest, substrate utilisation, and host signalling pathways (Canfora et al., 2019; Fan & Pedersen, 2021). The gut microbiota influences how energy derived from the diet is absorbed, stored, and expended, partly through microbial fermentation and metabolite production such as short-chain fatty acids (SCFAs) (Canfora et al., 2019; Dalile et al., 2019). The microbiota also contributes to the intestinal immune system, maintenance of gut barrier integrity, and regulation of host energy and substrate metabolism, thereby playing a central role in obesity and related metabolic disorders (Cani, 2018; Fan & Pedersen, 2021).

Early mouse studies demonstrated that obesity is associated with reduced microbial diversity and an altered Bacillota-to-Bacteroidota (Firmicutes/Bacteroidetes, F/B) ratio (Turnbaugh et al., 2006). However, human studies have been inconsistent, reporting increased, decreased, or unchanged ratios (Pinart et al., 2021). Such inconsistencies likely reflect inter-individual variability, dietary differences, metabolic heterogeneity, and methodological variation across studies. Consequently, reliance on phylum-level metrics such as the F/B ratio is now considered overly simplistic, with greater insight gained from lower taxonomic levels and microbial functionality (Companys et al., 2021; Pinart et al., 2021).

Dysbiosis—alterations in gut microbial composition, diversity, and functional capacity—has been associated with chronic conditions, including obesity, type 2 diabetes, cardiovascular diseases, and inflammatory bowel disease (Frank et al., 2007; Karlsson et al., 2013; Ley et al., 2006; Qin et al., 2012; Turnbaugh et al., 2008). Systematic reviews confirm disrupted microbial ecosystems in obesity, although no universal signature exists across populations (Magne et al., 2020; Pinart et al., 2021; Stanislawski et al., 2019; Sze & Schloss, 2016).

Reduced bacterial diversity and lower microbial gene richness have been linked to adverse metabolic profiles and diminished responsiveness to dietary or lifestyle interventions (Cotillard et al., 2013; Le Chatelier et al., 2013).

These findings suggest that microbial ecosystem resilience influences metabolic health and treatment response.

Weight loss interventions have been associated with modest increases in gut microbial diversity and shifts in specific taxa, although findings vary across study designs and intervention types (Dao et al., 2016; Remely et al., 2015). Individuals with higher baseline microbial richness are more likely to exhibit favourable metabolic responses to dietary and lifestyle interventions, highlighting the potential role of microbial richness in treatment responsiveness (Cotillard et al., 2013; Le Chatelier et al., 2013).

In this context, microbiota-targeted strategies, including dietary fibre supplementation, prebiotics, and faecal microbiota transplantation (FMT), have demonstrated potential for modulating gut microbial composition and selected metabolic outcomes, although long-term clinical efficacy remains uncertain (Depommier et al., 2019; Kootte et al., 2017).

Evidence for causality comes primarily from germ-free mouse experiments, where transfer of microbiota from donors with obesity induces greater adiposity than transfer from lean donors (Turnbaugh et al., 2006). In humans, FMT from lean donors to individuals with metabolic syndrome has been associated with transient improvements in insulin sensitivity, whereas effects on body weight have been limited or not sustained (Kootte et al., 2017; Vrieze et al., 2012). Collectively, microbiota-targeted interventions may improve selected metabolic parameters, but sustained weight loss remains modest and variable (Enache et al., 2024; Zhang et al., 2024).

Mechanistically, the gut microbiota may influence obesity through modulation of host metabolism and signalling along the gut–brain axis (Bauer et al., 2016; Kairupan et al., 2016; Lin et al., 2012). Microbial fermentation of dietary fibres produces short-chain fatty acids (SCFAs)—primarily acetate, propionate, and butyrate—which act as signalling molecules linking intestinal microbes to host metabolic regulation (Puddu et al., 2014). Early hypotheses proposed that the microbiota promotes obesity by enhancing dietary energy harvest, based largely on germ-free mouse transfer experiments showing increased adiposity following colonisation with microbiota from donors with obesity. However, translation of this mechanism to humans remains uncertain.

Current evidence instead supports a regulatory role of microbiota-derived metabolites in host metabolic homeostasis, thereby affecting satiety and/or

energy expenditure (Blaak et al., 2020; Canfora et al., 2015). Moreover, microbial metabolic traits such as SCFA production appear partly heritable, indicating that host genetics contributes to shaping microbiota composition and metabolic responses (Hughes et al., 2020; Tremaroli et al., 2015).

Despite the high burden of obesity in the Gulf region, integrated microbiome–metabolic research remains limited in Arab populations, as most mechanistic evidence originates from Western cohorts. Therefore, this thesis applies 16S rRNA gene sequencing integrated with metabolic and gut peptide phenotyping as a foundational step toward population-specific understanding of obesity pathophysiology.

3. Microbiota–Gut Peptide Crosstalk in Appetite and Metabolic Regulation

In addition to its strong link with type 2 diabetes and cardiovascular disease, obesity is frequently associated with insulin resistance (IR)—a condition where cells become less responsive to insulin, promoting metabolic dysfunction (Wu & Ballantyne, 2020). Research indicates that dysregulation of gut-derived peptide hormones—including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), ghrelin, cholecystokinin (CCK), and others—plays a pivotal role in appetite regulation, energy homeostasis, and glucose metabolism (Alhabeeb et al., 2021; Steinert et al., 2017). Disruptions in these hormone pathways are increasingly recognised as key elements of a gut–brain axis linking obesity and metabolic disease (Gribble & Reimann, 2016; Schwartz et al., 2017; Steinert et al., 2017).

Building on this hormonal dysregulation, alterations in gut microbiota composition in obesity have been increasingly linked to changes in gut peptide profiles. However, it remains unclear whether altered gut peptide levels are causal drivers of obesity-related metabolic dysfunction, or a consequence of obesity. Nonetheless, accumulating evidence supports a role for gut peptide dysregulation within broader metabolic signalling networks implicated in obesity (Covasa et al., 2019). Conversely, microbial metabolites and gut barrier-related signals may modulate enteroendocrine sensing and hormone release, suggesting bidirectional microbiota–hormone interactions contributing to metabolic heterogeneity. Circulating appetite-regulating hormones, including leptin, ghrelin, GLP-1, PYY, amylin, CCK, and glucose-dependent insulinotropic polypeptide (GIP), exhibit significant differences in individuals with obesity compared with lean individuals, reflecting dysregulated peripheral signals that impact central appetite control and energy balance. For example, people with obesity tend to show higher leptin levels with leptin resistance, lower basal and postprandial ghrelin, and attenuated PYY responses, although responses for some hormones vary across studies (Alhabeeb et al., 2021; Aukan et al., 2023; Klok et al., 2007).

GLP-1 and PYY are anorexigenic hormones secreted postprandially from enteroendocrine L-cells located predominantly in the distal ileum and colon, where they promote satiety and contribute to delayed gastric emptying (Alyar et al., 2024; Holst & Madsbad, 2016). In addition to its role in appetite

regulation, GLP-1—together with GIP—acts as an incretin hormone, enhancing glucose-stimulated insulin secretion following nutrient ingestion. While GLP-1 is produced by L-cells in the distal small intestine and colon, GIP is secreted by K-cells in the duodenum and proximal jejunum (Drucker, 2018; Holst & Madsbad, 2016). Both incretin hormones are secreted in response to oral nutrient ingestion, with carbohydrates and dietary fats representing major physiological stimuli for their postprandial release (Drucker, 2018; Holst & Gromada, 2004). Some studies have reported higher fasting GLP-1 levels in obesity, suggesting a compensatory response to chronic energy surplus or reduced hormone sensitivity (Bowen et al., 2006; Stinson et al., 2021). However, postprandial responses are inconsistent and impaired nutrient-stimulated GLP-1 secretion has also been described (Angelini et al., 2024). These contrasting findings likely reflect differences in study protocols and metabolic phenotypes. Importantly, obesity may involve relative incretin resistance rather than simple hormone deficiency (Rabbani & Thornalley, 2024; Yang et al., 2025). Native GLP-1 has a very short plasma half-life (1–2 minutes) due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), limiting therapeutic application. Long-acting GLP-1 receptor agonists (e.g., semaglutide) therefore provide pharmacological enhancement of physiological signalling and produce clinically meaningful weight loss and metabolic improvement (Wilding et al., 2021). Dual GLP-1/GIP agonists show even greater effects on body weight reduction (Jastreboff et al., 2022).

CCK, released from duodenal and jejunal I-cells in response to fats and proteins, promotes meal termination via vagal signalling. In obesity, CCK satiety signalling appears blunted as part of broader gut hormone dysregulation, potentially impairing short-term satiation (Alhabeeb et al., 2021). Despite physiological relevance, pharmacological targeting of CCK has shown limited long-term efficacy due to rapid degradation and compensatory pathways (Mahdi et al., 2025).

Ghrelin, the only known orexigenic hormone, is secreted predominantly during fasting and stimulates appetite. Individuals with obesity typically exhibit lower fasting ghrelin concentrations, along with impaired postprandial suppression, indicating altered signalling rather than excess secretion (Cummings et al., 2002; Hajishizari et al., 2022; Müller et al., 2015; Young & Jialal, 2023). Direct ghrelin-targeted therapies have shown limited success, likely due to redundancy within the gut–brain network (Murphy et al., 2006).

Leptin, secreted by adipose tissue, signals energy sufficiency to the hypothalamus. In obesity, elevated circulating leptin coexists with leptin resistance due to impaired central signalling (Friedman & Halaas, 1998; Münzberg et al., 2020). Thus, leptin functions primarily as a marker of adiposity rather than an effective satiety signal (Al Maskari & Alnaqdy, 2006; Münzberg et al., 2020).

Overall, gut peptides regulating appetite and meal size represent important therapeutic targets in obesity. However, clinical translation is limited by short half-lives, complex secretion dynamics, and pleiotropic actions across multiple organ systems (Drucker, 2018; Holst & Madsbad, 2016; Nauck & Meier, 2018). The success of GLP-1–based therapies highlights the effectiveness of targeting integrated gut–brain signalling pathways for sustained weight reduction.

4. Diet as a Shared Driver: Linking Microbiota Function and Gut Hormone Signalling

Furthermore, dietary modifications have a major impact on gut microbiota composition. High-fibre diets promote the growth of beneficial bacteria, increasing SCFA production and supporting appetite regulation and body-weight stability rather than uniform weight loss (Koh et al., 2016). In mice, transitioning from a high-fat, western diet to a plant-based, fibre-rich diet rapidly reshaped microbiota composition and attenuated diet-induced obesity, highlighting responsiveness (David et al., 2014). Human studies corroborate these findings; in 1,632 healthy female twins, higher dietary fibre intake was associated with greater microbiota diversity and lower long-term weight gain independent of calorie intake (Menni et al., 2017). Controlled trials further show that increased fibre intake enhances satiety and reduces subsequent energy intake (Clark & Slavin, 2013; Rebello et al., 2016).

Beyond host endocrine regulation, gut microbial metabolites—particularly SCFAs — directly influence enteroendocrine signalling. SCFAs stimulate colonic L-cells to secrete GLP-1 and PYY via activation of G-protein–coupled receptors, mainly free fatty acid receptor 2 (FFAR2/GPR43) and FFAR3 (GPR41) (Kimura et al., 2013; Tolhurst et al., 2012). Mice lacking FFAR2 show impaired GLP-1 secretion and increased food intake, supporting a causal role for microbial metabolites in appetite signalling (Zhao et al., 2018). Fermentable fibres also increase L-cell density, suggesting microbiota may modify hormone-producing cell populations in addition to acute secretion (Brooks et al., 2017; Cani et al., 2009).

The microbiota-enteroendocrine signalling axis may extend to other hormones. Microbial products have been implicated in modulating GIP and possibly ghrelin secretion, although mechanisms remain less defined in humans (Ashraf & Hassan, 2024; Everard et al., 2013). Collectively, these findings indicate that diet shapes metabolic physiology indirectly through microbiota-dependent hormone signalling. Given that diet is a dominant determinant of microbiota composition, population-specific dietary patterns may partly explain inconsistencies in microbiota composition and related gut peptides across cohorts.

5. Rationale for Focusing on Arab Populations

Most current evidence linking gut microbiota and gut-derived peptide hormones to obesity originates from Western cohorts, limiting its applicability to underrepresented populations. This is particularly important because microbiota composition is strongly shaped by ethnicity, habitual diet, environment, and host genetics.

Arab populations represent a unique context: they are experiencing rapid nutrition and lifestyle transitions alongside some of the highest global obesity rates. Regional dietary practices, meal timing patterns, and sociocultural behaviours may alter microbiota-accessible carbohydrate intake, microbial metabolite production, and gut hormone signalling. In addition, genetic background and high urbanisation may further modify host–microbiota interactions.

Therefore, extrapolating findings from Western populations may overlook biologically relevant mechanisms in other regions.

By investigating gut microbiota composition and circulating gut peptides in Emirati and Lebanese adults, this thesis provides population-specific evidence to improve external validity and support culturally tailored metabolic and nutritional interventions.

6. Treatment Context: Why Long-Term Weight Control Remains Challenging

Although lifestyle modification and pharmacological treatments are widely used to induce weight loss in individuals with obesity, sustained long-term success remains limited, with many individuals experiencing insufficient weight loss, weight regain, and incomplete resolution of obesity-related comorbidities (Nunes et al., 2022). Long-term weight maintenance following weight loss is generally poor, reflecting the chronic and relapsing nature of obesity (Dulloo, 2025).

A substantial body of research has demonstrated that weight loss induces coordinated physiological adaptations that favour weight regain. Reductions in body weight are accompanied by compensatory decreases in resting energy expenditure, alterations in substrate oxidation, and changes in appetite regulation that collectively promote energy conservation and increased drive to eat (Van Baak & Mariman, 2019). These adaptations indicate that long-term weight regulation is influenced by biological compensatory mechanisms rather than behavioural factors alone.

Obesity is characterised by chronic, low-grade inflammation and immune cell infiltration in adipose tissue, which may contribute to a form of “obesogenic memory” that predisposes individuals to weight regain after weight loss. Emerging evidence indicates that obesity-induced immune and inflammatory alterations in adipose tissue can persist despite weight reduction and may be rapidly reactivated during weight regain (Hinte et al., 2024).

Dysregulation of appetite-related gut hormones, including GLP-1, PYY, and ghrelin, further complicates appetite control in obesity. Weight loss is often accompanied by changes in these hormonal signals that reinforce hunger and reduce satiety (Sumithran & Proietto, 2013). Although pharmacotherapies targeting these pathways—particularly GLP-1 receptor agonists—demonstrate substantial efficacy, treatment discontinuation is frequently followed by significant weight regain (Wilding et al., 2022), underscoring the persistence of underlying biological adaptations.

Against this background, bariatric surgery has emerged as the most effective treatment for achieving durable weight loss in severe obesity (Aron-Wisnewsky et al., 2012). Beyond anatomical restriction, these procedures induce physiological changes, including alterations in gut peptide secretion, bile acid signalling, and gut microbiota composition, which are associated with improvements in appetite regulation and glucose homeostasis (Li & Richard, 2017; Meek et al., 2016). Nevertheless, weight regain after bariatric surgery is recognised as a multifactorial rather than a simple mechanical failure (Noria et al., 2023).

Although bariatric surgery and modern pharmacotherapies such as GLP-1 receptor agonists and dual incretin agonists provide substantial metabolic improvements, the precise interplay between gut hormones, gut microbiota, and long-term weight regulation remains incompletely understood (Rubino et al., 2025; Seganfredo et al., 2017). Further research is therefore required to clarify the biological mechanisms contributing to inter-individual variability in treatment response.

7. Bariatric Surgery: Gut Peptides, Gut Microbiota, and Metabolic Outcomes

Bariatric surgery (BS) is an effective treatment for obesity-related metabolic disorders (Medina et al., 2017). Roux-en-Y gastric bypass (RYGB) generally results in greater long-term weight loss than sleeve gastrectomy (SG), but is associated with higher complications.

Beyond anatomical restriction, bariatric procedures are accompanied by physiological changes, including alterations in gut peptide secretion, bile acid signalling, and gut microbiota composition, that are associated with changes in appetite regulation, energy balance, and insulin sensitivity (Meek et al., 2016). Within the scope of this thesis, these relationships are examined at an associative level, and causal inferences cannot be drawn.

SG is associated with reduced circulating ghrelin concentrations, while postoperative increases in GLP-1 and PYY are consistently observed and are linked to greater satiety signalling and glycaemic regulation (Holst & Madsbad, 2016; Müller et al., 2015; Sakata & Takemi, 2021; Svane et al., 2019).

However, the magnitude and durability of gut hormone responses vary between individuals and procedures, indicating inter-individual variability in nutrient sensing and metabolic responses (Çalık Başaran et al., 2025; Lampropoulos et al., 2022).

In parallel, bariatric surgery is accompanied by a remodelling of the gut microbiota through changes in luminal pH, bile acid flow, oxygen tension, and nutrient availability (Aron-Wisnewsky et al., 2020; Tremaroli et al., 2015). Surgery-associated alterations in microbial communities have been linked to changes in glucose homeostasis, insulin sensitivity, and energy metabolism, occurring in parallel with changes in gut hormone secretion and bile acid signalling and not fully explained by weight loss alone (Aron-Wisnewsky et al., 2020; Palleja et al., 2016; Tremaroli et al., 2015). In addition, transplantation experiments suggest a potential functional role of post-surgical microbiota in reduced adiposity in germ-free mice (Tremaroli et al., 2015). Despite these advances, the precise mechanisms through which gut peptides, gut microbiota, and their interactions mediate the metabolic effects

of bariatric surgery remain incompletely understood, supporting the need for integrative studies in diverse populations.

8. Microbiota Profiling Approach

Gut microbiota composition in this thesis was characterised using 16S rRNA gene sequencing, a widely accepted approach for profiling microbial community structure at the genus level (Klindworth et al., 2012). This method provides a reliable assessment of microbial diversity and compositional differences across populations but does not directly capture microbial gene function or metabolite production. Consequently, functional pathways such as short-chain fatty acid synthesis or bile acid metabolism cannot be inferred with certainty from taxonomic data alone. More comprehensive techniques, including shotgun metagenomics and metabolomics, would allow functional characterisation (Durazzi et al., 2021; Quince et al., 2017). Nevertheless, 16S rRNA sequencing represents an appropriate first step for identifying microbiota patterns in underrepresented Arab populations and provides a foundation for future functional investigations.

9. Objectives and Outline of the Thesis

Understanding gut microbiota composition and gut-derived peptide hormone profiles in Emirati and Lebanese populations may improve understanding of biological variation related to obesity and its metabolic complications. Given the influence of ethnicity, adiposity, and lifestyle on both microbial composition and peptide secretion, population-specific investigations are warranted to improve the interpretation and applicability of obesity research findings. In addition, changes in gut microbiota following weight loss interventions have been associated with variability in long-term outcomes, including weight regain.

Against this background, this thesis investigates the relationships between gut-derived peptide hormones, gut microbiota composition, and metabolic health in Emirati and Lebanese adults, with emphasis on obesity and weight loss interventions.

Objectives

Specifically, this thesis aimed to:

- Characterise circulating gut peptide profiles and faecal gut microbiota composition, and examine their associations in Emirati adults with obesity compared with lean counterparts (cross-sectional study).
- Evaluate longitudinal changes in gut microbiota composition, circulating gut peptides, and metabolic parameters—including energy intake, energy expenditure, and glucose homeostasis—following bariatric surgery in Emirati adults with obesity (prospective study).
- Compare gut microbiota composition between Emirati and Lebanese adults with obesity to identify population-specific microbial patterns (comparative study).

10. Gap Analysis and Dissertation Overview

Despite growing recognition of the role of gut microbiota and peptide hormones in the pathophysiology of obesity, current research addressing the interaction between these systems remains limited, particularly in Arab populations.

To address this knowledge gap, this dissertation undertakes a multi-dimensional investigation into the relationships between gut-derived peptide hormones, gut microbiota, and obesity across different study designs and populations. The research is structured across several chapters, each contributing to a broader understanding of metabolic and microbial variation in obesity.

Chapter 2 examines hormonal differences between lean adults and adults with obesity among Emiratis, characterising plasma concentrations of key gut peptides—including GLP-1, PYY, ghrelin, and CCK—and exploring their associations with anthropometric measures and markers of insulin resistance.

Chapter 3 investigates differences in gut microbial composition between lean adults and adults with obesity among Emiratis, with emphasis on identifying microbial genera associated with obesity-related markers.

Building on these findings, Chapter 4 examines changes observed after bariatric surgery in Emirati adults with obesity, including alterations in energy intake, energy expenditure, gut peptides, and microbiota composition.

Chapter 5 provides a comparative perspective by evaluating gut microbiota profiles in Emirati and Lebanese adults with obesity to identify population-specific microbial patterns potentially related to diet, environment, and host factors.

Finally, Chapter 6 synthesises the major findings of the dissertation, discussing clinical relevance, methodological considerations, strengths and limitations, and outlining directions for future research.

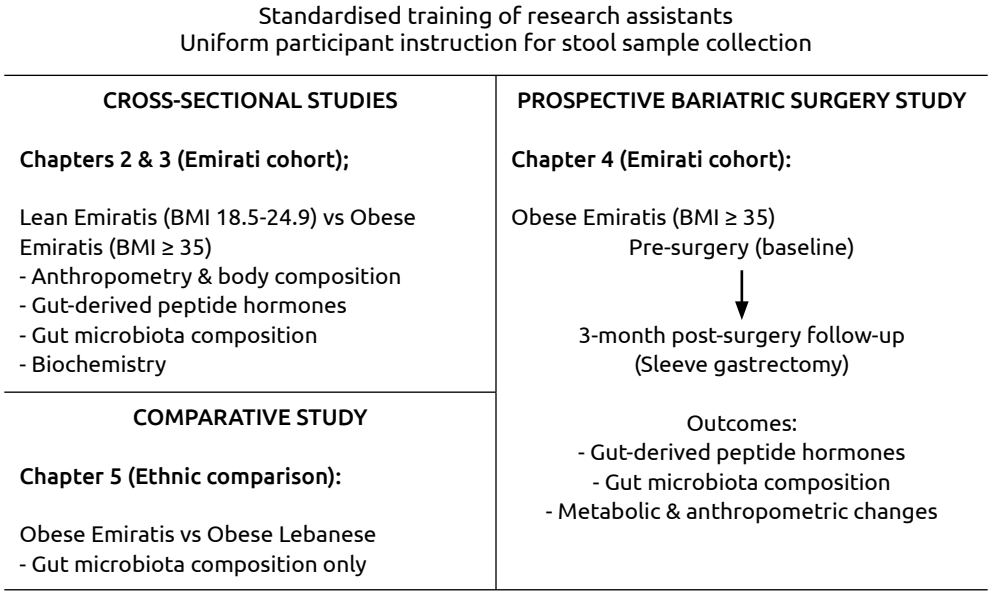


Figure 1.1. Overview of the study design and analytical framework of the dissertation

The figure outlines the study structure, comprising cross-sectional and prospective components. Cross-sectional analyses (Chapters 2 and 3) compared lean and obese Emirati adults, while Chapter 5 presents an ethnic comparison between obese Emirati and Lebanese adults, focusing on gut microbiota composition. The prospective study (Chapter 4) followed obese Emirati participants before and three months after sleeve gastrectomy. Outcomes included anthropometric, metabolic, gut-derived peptide hormone, and gut microbiota measures, assessed using standardised procedures across all study components.

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2

Chapter 2

The Association between Peptide Hormones with Obesity and Insulin Resistance Markers in Lean and Obese Individuals in the United Arab Emirates

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Abstract

Peptide hormones play a crucial role in body weight and glucose homeostasis. In this study, we aimed to explore this association and recruited 43 obese and 31 age- and sex-matched lean participants. We assessed their body mass index (BMI), waist circumference (WC), waist-toheight ratio (WtHR), percentage body fat (PBF), fasting blood levels of peptide hormones (GLP-1, GLP-2, insulin, leptin, ghrelin, CCK, and PYY), fasting blood sugar (FBS), and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). We tested the associations between peptide hormones and markers of obesity and insulin resistance (IR) by using the Independent-Samples *t*-test and Mann- Whitney U test, partial correlation, and logistic regression. FBS, insulin, HOMA-IR, GLP-1, GLP-2, and leptin were significantly higher in the obese group; ghrelin and CCK were significantly higher in lean participants, and no difference was seen for PYY. Controlling for BMI, GLP-1 was positively correlated with WtHR, while ghrelin was inversely correlated with WtHR. GLP-1 was correlated with HOMA-IR. GLP-1 was associated with obesity and IR markers in the regression model. Our results show that obese and lean adults display significant differences in plasma peptide hormone levels. GLP-1 levels were independently associated with markers of obesity and IR. Restoring the appetite hormone balance in obesity may represent a potential therapeutic target.

Keywords: obesity; brain–gut axis; insulin resistance; glucagon-like peptide-1; glucagon-like peptide-2; insulin; leptin; cholecystokinin; peptide yy; ghrelin

1. Introduction

Obesity is reaching unprecedented epidemic levels. Globally, in 2016, 39% and 13% of adults were estimated as overweight and obese, respectively [1]. Extending from its simplistic description as an imbalance between energy intake and expenditure, obesity ensues from multifaceted interactions between genetic, environmental, psychological, lifestyle, and dietary factors, making it a complex disease to understand and address [2]. Specifically, a growing body of evidence supports the role of the gut–brain axis in the pathogenesis of obesity [3]. On the one hand, the brain signals to the gut via efferent vagal and neuroendocrine pathways [4], and on the other hand, peptide hormones act as signaling molecules [5], triggering autonomic reflexes to regulate appetite, energy, and glucose homeostasis [6]. These peptides are divided into short-term effectors, such as glucagon-like peptides (GLP)-1 and -2, cholecystokinin (CCK), peptide YY (PPY), and ghrelin, and long-term effectors, including insulin, leptin, and adipokines [7]. Significant alterations in the expression and secretion of peptide hormones may disrupt intermediary metabolism, ultimately manifesting in increased body weight and insulin resistance (IR), leading to diabetes, metabolic syndrome, cardiovascular disease, or dyslipidemia [8]. In obesity, neural, gut- and adipose-tissue-derived hormone signaling are altered [9]. For instance, compared with normal-weighted individuals, people with obesity have reduced fasting ghrelin levels which could be a counter-regulatory mechanism to excess body weight and reduced post–meal suppression [10].

Furthermore, individuals with obesity have reduced fasting levels of PYY and GLP-1 and blunted meal-stimulated levels of these anorectic peptides, in addition to an attenuated satiety-promoting effect of CCK [11], leptin resistance, and IR [12,13]. However, it is unclear whether these alterations are a cause or a consequence of obesity [14]. Moreover, microbiota dysbiosis has been associated with impairments in the secretion of many peptide hormones, coupled with increased appetite, enhanced energy harvest from food intake, and fat storage [15]. Apart from bariatric surgery, treatment options for obesity are ineffective in achieving sustainable weight loss [16], making the search for potential alternative treatments a necessity [14]. The effectiveness of a bariatric surgery procedure could partly be lying in its effect on peptide hormones and subsequent regulation of energy homeostasis [16].

Nevertheless, surgical treatment of obesity can never be the sole solution, as it is an invasive, risky, and costly procedure [17]. Consequently, the field of neuroendocrinology, specifically the modulation of peptide hormones, holds promising therapeutic implications [10]. However, the definitive roles of each of these molecules remain not fully understood and are yet to be uncovered [18]. Further research is needed to address knowledge gaps and unresolved issues in the field of peptide hormones and obesity [11]. Understanding underlying pathophysiological links have the potential to allow for more accurate identification of high-risk participants and open the door for new therapeutic implications [19]. This is of utmost importance for communities exhibiting alarming rates of obesity, such as in the United Arab Emirates (UAE), amounting, in 2016, to 31.6% among men and 41.2% among women [20]. Accordingly, this study aimed to assess plasma peptide hormones within the context of obesity and IR among lean and obese adult Emirati participants.

2. Materials and Methods

2.1. Study Design

This was a cross-sectional comparative study between lean and obese Emirati individuals residing in the UAE. It was part of a pre–post study exploring the effect of a bariatric procedure on gut microbiota, peptide hormones, food intake, and metabolism. The study was registered on ClinicalTrials.gov (ID: NCT04200521). Raw data are available at the Mendeley Data repository (https://data.mendeley.com/datasets/w297t54m98/1, accessed on 7 February 2022) [21].

2.2. Ethics Statement

All participants gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Ministry of Health and Prevention (MOH), Dubai Health Care Regulatory Research Ethics Committee (DHCR-REC), and the Zayed University Ethical Committee Board (ZU19_51_F).

2.3. Participants and Sample Size

The current study utilized data from a mother study that aimed to assess gut microbiota among lean and obese Emirati participants and changes in microbiota post-bariatric surgery. In the mother study, the primary outcome was the change in the Firmicutes-to- Bacteroidetes ratio. The sample size calculation was performed according to change in Bacteroidetes/Firmicutes between pre- and post-bariatric procedure [22] based on the study by Damms-Machado et al. [23] where the mean (SD) fecal Bacteroidetes-to-Firmicutes ratio changed significantly from 5.9 (2.1) to 10.4 (1.4) in 3 months post-bariatric surgery [23] A sample size of 2 participants was required to achieve an 80% power at a two-sided 5% significance level (Ali Ahmad et al., in preparation). To allow for the high expected dropout rate, the minimum sample size was multiplied by 15. Hence, a total of 30 obese planning to undergo a bariatric procedure, and 30 lean Emirati, matched by age and sex, were targeted. Eligibility criteria included stable body weight and free of antibiotic use for the last three months, between 18 and 60 years, residing in the UAE, from both sexes. Consenting participants with a body mass index (BMI) ≥ 35 kg/m2 planning to undergo bariatric surgery with a clearance from the bariatric surgeon were assigned to the “obese” study group. Afterward, individuals with a BMI

between 18.5 and 24.9 kg/m2, matched for ageand sex of the initially recruited obese participants, were assigned to the “lean” study group. Exclusion criteria were as follows: weight loss ≥ 5% in the last three months, pregnancy, alcohol consumption of more than two drinks in a day for men and more than one drink in a day for women [24], or unwilling to provide written informed consent. Obese participants were recruited via a direct approach from two hospitals (one in Dubai and one in Sharjah), whereas lean participants were recruited from the general community in Dubai, using flyer postings and word of mouth. Recruitment was conducted between October 2019 and March 2021.

2.4. Outcome Measures and Data Collection

Inclusion criteria were assessed by using a screening questionnaire addressing general health, weight (loss), medication and supplement use, physical activity, antibiotic usage, alcohol consumption, and comorbidities. Eligible participants were asked to avoid alcohol consumption and any strenuous exercise 24 h before the screening and come for data collection after a 12-h fast. Outcome measures, collected by trained dietitians and research assistants, included the following:

2.5. Biochemical Parameters

Peptide hormones: venous blood samples were collected after fasting for 12 h, using a 22-gauge needle, by a licensed nurse, following standard techniques and three vacutainers tubes. One 5 mL sample was drawn into Ethylenediaminetetraacetic acid (EDTA) tube to analyze GLP-1, GLP-2, insulin, leptin, and CCK without adding any stabilizer. Another two 3-mL samples were drawn into EDTA tubes. For the first one, 30 µL of Pefabloc (Aminoethyl-benzenesulfonyl fluoride hydrochloride, i.e., AEBSF (Sigma Aldrich, St. Louis, MO, USA; 100 mg/mL in distilled water) was added to stabilize ghrelin. For the other tube, 30 µL of DPP IV inhibitor (Sigma Aldrich) was added to stabilize PYY. According to the manufacturer’s instructions, hormones were analyzed by using Enzyme-Linked Immunosorbent Assay (ELISA). Kits used were purchased from Diametra Millipore (St. Louis, MO, USA) for GLP-1, GLP-2, PYY, ghrelin, insulin, and leptin; and ABclonal Technology (Wuhan, China) for CCK.

Fasting blood sugar (FBS) was measured by using a portable Lux Meter Blood Test following the manufacturer’s instructions (Biochemical Systems International, S.p.A; Arezzo, Italy).

Homeostatic Model Assessment of IR (HOMA-IR) was calculated as fasting serum insulin (mU/mL) × FBS (mg/dL)/405 [25]; values higher than 1.8 denoted IR [26].

2.6. Anthropometric Measurements

Height and weight were measured to determine BMI. Body weight (Kg) was assessed by using an electronic portable Seca 762 scale (Vogel & Halke, Hamburg, Germany), without shoes, with the participant wearing light clothes. Height (cm) was measured by using a portable stadiometer attached to the Seca weighing scale and measured to the nearest 0.1 cm, without shoes, with the participant stretching to the maximum height. BMI (kg/m^2) was calculated by dividing kilogram weight by squared height in meters.

Waist circumference (WC) (cm) was measured to the nearest 0.1 cm at the mid-point, halfway between the right iliac crest and the lower costal region [27], using measuring tapes Seca 201 Ergonomic Circumference Measuring Tape. WC values were categorized as elevated according to the cut-off points of ≥94 cm for men and ≥80 cm for women [28].

Waist-to-height ratio (WtHR) was calculated by dividing the WC (cm) by height (cm). Values ≥ 0.5 indicated abdominal obesity [29].

Percent body fat (PBF) was evaluated by using a bioelectrical impedance analyzer (BC-420 MA, Tanita Corporation, Tokyo, Japan). Participants were asked to be well hydrated, to not drink caffeine for 12 h, and to not participate in any excessive physical activity 24 h before the body-composition analysis. Cutoffs of ≥25% and ≥35% were used to define elevated PBF among men and women, respectively [30].

2.7. Statistical Analyses

Statistical analyses were performed by using the Statistical Package for the Social Sciences software version 21.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was tested by using skewness and kurtosis. Data were expressed as means ± standard deviations and frequencies and percentages for continuous and categorical variables, respectively. Differences between the obese and lean participants were examined by using Independent-Samples *t*-test and Mann-Whitney U test for normally distributed and skewed continuous variables, respectively, and Chi-square for categorical variables. Pearson and Spearman's correlations were used to assess the correlations between peptide hormones (GLP-1, GLP-2, insulin, leptin, CCK, PYY, and ghrelin) and markers of obesity and IR (BMI, WC, WtHR, PBF, insulin, FBS, and HOMA-IR). These analyses were followed by partial correlations, adjusting for BMI, for all variables, except for BMI. A correlation coefficient (*r*) ranging between |0.10| and |0.39|; |0.4| and |0.69|; |0.70| and |0.89|; and |0.90| and |1.00| denoted a weak, moderate, strong, and very strong

correlation, respectively [31]. Binary regression analyses were conducted by using the forward method, with categories of weight status, HOMA-IR, WC, WtHR, and PBF being the dependent variables and the peptide hormones being the independent variables. The number of independent variables entered into each model was set at 10% of the group with the outcome of interest. The choice of the independent variables was based on the results of the bivariate analyses ($p < 0.2$) and the pertaining scientific literature. A *p*-value less than 0.05 was considered statistically significant.

3. Results

In total, 74 adults were included: 43 obese (16 males, 27 females) and 31 lean (12 males, 19 females). Their characteristics are detailed below in Table 1. There was no between-group significant difference regarding age and sex. Obese participants exhibited significantly higher levels of FBS, insulin, HOMA-IR, GLP-1, GLP-2, and leptin compared with lean participants. In contrast, lean participants showed significantly higher levels of ghrelin and CCK than obese participants, while no between-group differences were noted regarding PYY. As for comorbidities, 2.3% and 11.6% of the obese group had dyslipidemia and hypertension, respectively.

Table 1. Comparison of demographic, anthropometric, and biochemical parameters between lean and obese participants.

	Lean (Mean ± SD or n (%))	Obese (Mean ± SD or n (%))	p-Value
Age (years)	29.67 ± 10.73	29.95 ± 9.13	0.565
Female	19 (61.3)	27 (62.8)	0.896
BMI (kg/m^2)	22.49 ± 1.93	43.12 ± 6.83	<0.001 *
WC (cm)	76.70 ± 14.83	123.29 ± 17.76	<0.001 *
Appropriate	23 (74.2)	0 (0)	
Increased risk	8 (25.8)	43 (100)	<0.001 *
WtHR	0.48 ± 0.05	0.74 ± 0.08	<0.001 *
Normal	16 (51.6)	0 (0)	
High	15 (48.4)	43 (100)	<0.001 *
PBF (%)	26.62 ± 9.39	46.13 ± 30	<0.001 *
Adequate	24 (77.4)	0 (0)	
Increased risk	7 (22.6)	41 (95.3)	<0.001 *
FBS (mg/dL)	91.67 ± 11.03	103.11 ± 27.29	0.003 *
Insulin (mU/mL)	3.71 ± 4.41	22.0 ± 14.01	<0.001 *
HOMA-IR	0.86 ± 1.03	5.65 ± 4.14	<0.001 *
Leptin (ng/mL)	20.94 ± 7.96	55.18 ± 18.58	<0.001 *
GLP-1 (pM)	12.64 ± 8.57	23.99 ± 12.83	<0.001 *
GLP-2 (ng/mL)	2.29 ± 1.06	3.59 ± 1.76	<0.001 *
CCK (pg/mL)	68.64 ± 34.39	53.01 ± 28.16	0.037 *
PYY (pg/mL)	61.85 ± 33.99	74.98 ± 50.51	0.355
Ghrelin (pg/mL)	796.08 ± 266.79	531.75 ± 96.12	<0.001 *

* Denotes statistical significance ($p < 0.05$) between groups. Independent-sample t-test was used for normally distributed continuous variables (age, BMI, WC, WtHR, PBF, insulin, leptin, GLP-1, GLP-2, CCK), Mann–Whitney U-test for skewed continuous variables (PYY, ghrelin, FBS, and HOMA-IR), and Chi-square test was used for categorical variables. BMI, body mass index; WC, waist circumference; PBF, percentage body fat; WtHR, waist-toheight ratio; FBS, fasting blood sugar; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; peptide hormones: GLP-1 and GLP-2, glucagon-like peptides 1 and 2; CCK, cholecystokinin; PYY, peptide YY.

The results of the correlation analyses between peptide hormones and markers of obesity and IR for the whole sample are detailed in Table 2. All peptide hormones were significantly correlated with BMI, whereby GLP-1, GLP-2, insulin, and leptin showed a positive correlation (r = 0.426, p < 0.001; r = 0.403, p < 0.001; r = 0.61, p < 0.001; r = 0.801, p < 0.001, respectively), whereas CCK and ghrelin showed a negative correlation (r = −0.356, p = 0.002; r = −0.680, p < 0.001, respectively). Specifically, GLP-1, GLP-2, insulin and leptin were positively correlated with WtHR (r = 0.549, p < 0.001; r = 0.444, p < 0.001; r = 0.651, p < 0.001; r = 0.756, p < 0.001, respectively), while CCK and ghrelin were negatively correlated with WtHR (r = −0.291, p = 0.012; r = −0.706, p < 0.001). Regarding IR markers, GLP-1, GLP-2, and leptin were positively correlated with HOMA-IR (r = 0.738, p < 0.001; r = 0.368, p = 0.001; r = 0.588, p < 0.001), while ghrelin was negatively correlated with HOMA-IR (r = −0.514; p < 0.001). PYY was not correlated with any of the assessed markers.

Table 2. Correlations between peptide hormones and markers of obesity and IR.

		GLP-1	GLP-2	Insulin	Leptin	CCK	PYY	Ghrelin
WC (M)	*r* *p*	0.687 [a] <0.001 *	0.423 [a] 0.025 *	0.713 [a] <0.001 *	0.801 [a] <0.001 *	0.266 [a] 0.172	0.21 [b] 0.28	−0.722 [b] <0.001 *
WC (F)	r p	0.382 [a] 0.01 *	0.286 [a] 0.057	0.61 [a] <0.001 *	0.762 [a] <0.001 *	−0.346 [a] 0.020 *	0.07 [b] 0.65	−0.603 [b] <0.001 *
PBF (M)	*r* *p*	0.644 [a] <0.001 *	0.517 [a] 0.007 *	0.655 [a] <0.001 *	0.854 [a] <0.001 *	−0.143 [a] 0.484	0.26 [b] 0.2	−0.681 [b] <0.001 *
PBF (F)	*r* *p*	0.224 [a] 0.139	0.211 [a] 0.164	0.525 [a] <0.001 *	0.714 [a] <0.001 *	−0.384 [a] 0.009 *	0.07 [b] 0.66	−0.593 [b] <0.001 *
BMI	*r* *p*	0.426 [a] <0.001 *	0.403 [a] <0.001 *	0.614 [a] <0.001 *	0.801 [a] <0.001 *	−0.356 [a] 0.002 *	0.09 [b] 0.44	−0.680 [b] <0.001 *
WtHR	*r* *p*	0.549 [a] <0.001 *	0.444 [a] <0.001 *	0.651 [a] <0.001 *	0.756 [a] <0.001 *	−0.291 [a] 0.012 *	0.18 [b] 0.13	−0.706 [b] <0.001 *
Insulin	*r* *p*	0.699 [a] <0.001 *	0.418 [a] <0.001 *	- -	0.474 [a] <0.001 *	−0.064 [a] 0.589	0.11 [b] 0.34	−0.495 [b] <0.001 *
FBS	*r* *p*	0.242 [b] 0.039 *	0.175 [b] 0.139	0.29 [b] 0.013 *	0.278 [b] 0.017 *	−0.193 [b] 0.102	0.17 [b] 0.14	−0.309 [b] 0.008 *
HOMA-IR	*r* *p*	0.738 [b] <0.001 *	0.368 [b] 0.001 *	0.992 [b] <0.001 *	0.588 [b] <0.001 *	−0.071 [b] 0.553	0.14 [b] 0.25	−0.514 [b] <0.001 *

Spearman correlation was conducted for correlations involving FBS, HOMA-IR, PYY, and ghrelin, while Pearson correlation was conducted for correlations involving other variables:

[a] Pearson correlation, [b] Spearman correlation, r = correlation coefficient. * Statistically significant correlation ($p < 0.05$). BMI, body mass index; WC, waist circumference; PBF, percentage body fat; WtHR, waist-to-height ratio; FBS, fasting blood sugar; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; peptide hormones: GLP-1 and GLP-2, glucagon-like peptides 1 and 2; CCK, cholecystokinin; PYY, peptide YY; M, males; F, females.

The results of partial correlations adjusting for BMI are presented in Table 3. Leptin, GLP-2, and CCK correlations with obesity markers were annulled when adjusting for BMI. In contrast, GLP-1 remained correlated with WtHR ($r = 0.312$, $p = 0.039$), and with WC among females only ($r = 0.447$, $p < 0.001$). Insulin remained positively correlated with WtHR ($r = 0.275$, $p = 0.019$) and ghrelin remained inversely correlated with WtHR ($r = -0.302$, $p = 0.019$). As for the markers of IR, GLP-1 and GLP-2 were positively correlated with insulin ($r = 0.612$, $p < 0.001$; $r = 0.236$, $p = 0.046$, respectively). Moreover, GLP-1 showed a positive correlation with HOMA-IR ($r = 0.667$, $p < 0.001$). None of the peptide hormones was correlated with FBS. Finally, PYY was not correlated with any of the assessed markers.

Table 3. Partial correlations, adjusting for BMI, between peptide hormones and markers of obesity and IR.

		GLP-1	GLP-2	Insulin	Leptin	CCK	PYY	Ghrelin
BMI ˆ	*r*	0.426 [a]	0.403 [a]	0.61 [a]	0.801 [a]	−0.356 [a]	0.093 [b]	−0.680 [b]
	p	<0.001 *	<0.001 *	<0.001 *	<0.001 *	0.002 *	0.435	<0.001 *
WC (M)	*r*	0.361 [a]	−0.224 [a]	0.324 [a]	0.095 [a]	0.099 [a]	0.060 [b]	−0.146 [b]
	p	0.064	0.260	0.099	0.636	0.622	0.766	0.466
WC (F)	*r*	0.312 [a]	0.015 [a]	0.297 [a]	0.150 [a]	0.012 [a]	0.130 [b]	−0.154 [b]
	p	0.039 *	0.923	0.050	0.330	0.936	0.400	0.317
PBF (M)	*r*	0.281 [a]	−0.058 [a]	0.110 [a]	0.245 [a]	0.346 [a]	0.154 [b]	0.103 [b]
	p	0.174	0.783	0.601	0.238	0.091	0.464	0.625
PBF (F)	*r*	−0.044 [a]	−0.163 [a]	0.070 [a]	−0.053 [a]	−0.071 [a]	0.164 [b]	−0.040 [b]
	p	0.776	0.290	0.652	0.732	0.648	0.287	0.796
WtHR	*r*	0.447 [a]	0.203 [a]	0.275 [a]	0.071 [a]	0.103 [a]	0.209 [b]	−0.302 [b]
	p	<0.001 *	0.087	0.019 *	0.553	0.389	0.078	0.019 *
Insulin	*r*	0.612 [a]	0.236 [a]	-	−0.038 [a]	0.209 [a]	0.070 [b]	−0.093 [b]
	p	<0.001 *	0.046 *	-	0.749	0.077	0.557	0.438
FBS	*r*	0.074 [b]	0.027 [b]	0.032 [b]	−0.161 [b]	−0.046 [b]	0.149 [b]	−0.044 [b]
	p	0.535	0.825	0.787	0.176	0.704	0.213	0.716
HOMA	*r*	0.667 [b]	0.170 [b]	0.987 [b]	0.009 [b]	0.273 [b]	0.100 [b]	−0.094 [b]
	p	<0.001 *	0.154	<0.001 *	0.940	0.021 *	0.405	0.432

ˆ Correlation was presented without adjustment for BMI. Spearman partial correlation was conducted for correlations involving FBS, HOMA-IR, PYY, and ghrelin, while Pearson partial correlation was performed for correlations involving other variables. [a] Pearson partial correlation. [b] Spearman partial correlation. * Statistically significant correlation ($p < 0.05$). BMI, body mass index; WC, waist circumference; PBF, percentage body fat; WtHR, waist-toheight ratio; FBS, fasting blood sugar; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; GLP-1 and GLP-2, glucagon-like peptides 1 and 2; CCK, cholecystokinin; PYY, peptide YY; M, males; F, females.

The binary logistic regression adjusting for BMI results are presented in Table 4 and show that GLP-1 was positively associated with HOMA-IR (odds ratio (OR) = 1.221, and 95% confidence interval (CI) = 1.079–1.382). No significant associations were noted between leptin nor ghrelin and HOMA-IR. Moreover, GLP-1 was positively associated with WC and WtHR (OR = 1.196, and 95% CI = 1.001–1.430; OR = 1.591, and 95% CI = 1.072–2.363, respectively), but negatively associated with PBF (OR = 0.717, and 95% CI = 0.542–0.949). Finally, leptin andGLP-1were positively

associatedwith obesity (OR = 1.367, and 95% CI = 1.117–1.672; OR = 1.239, and 95% CI = 1.018–1.508, respectively).

Table 4. Predictors of markers of obesity and IR.

	Predictors	OR	p-Value	R Square	95% CI
HOMA-IR [a]	BMI GLP-1	1.229 1.221	<0.001 0.002	0.764	1.108–1.363 1.079–1.382
Weight status [b]	Leptin GLP-1	1.367 1.239	0.002 0.033	0.898	1.117–1.672 1.018–1.508
WC [c]	BMI GLP-1	3.876 1.196	0.027 0.048	0.871	1.169–12.848 1.001–1.430
WtHR [d]	BMI GLP-1	10.276 1.591	0.023 0.021	0.900	1.373–76.934 1.072–2.363
PBF [e]	BMI GLP-1	4.847 0.717	0.008 0.020	0.910	1.503–15.636 0.542–0.949

[a] Reference category: HOMA-IR < 1.8 vs. HOMA-IR ≥ 1.8. Variables entered in the model: GLP-1, leptin, ghrelin, and BMI. [b] Reference category: lean vs. obese. Variables entered in the model: leptin, GLP-1, and ghrelin. [c] Reference category: appropriate WC vs. increased WC. Variables entered in the model: leptin, GLP-1, and BMI. [d] Reference category: normal WtHR vs. high WtHR. Variables entered in the model: GLP-1 and BMI. [e] Reference category: normal PBF vs. elevated PBF. Variables entered in the model: leptin, GLP-1, and BMI. HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; GLP-1, glucagon-like peptides 1; PBF, percentage body fat; WC, waist circumference; WtHR, waist-to-height ratio.

4. Discussion

Obesity and its complications are an ever-increasing public-health challenge. The relationship between gut-derived hormonal dysregulation and obesity is long-known [10]. More specifically, peptide hormones, such as PYY, GLP-1, CCK, insulin, leptin, and ghrelin, are implicated in appetite regulation. Of these, only ghrelin is orexigenic, while the others have anorexigenic properties [11]. The interplay between peptide hormones and cardiometabolic outcomes in Arabs has received little attention in the scientific literature, thus justifying the need for this research. Exploring interventions to reduce obesity—specifically in the UAE—is a national health priority, given the alarmingly high obesity rate [32].

This study reported statistically significant differences in GLP-1, GLP-2, insulin, leptin, ghrelin, and CCK between obese and lean participants. Our results further highlight the dysregulation of peptide hormone secretion profiles with obesity and IR [19,33]. Whether these alterations are consequential or inductive to weight gain remains to be explored [34].

Moreover, we found that GLP-1 predicted obesity status and IR, even after controlling for BMI, whereas leptin predicted obesity and its markers, but after controlling for BMI, this association was annulled. As expected, individuals with obesity had higher fasting insulin levels and HOMA-IR than lean participants [35]. Moreover, 92.5% of obese participants had IR, compared with only 7.5% of lean participants. Interestingly, insulin remained positively correlated with WtHR after controlling for BMI, emphasizing the latter as a promising anthropometric screening parameter indicative of IR [36], being a sensitive, inexpensive, non-invasive, simple-to-assess, and easy-to-calculate tool [37,38].

We found that fasting GLP-1 was significantly higher in obese participants, as seen elsewhere [39,40]. Notably, GLP-1 was the only independent gut peptide predictor of obesity markers and IR. The inflammatory cytokine interleukin-6 (IL-6) stimulates GLP-1 secretion from pancreatic _-cells, subsequently promoting insulin secretion, hepatic lipogenesis, and adipogenesis, which might explain the positive association between GLP-1 and IR and adiposity [41]. It is also possible that GLP-1 levels are naturally increased as a homeostatic protective mechanism to counteract energy surplus in obese participants [41]. This suggestion is plausible, as overfeeding was shown to increase fasting levels of GLP-1 [42]. Obesity is also associated with intestinal microbiota dysbiosis, altering GLP-1 secretion [40]. Our findings seem to be aligned with the emerging literature [40,41], whereby

fasting GLP-1 may be considered an indicator of cardiometabolic risk. Most importantly, these findings suggest therapeutic implications. For instance, GLP-1, an incretin hormone, regulates glucose homeostasis and suppresses appetite [19], and GLP-1 treatment in controlling blood glucose levels, hunger, and energy consumption has been proven effective in recent studies [43,44]. Although obesity affects postprandial GLP-1 secretion, obese participants are sensitive to systematically administered GLP-1 with reduced hunger, slowed gastric emptying [10], and decreased IR [45]. Moreover, administration of GLP-1 receptor agonists in combination with related gut-derived hormones imparts metabolic advantages beyond those seen with GLP-1 alone [46].

Obese participants exhibited significantly higher leptin levels, positively correlating with obesity and IR markers [47]. Since leptin is excreted by the adipose tissue [48], a positive correlation between body fat and leptin was expected [49] and was annulled after controlling for BMI. Moreover, leptin levels decrease with a reduction of body fat [50], indicating enhanced leptin sensitivity [12], which correlates with maintaining the weight loss [51]. The concept of leptin resistance may explain the paradoxically elevated leptin levels in obesity, notably through impaired transportation of leptin through the blood-brain barrier [12] and the decreased hypothalamic leptin receptor expression [12]. Preventing and treating leptin resistance may open new therapeutic strategies [12,50], especially since approaches to enhancing leptin sensitivity in animal models have shown some success; however, these findings are without a clinically relevant application to date [12].

While PYY is known to reduce appetite and energy intake, delay gastric emptying, and promote insulin secretion [15], its relationship with obesity and IR remains controversial [19,52]. In our study, no between-group significant differences were noted. We did not find any association between fasting PYY and obesity nor IR, except for a positive correlation with FBS in obese participants. It is highly plausible that, in contrast to other peptide hormones, obesity is not associated with resistance to PYY, thus explaining the lack of difference in its fasting concentrations between lean and obese individuals [53,54]. Furthermore, PYY levels are affected by numerous factors beyond weight. For example, reduced concentrations in people with a high BMI might be related to consuming a lowfiber diet rather than fat stores or IR [55]. Targeted studies examining adiposity and dietary intake are required to establish the underlying causality.

In our study, fasting CCK was significantly higher in lean participants. Moreover, CCK was negatively correlated with all obesity markers, which was annulled after

controlling for BMI. CCK is known to reduce energy intake and promote insulin secretion [56]. Whether obesity affects CCK secretion is controversial [19] and could be due to methodological problems in measuring CCK [57]. CCK-resistance in obesity is evident, making obese individuals less sensitive to CCK's satiety effect [58]. The biological action profile of CCK has strong parallels with those of GLP-1 [56], and a combined activation of their receptors induces body-weight reduction and blood-glucose control [59].

Furthermore, CCK and leptin synergistically inhibit caloric intake [56]. The coadministration of CCK with GLP-1 and leptin substantially enhances metabolic benefits under conditions of obesity and diabetes [56]. CCK combinatorial therapeutics may have yet unexploited therapeutic potential.

Finally, we found that fasting ghrelin was significantly lower in obese participants, and after controlling for BMI, it was negatively correlated only with WtHR [3]. Fasting ghrelin decreases with obesity and increases by diet-induced weight loss [19]. The underlying mechanisms have not been elucidated, but circulating plasma ghrelin was reported to decrease significantly after food intake [11]. Seemingly, increased caloric intake suppresses plasma ghrelin levels, and reduced ghrelin may be compensatory rather than causal, being a physiological adaptation to the positive caloric balance and excess body weight [10]. In human primary funding cultures, obesity decreased ghrelin production at the cellular protein level, leading to a reduced secretion in the cell supernatant [10].

Moreover, downregulation of ghrelin secretion may result from high IR [60]. Ghrelin administration increases food intake, lowers energy expenditure, and upregulates gene expression of fat-storage-promoting enzymes in white adipose tissue [61]. In contrast, neutralization of bioavailable ghrelin and administration of growth hormone secretagogue receptor or ghrelin-O-acyltransferase antagonists to mice fed a high-fat diet lower body weight and food intake [10].

Strengths and Limitations

To our knowledge, this is the first study providing information regarding seven peptide hormones in adults Emiratis and exploring the associations between these hormones and validated markers of obesity and IR. Our findings present important implications for clinical practice and future diagnostic and interventional studies, especially that combinatorial therapies of hormones involved in energy regulation act through various pathways and avoid compensatory mechanisms [12]. Moreover, we measured total GLP-1, providing better information about the secretion of the hormone and its effects, compared with measurements of

intact (or active) GLP-1 [62]. However, this analysis had several limitations. First, it focused only on fasting peptide hormone concentrations, varying in food intake and macronutrient composition. Exploring postprandial concentrations and their relationship with obesity and IR could provide additional insights into unanswered questions in this study. Moreover, our sample consisted of Emiratis aged 18–60 years. Future studies are needed to uncover whether the relationships identified here hold other age ranges and ethnic groups. Finally, our results are hindered by the relatively small sample size and the study's cross-sectional nature. Therefore, prospective studies should be carried out with powered samples to validate our findings and uncover potential cause-and-effect relationships.

5. Conclusions

In this paper, we reported significant differences in the plasma concentrations of peptide hormones between obese and lean adult Emiratis. Despite the small number of participants, a notable relationship between the circulating fasting GLP-1 levels and obesity and IR was observed. Restoring the disordered peptide hormones balance in obesity by targeting nutrient sensors in selective regions of the gut or by combined administration of peptide hormone mimetics represent a primary potential therapeutic target to improve the prevention and management of obesity and its comorbidities. Understanding peptide hormones biology is the first step in this regard. To this end, we follow up with the obese individuals after they have undergone bariatric surgery, investigate changes in their peptide hormones profile and include analyses on gut microbiota composition.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Ministry of Health and Prevention (MOHAP/DXB-REC-52/2018 and approval on 26 February 2018), Zayed University Ethical Committee Board (protocol code ZU19_51_F and approval on 8 May 2019) and Dubai Health Care Regulatory Research Ethics Committee (DHCR-REC and approval on 4 October 2020). All participants gave their informed consent for inclusion before they participated in the study.

Informed Consent Statement: Informed consent was obtained from all participants involved in thestudy. Written informed consent has been obtained from the participants to publish this paper.

Data Availability Statement: The raw data presented in this study are openly available in Mendeley Data repository: https://data.mendeley.com/datasets/w297t54m98/1 (accessed on 7 February 2022) at https://doi.org/10.17632/w297t54m98.1.

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Supplementary Materials

No supplementary materials are associated with this chapter. All data are included in the main manuscript.

3

Chapter 3

Association of the gut microbiota with clinical variables in obese and lean Emirati subjects

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Abstract

Background

Growing evidence supports the role of gut microbiota in obesity, yet exact associations remain largely unknown. Specifically, very little is known about this association in the Emirati population.

Methods

We explored differences in gut microbiota composition, particularly the Firmicutes/Bacteroidetes (F/B) ratio, between 43 obese and 31 lean adult Emirate counterparts, and its association with obesity markers, by using V3-V4 regions of 16 S ribosomal RNA gene sequencing data. Furthermore, we collected anthropometric and biochemical data.

Results

The two major phyla in obese and lean groups were Firmicutes and Bacteroidetes. We observed a significantly lower alpha diversity (Shannon index) in obese subjects and a significant difference in beta diversity and phylum and genus levels between the two groups. The obese group had higher abundances of Verrucomicrobia and Saccharibacteira and lower abundances of Lentisphaerae. Acidaminococcus and Lachnospira were more abundant in obese subjects and positively correlated with adiposity markers. No correlations were found between the gut microbiota and biochemical variables, such as fasting blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

Conclusion

We reveal significant differences in the gut microbiota between obese and lean adult Emiratis and an association between certain microbial genera of the gut microbiota and obesity. A better understanding of the interactions between gut microbes, diet, lifestyle, and health is warranted.

Keywords: gut microbiota, obesity, firmicutes, bacteroidetes, 16S rRNA, United Arab Emirates

1. Introduction

Obesity is a multifactorial disease (Cannon and Kumar, 2009), declared by the World Health Organization (WHO) in 2016 as a pandemic (World Health Organization, 2016). Long-standing factors involved in obesity include excessive caloric intake and a sedentary lifestyle (Morgen and Sørensen, 2014). More recently, obesity was also found to present a complicated disequilibrium of the diversity, richness, and evenness of the bacterial component of the gut microbiota (Aguirre and Venema, 2015), known as dysbiosis (Adlerberth and Wold, 2009; Round and Mazmanian, 2009). The latter has been proposed as part of the etiology of obesity (Davis, 2016) through its effect on digestion, regulation of metabolism, adipose tissue composition, short-chain fatty acid (SCFA) production, modulation of the production of gut peptides and hormones, among others (Corfe et al., 2015; Patrone et al., 2016). The human gut microbiota is primarily composed of Firmicutes and Bacteroidetes, which make up about 90% of all bacterial species, in addition to Actinobacteria, Fusobacteria, Proteobacteria, and Verrucomicrobia (Abenavoli et al., 2019; Rinninella et al., 2019). Nevertheless, substantial differences in composition and function in the microbiota between obese and healthy individuals have been established (Turnbaugh and Gordon, 2009; Tremaroli and Bäckhed, 2012; Pinart et al., 2021). In some studies, obesity in humans is typically characterized by high intestinal concentrations of Firmicutes and low concentrations of Bacteroidetes (Seganfredo et al., 2017; Crovesy et al., 2020); whereby the higher Firmicutes-to-Bacteroidetes ratio (F/B) among obese (Armougom et al., 2009; Furet et al., 2010; Kong et al., 2013) is potentially associated with a greater energy harvest from host diet (Turnbaugh et al., 2006). However, other studies show the opposite F/B ratio in obesity (Schwiertz et al., 2010), or no relation at all (Duncan et al., 2008) and thus, the cause-and-effect relationship between F/B and obesity is still to be elucidated.

Improvements in bacterial DNA sequencing allowed researchers to understand the gut microbiota and its composition and explore its complex relationship with health and disease (Gordon et al., 2007; Duncan et al., 2008). However, there are still gaps in our understanding of the role of the gut microbiota in the etiology of obesity and the effectiveness of interventions targeting gut microbiota for preventing and managing obesity (Tehrani et al., 2012), “e.g., it is still not entirely clear whether differences in the microbiota cause obesity, or whether obesity causes a difference in microbiota composition.” Primarily, this is because most studies have used rodent models, which have different gut microbiota

composition, fermentation process, and dietary practices than humans (Heinritz et al., 2013; Nguyen et al., 2015). Moreover, inconsistencies in human studies might be attributed to the different approaches to analyzing the composition of the gut microbiota, as well as the recruitment of subjects with ethnic differences and inter-individual dissimilarities in genetics, diets, and lifestyles which can shape the composition of the gut microbiota (Seganfredo et al., 2017; Crovesy et al., 2020; Pinart et al., 2021; Zeng et al., 2021). The characteristics of the gut microbiota in subjects with obesity are highlighted. Nevertheless, little is known about the association between gut microbiota and clinical variables (fasting blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and anthropometrics) linked to obesity in humans. This warrants scientific investigations to explore microbial patterns associated with obesity markers.

In the Gulf countries, the prevalence of obesity is steadily increasing. Specifically, in the United Arab Emirates (UAE), the prevalence of overweight and obesity doubled between 1989 and 2017 (Radwan et al., 2018), and there are 27.8% of adults obese, according to the National Health Survey 2017–2018 (Sulaiman et al., 2017; Ministry of Health and Prevention, 2023). In this work, we aimed to profile the gut microbiota and its association with clinical variables and explore differences (through a comparative analysis) between obese and lean Emirate subjects. Exploring the gut microbiome of Emiratis adds a piece of the puzzle to our understanding of obesity, with the ultimate goal of uncovering preventive and interventional measures tailored to the Emirati population aiming to curb the obesity epidemic in the country.

2. Materials and methods

2.1. Study design

This is a cross-sectional study conducted among Emirati subjects living in the UAE. The present study is part of a pre-post study registered at clinicaltrials.gov (NCT04200521) and performed in the UAE.

2.2. Ethical considerations

Ethical approval was granted by the Research Ethics Committee of the Ministry of Health and Prevention of UAE (MOHP/DXB-REC-52/2018), the Dubai Health Care Regulatory Research Ethics Committee (DHCR-REC), and the Zayed University Ethical Committee Board (ZU19_51_F). The study followed the Declaration of Helsinki. Written informed consent was collected from all study subjects.

2.3. Participants and sample size

We determined the sample size by following standard calculations based on normal distributions. The sample size was calculated based on the change in F/B from pre- to post-bariatric surgery (Brant, 2015), based on the study by Damms-Machado et al. (2015). In that study, the mean(SD) fecal F/B increased significantly from 5.9 (2.1) to 10.4 (1.4) in 3 months post-bariatric surgery (Damms-Machado et al., 2015). To detect a similarly significant effect, two patients were needed to achieve 80% power at a two-sided alpha level of 5%. To allow for the high expected dropout rate, the minimum sample size was multiplied by 15. Hence, we targeted 30 Emirati obese adults residing in the UAE of both sex and planning to undergo the bariatric procedure. In addition, we recruited a sample of 30 age and sex-matched control subjects (lean adults living in the UAE).

2.4. Inclusion criteria

Emirati residents of UAE, aged between 18 and 60 years, of either sex, free of antibiotics for at least 3 months, falling into one of the two body mass index (BMI) categories were included: (1) obese with a BMI of ≥35 kg/m^2 and willing to undergo bariatric surgery; (2) lean counterparts with a BMI of 18.5–24.9 kg/m^2 and consenting to participate in the study.

Obese participants were recruited from one hospital in Dubai and another in Sharjah. In contrast, lean subjects were recruited from community settings in

Dubai through word-of-mouth and flyer postings. Recruitment took place from October 2019 till March 2021.

2.5. Exclusion criteria

Individuals who consumed alcohol exceeding two drinks per day for men and one drink per day for women (Snetselaar et al., 2021), were pregnant at the time of the study, experienced significant weight loss (≥5%) in the past 3 months, or were not willing to consent for the study were excluded.

2.6. Outcome measures and data collection

General demographic characteristics collected from the patient included age and sex. Furthermore, health-related information was collected using a subjective screening questionnaire, including the presence of any chronic diseases such as dyslipidemia, diabetes, and hypertension, surgical history in the past 5 years, weight loss of at least 5% in the past 3 months, current intake of medication including antibiotics, and current consumption of prebiotic/probiotic/fiber supplement and probiotic foods, consumption of other nutrition supplements, and engagement in a physically active lifestyle and exercise.

Physical activity level was analyzed using two questions from our initial screening questionnaire. A “yes” or “no” answer was required for the following two questions: “Do you integrate physical activity in your daily routine” and “Do you incorporate any exercise program.” Sedentary was denoted if “no” was answered to both questions; light physical activity if “yes” was only answered to the first question; moderate physical activity if “yes” was only responded to the second question; and high physical activity if “yes” was answered to both questions.

2.7. Anthropometric and clinical variables

For each participant, anthropometric measurements, lipid profile, fasting blood sugar (FBS), and microbiota analyses were done.

Anthropometric data were collected by trained research assistants and dietitians. Body weight (kg): measured via portable Seca 762 scale (Vogel & Halke, Hamburg, Germany), following best practices, i.e., with light clothes and without shoes. Height (cm): measured using a portable stadiometer attached to the weighing scale following best practices, i.e., to the nearest 0.1 cm, without shoes, with the participant stretching to the maximum height while having the head positioned in the Frankfort plane. BMI (kg/m^2): calculated according to the standard formula by dividing weight in kilograms by squared height in meters. Waist circumference

(WC) (cm): measured using a Seca 201 ergonomic circumference measuring tape, at the mid-point between the right iliac crest and the lower costal region, to the nearest 0.1 cm (Van der Kooy and Seidell, 1993). WC was categorized as appropriate (<94 cm in men and < 80 cm in women) or increased (≥94 cm for men and ≥80 cm for women; Ford, 2005).

Waist-to-height ratio (WHtR): calculated by dividing the WC (cm) by height (cm), whereby abdominal obesity was defined as a WHtR ≥0.5 (Ashwell and Gibson, 2016). Fat mass (FM) and Percent Body Fat (PBF): measured via bioelectrical impedance analyzer (BC-420 MA, Tanita Corporation, Tokyo, Japan) with the participants being well hydrated, without drinking caffeine for 12 h, not participating in excessive physical activity 24 h before the analysis, and wearing comfortable clothes. Elevated PBF was defined as PBF ≥ 25% and ≥ 35% in men and women, respectively (Romero-Corral et al., 2008).

2.8. Biochemical parameters

Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and FBS: measured after 12 h of fasting via portable Lux Meter Blood Test (Biochemical Systems International, S.p.A; Arezzo, Italy) following the manufacturer's instructions.

2.9. Stool sample collection

Stool samples were collected in Zymo DNA/RNA Shield fecal collection tubes and stored at room temperature. Two samples were collected from each participant, one of which was analyzed, and the second was held for accuracy verification. Sample collection followed standard protocols and regulations. Collection tubes (with a spoon attached to the cap for collecting 1 gram of feces) were pre-filled with DNA/RNA Shield™ (9 mL). The nucleic acids (DNA & RNA) in the samples are preserved at room temperature (DNA > 1 year, RNA up to 1 month).

2.10. DNA isolation and sequencing of the V3–V4 region of the 16S rRNA gene

DNA isolation and sequencing of the barcoded amplicons of the V3–V4 region of the 16S rRNA gene was done as per the protocols of Illumina (Illumina, Eindhoven, The Netherlands; Surono et al., 2022). The sequencing was performed using the Illumina MiSeq system (San Diego, CA, United States) using barcodes and the 2 ×

300 bp protocol. We used Quantitative Insights Into Microbial Ecology: QIIME 2[1] software to analyze raw sequences; the latter were classified using the Silva database (version 132) as a reference 16S rRNA gene database. Reads were filtered, and only those present in at least 20% of the samples were taken.

2.10.1. Diversity analysis

α Diversity indices: observed-OTUs, Chao1 index, Phylogenetic diversity (Faith's PD), Pielou evenness, and Shannon diversity index, which were calculated with QIIME 2 and shown using the R software [R (4.1.x) (R Core Team)][2] in RStudio. The rarefaction curves were generated using the ggplot2 package for R. Rarefication depth was set at 3800.

β Diversity indices were visualized in a Principal Coordinate Analysis (PCoA) based on Bray–Curtis dissimilarity, Jaccard distance, and weighted and unweighted UniFrac using QIIME2 software.

The statistical significance of β diversity differences between the two groups was determined using Permutational Multivariate Analysis of Variance (PERMANOVA). The value of p was calculated through the Pairwise permanova method to compare β diversity between each category in all samples. Differences between obesity and lean samples (at phyla and genus levels) were analyzed via the non-parametric Kruskal–Wallis test corrected with the Benjamini–Hochberg false discovery rate (FDR) for multiple comparisons in Rstudio (the software package R (4.1.x), R Core Team, footnote 2).

The composition of the two groups was visualized using the Krona tool.[3]
Linear discriminant analysis (LDA) effect size (LEfSe) was used to explore microbial taxa with differential abundance between lean and obese (version 1.0).[4] Taxa showing LDA values above two at a value of p <0.05 were considered enriched taxa in each group.

The non-parametric Spearman's rank-order correlations between the Amplicon Sequence Variant (ASVs) and continuous variables (BMI, WC, WHtR, PBF, FM, LDL, HDL, TC, TG, TC/HDL, and FBS) were calculated. *Q*-values, i.e., adjusted value of *p*s after the FDR, were considered significantly different at a cut-off of <0.05. The F/B ratio was calculated by dividing the relative abundances of Firmicutes and Bacteroidetes.

[1] https://qiime2.org/
[2] http://www.R-project.org
[3] https://github.com/marbl/Krona/wiki/KronaTools
[4] http://huttenhower.sph.harvard.edu/galaxy/

A heatmap of Spearman correlation analysis was generated in R software (ggplot2 package).

2.11. Statistical analyses

We analyzed 'participants' characteristics using the Statistical Package for the Social Sciences software version 21 (SPSS Inc. Chicago, IL, United States). We assessed the normality of the data using Skewness and Kurtosis. Normal data were summarized as mean (M) ± standard deviation (SD) and skewed data as median (Mdn) and interquartile range (IQR). Between-group differences were explored using independent samples t-test for normally distributed continuous variables, Mann–Whitney U-test for skewed continuous variables, and Chi-square for categorical values. A value of $p < 0.05$ was used to denote statistical significance.

3. Results

The characteristics of participant groups are presented in Table 1. Forty-three obese subjects were included (37.2% men; mean ± SD age of 29.95 ± 9.13 years), whereas 31 lean subjects participated (38.7% men; mean ± SD age 29.67 ± 10.73 years). No significant differences in gender and age were observed between the groups. The obese group had higher anthropometric (BMI, WC, WHtR, and PBF) and biochemical parameters (FBS, LDL, TC, and TC/HDL-c ratio) than the lean group, as expected. There was no significant difference in lifestyle factors between the two groups (prebiotic, probiotic, fiber, alcohol consumption, and smoking). The level of physical activity in the obese group was mainly light and significantly lower than that of the lean group (Supplementary Table S1).

TABLE 1 Demographic, anthropometric, and biochemical parameters between lean (n = 31) and obese participants (n = 43).

	Lean [mean ± SD or n (%)]	Obese [mean ± SD or n (%)]	Value of p
Age (years)	29.67 ± 10.73	29.95 ± 9.13	0.565
Female	19 (61.3)	27 (62.8)	0.896
Weight (kg)	62.39 ± 8.17	118.23 ± 25.6	<0.001*
Height (cm)	166.29 ± 8.38	165.16 ± 9.77	0.603
BMI (kg/m^2)	22.49 ± 1.93	43.12 ± 6.83	<0.001*
WC (cm)	76.70 ± 14.83	123.29 ± 17.76	<0.001*
Appropriate	23 (74.2)	0 (0)	<0.001*
Increased risk	8 (25.8)	43 (100)	
WtHR	0.48 ± 0.05	0.74 ± 0.08	<0.001*
Normal	16 (51.6)	0 (0)	<0.001*
High	15 (48.4)	43 (100)	
PBF (%)	26.62 ± 9.39	46.13 ± 30	<0.001*
FM (kg)	17.13 ± 7.12	53.8 ± 13.3	<0.001*
MM (kg)	43.14 ± 9.02	57.43 ± 11.76	<0.001*
FFM in (kg)	45.91 ± 9.27	62.08 ± 11.83	<0.001*
FFMI (FFM kg/m^2)	16.46 ± 2.22	22.77 ± 2.72	<0.001*
FBS (mg/dL) Median (IQR)	92 (87–98)	97 (93.6–104)	0.003*
HDL (mg/dL)	43.63 ± 15.78	41.74 ± 11.05	0.547
LDL (mg/dl)	73.93 ± 20.99	98.65 ± 32.16	<0.001*
TG (mg/dL)	123.24 ± 35.49	128.53 ± 62.07	0.645
TC (mg/dL)	138 (120–159)	161.6 (143–181.7)	0.001*
TC/HDL ratio	3.54 ± 1.10	4.18 ± 1.22	0.022*

*Denotes statistical significance ($p < 0.05$) between groups. Independent-sample t-test was used for normally distributed continuous variables with mean, and SD (Age, BMI, WC, WtHR, PBF, FM, MM, FFM, FFMI, LDL, HDL, TG, TC/HDL-c), Mann–Whitney U-test for skewed continuous variables (FBS, TC) with IQR and medians, and Chi-square test was used for categorical variables. BMI, body mass index; WC, waist circumference; PBF, percentage body fat; FM, fat mass; WtHR, waist-to-height ratio; MM, muscle mass; FFM, fat-free mass; FFMI, fat-free mass index; FBS, fasting blood sugar; HDL, high- density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio.

3.1. Differences in bacterial composition between the obese and lean groups

After filtering for taxa that were present in at least 20% of the samples, the microbiota was composed of eight phyla and 109 genera.

At the phylum level, Firmicutes (50% in lean vs. 47% in obese) and Bacteroidetes (44% in lean vs. 49% in obese) were the two most abundant bacterial phyla in the gut of obese and lean subjects. The obese group had significantly higher abundances of the phyla Verrucomicrobia (0.5% in obese vs. 0.3% in lean, Benjamini-Hochberg correction, q = 0.048), and Saccharibacteira (0.003% in obese vs. 0.0009% in lean, q = 0.0002) than the lean group and significantly lower abundances of the phyla Lentisphaerae (0.03% in obese vs. 0.08% in lean, q = 0.004). However, there was no significant difference in the relative abundance of Bacteroidetes (q = 0.12), Firmicutes (q = 0.32), Fusobacteria (q = 0.2), Actinobacteria (q = 0.54), and Proteobacteria (q = 0.85) among the two groups. Furthermore, there was no significant difference in the F/B ratio between the obese (0.95) and lean group (1.1); p = 0.315 (Supplementary Figures S1A,B; Table 2).

TABLE 2 The gut microbial composition (relative abundance in %) of obese and lean participants (phylum level).

Phylum	Lean (%)	Obese (%)	*q**
Firmicutes	50	47	0.32
Bacteroidetes	44	49	0.12
Proteobacteria	4	3	0.85
Actinobacteria	0.6	0.5	0.54
Verrucomicrobia	0.3	0.5	0.04*
Lentisphaerae	0.08	0.03	0.004*
Fusobacteria	0.0003	0.0001	0.20
Saccharibacteria	0.0009	0.003	0.0002*
F/B ratio	1.1	0.95	0.315

*$q \leq 0.05$ was considered statistically significant.

3.2. Genus level

Taxonomic assignment was also performed at the genus level and revealed a total of 21 major genera with a significant difference between the obese and lean group, where 16 of these belonged to Firmicutes, as depicted in Table 3.

TABLE 3 The difference in bacterial composition (relative abundance in %) between obese and lean subjects (genus level).

Genus	Lean (%)	Obese (%)	q value
Higher in lean subjects			
Clostridiales.vadinBB60.group.D_5-uncultured. Bacterium	0.1	0.01	0.001*
Anaerotruncus	0.3	0.1	0.001*
Ruminococcaceae.D_5__uncultured	0.7	0.2	0.003*
Ruminococcaceae.UCG.014	1	0.4	0.004*
Ruminococcaceae.UCG.010	0.4	0.05	0.008*
Family.XIII.UCG.001	0.03	0.01	0.006*
Erysipelotrichaceae.D_5__uncultured	0.2	0.02	0.007*
Christensenellaceae.R.7.group	2	0.3	0.008*
Rhodospirillaceae.D_5__uncultured	0.5	0.03	0.001*
Victivallis	0.07	0.01	0.002*
Alistipes	3	2	0.04*
Lachnospiraceae.UCG.010	0.2	0.1	0.013*
Ruminococcaceae.UCG.005	1	0.6	0.013*
Ruminococcaceae.UCG.002	2	1	0.02*
Ruminiclostridium.6	0.5	01	0.02*
Lachnospiraceae.D_5__uncultured	0.2	0.1	0.02*
Odoribacter	0.4	0.2	0.03*
Barnesiella	0.6	0.2	0.03*
Lachnospiraceae.NK4A136.group	1	0.9	0.04*
Increased in obese peoples			
Acidaminococcus	0.1	0.7	0.01*
Lachnospira	0.9	2	0.04*

*$q \leq 0.05$ was considered statistically significant.

Of the 21 genera, *Acidaminococcus* and *Lachnospira* (belonging to the Firmicutes phylum) were higher in the obese group, while the remaining 19 were lower, including (a) from the Firmicutes phylum, an uncharacterized taxon in the Clostridiales.vadinBB60.group (q = 0.001), *Anaerotruncus* (q = 0.001), an uncharacterized Ruminococcaceae (q = 0.003), *Ruminococcaceae*.UCG.014 (q

= 0.004), *Ruminococcaceae*.UCG.010 (*q* = 0.008), Family.XIII.UCG.001 (of the Clostridiales order, Family XIII; *q* = 0.006), an uncharacterized Erysipelotrichaceae (*q* = 0.007), *Christensenellaceae*.R.7.group (*q* = 0.008), *Lachnospiraceae*.UCG.010 (*q* = 0.013), *Ruminococcaceae*.UCG.005 (*q* = 0.013), *Ruminococcaceae*.UCG.002 (*q* = 0.02), *Ruminiclostridium*.6 (*q* = 0.02), an uncharacterized Lachnospiraceae (*q* = 0.02), *Lachnospiraceae*.NK4A136.group (*q* = 0.04), and (b) from the Bacteroidetes phylum, *Alistipes* (*q* = 0.04), *Odoribacter* (*q* = 0.03), *Barnesiella* (*q* = 0.03), (c) from the Proteobacteria phylum, an uncharacterized Rhodospirillaceae (*q* = 0.001), and (d) from the Verrucomicrobia phylum, *Victivallis* (*q* = 0.002; Table 3; Figures 1A,B; Supplementary Figures 2A,B).

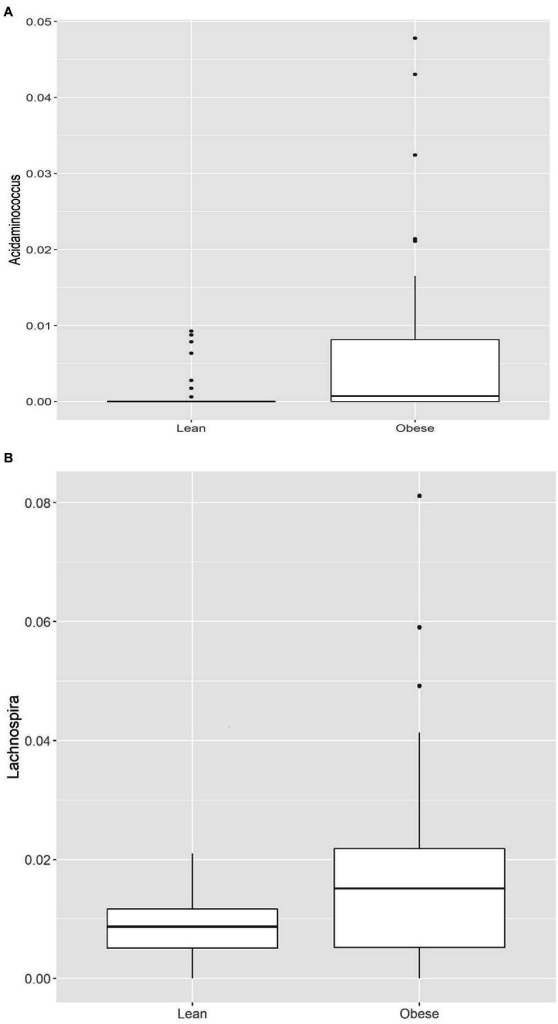


FIGURE 1

(A) Comparison of relative abundance of Acidaminococcus (genus level); **(B)** Comparison of relative abundance of Lachnospira (genus level) between lean and obese participants. *$q < 0.05$.

We performed a Linear Discriminant Analysis Effect Size (LEfSe) on the taxa from the obese and lean groups. A total of 26 genera showed significantly different abundances between the two groups with LDA scores >2. In this case, 23 genera were higher in the lean group, and three genera were higher in the obese group, as shown in Figure 2.

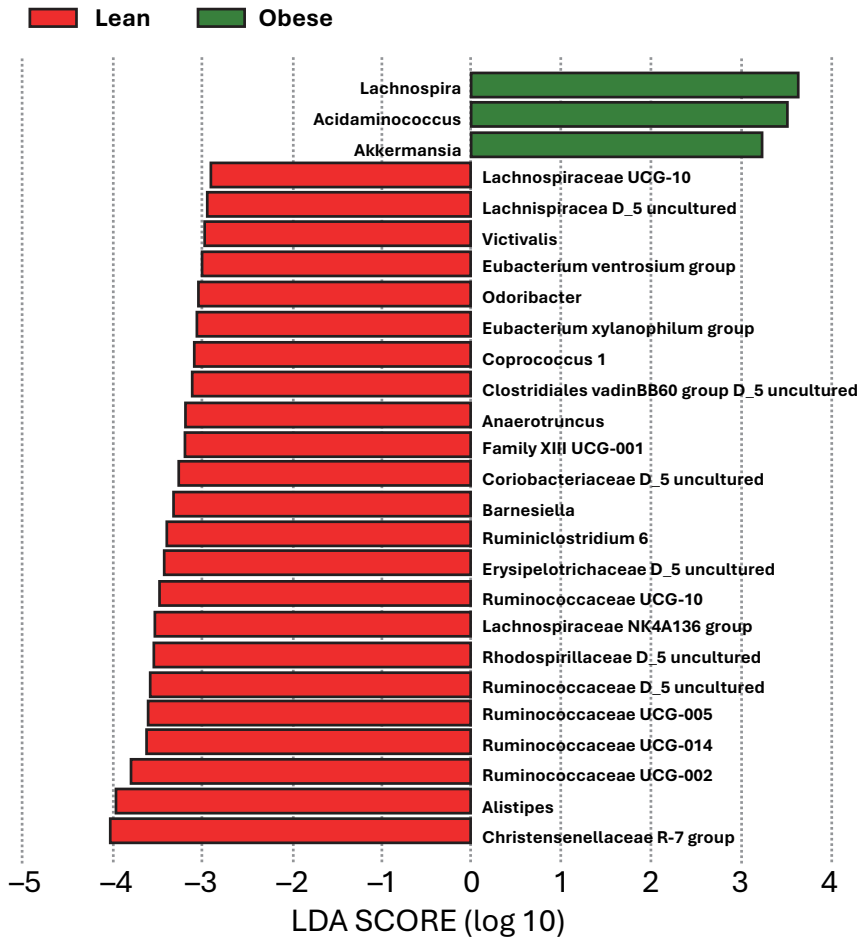


FIGURE 2

LEfSe analysis between the obese and lean groups (LDA score > 2). The LDA score (log10) for the more prevalent genera in the obese group is represented on a positive scale (green), and the LDA score for the more prevalent genera in the lean group is defined on a negative scale (red).

Of the three genera in the obese group, two belonged to Firmicutes (*Lachnospira* and *Acidaminococcus*) and one to Verrucomicrobia (*Akkermansia*). In the Kruskal-Wallis test, the latter was not statistically significant. In contrast, 17, 3, one, one, and one of the 23 genera for the lean group belonged to Firmicutes, Bacteroidetes, Actinobacteria, and Verrucumictobia phyla.

3.3. α- and β-Diversity (microbial diversity and richness, microbial dissimilarities)

According to the α -diversity metrics (Figure 3), obese adults showed significantly lower diversity (Shannon index, p = 0.031), coinciding with the lower observed OTUs (p = 0.006) and lower Chao1 richness estimator (p = 0.008). Furthermore, the obese group showed lower "Faith's phylogenetic diversity (PD; p = 0.069) and lower evenness ('Pielou's evenness, p = 0.53). However, the latter two were not statistically significant.

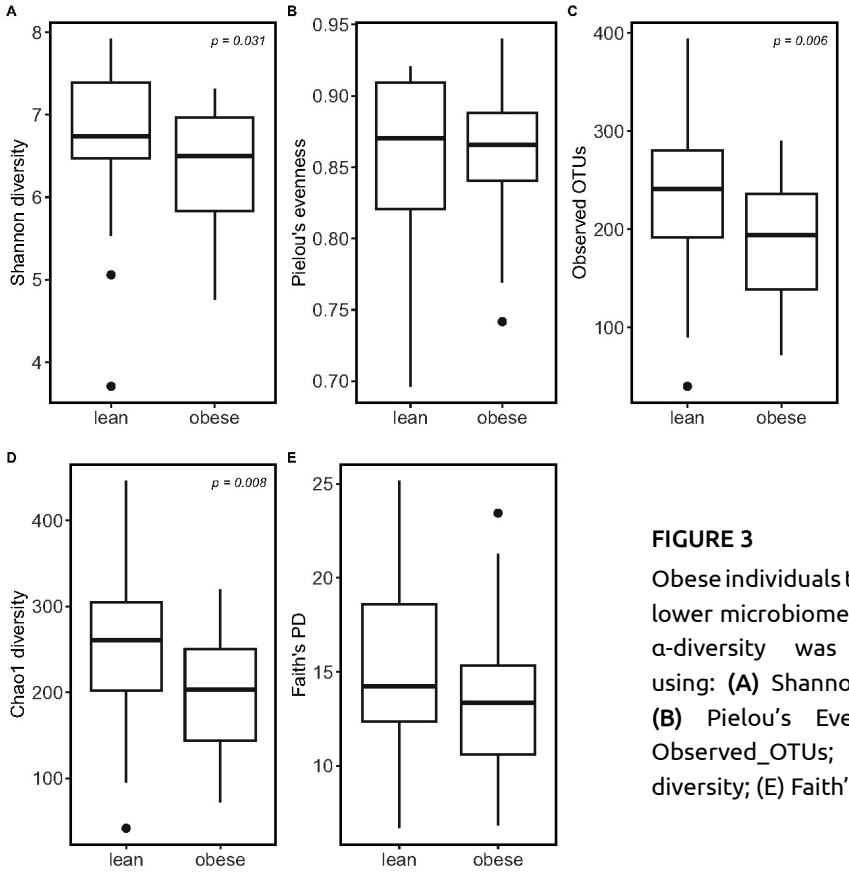


FIGURE 3

Obese individuals tend to have lower microbiome α-diversity. α-diversity was calculated using: **(A)** Shannon diversity; **(B)** Pielou's Evenness; **(C)** Observed_OTUs; **(D)** Choa1 diversity; (E) Faith's PD.

Principal coordinate Analysis (PCoA) based on unweighted UniFrac, weighted UniFrac, Bray–Curtis, and Jaccard showed a marked separation between the gut microbiota community of obese and lean groups, confirmed by the pairwise permanova analysis that indicated a significant difference in β-diversity between the two groups (Figure 4; $p = 0.009$; $p = 0.034$; $p = 0.029$; $p = 0.002$, respectively).

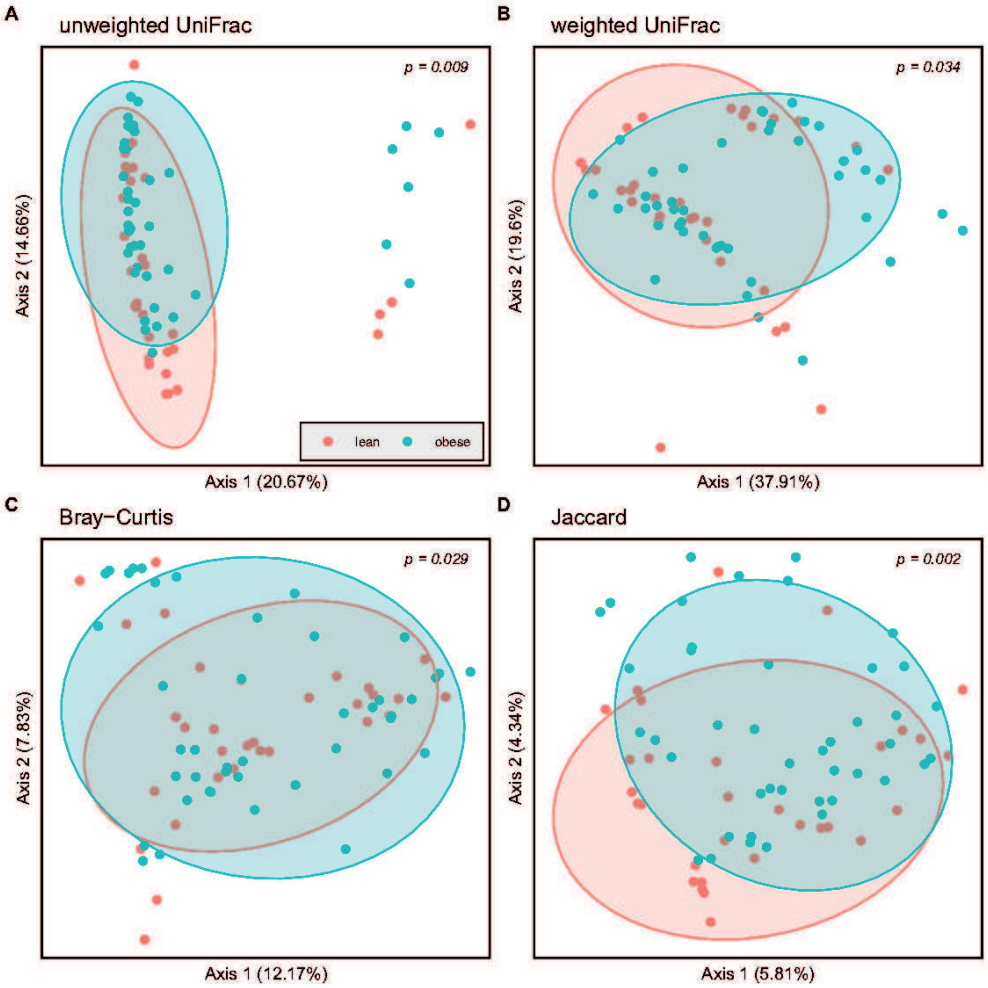


FIGURE 4

Principal coordinate Analysis (PCoA) based on: **(A)** Unweighted UniFrac; **(B)** Weighted UniFrac; **(C)** Bray–Curtis and **(D)** Jaccard; Obese (blue spheres) and lean participants (red spheres).

3.4. Correlation between gut microbiota (at genus level) and clinical variables

Certain microbes were positively or negatively correlated with BMI, WC, WHtR, PBF, and FM. Statistically significant correlations between microbes and anthropometric measurements are provided in (Supplementary Table S2) and the heat map (Figure 5).

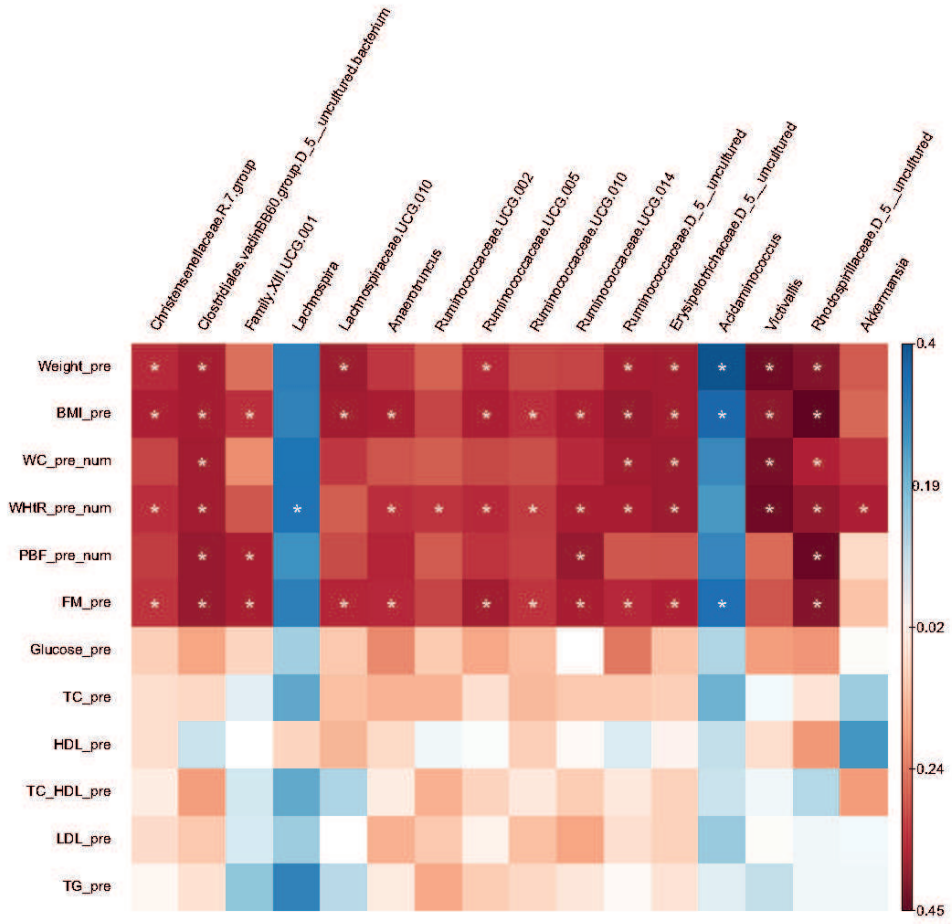


FIGURE 5

Heatmap of Spearman correlation analysis between gut microbiota (at genus level) and clinical variables.

Several taxa that were significantly lower in obese compared with lean using Kruskal–Wallis or LEfSe were negatively correlated with BMI, WC, WHtR, PBF, and FM (uncharacterized Rhodospirillaceae), (uncharacterized Clostridiales.vadinBB60. group), BMI, WHtR (*Victivallis*), BMI, WC and FM (uncharacterized Ruminococcaceae), BMI, WC, WHtR and FM (uncharacterized Erysipelotrichaceae), BMI & FM (*Lachnospiraceae*.UCG.010), BMI, WHtR and FM (*Christensenellaceae*.R.7.group, *Ruminococcaceae*.UCG.005, *Ruminococcaceae*.UCG.010, *Anaerotruncus*), BMI, WHtR, PBF and FM (Ruminococcaceae.UCG.014); BMI, PBF and FM (Family.XIII. UCG.001), WHtR (*Ruminococcaceae*.UCG.002). On the other hand, the taxa which were higher in the obese group presented positive correlations with BMI and FM (*Acidaminococcus*), and WHtR (*Lachnospira*); except for *Akkermansia,* which was prevalent in the obese group (LEfSe) was found to be negatively correlated with WHtR.

No correlations were found between the gut microbiota at the genus level and the following clinical variables: FBS, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Furthermore, There were no correlations with age or gender.

4. Discussion

Recent research on the human gut microbiota has revealed its various roles in health and disease, with obesity being among the many conditions to which changes in the gut microbiota have been linked (Jinatham et al., 2018). Research on gut microbiota and obesity has mainly focused on Western populations, with limited studies on Arabs and almost none on Emiratis. This study pioneered in contrasting the fecal microbial composition of obese and lean Emirati people using 16S rRNA gene sequencing (V3-V4 region) and exploring its association with clinical parameters. It is difficult to compare this with previous studies in Western populations, because also diet, which differs between the Arabic and Western culture, also significantly affects microbiota composition.

To the best of our knowledge, the present cross-sectional study is first to provide insights into the relationships between clinical variables and the gut microbiota in obese and lean Emirati subjects. The α- diversity richness was significantly lower in the obese than the lean Emirate without significant difference in evenness. These data are in line with the majority of available studies (Pinart et al., 2021). Conversely, β-diversity, denoting dissimilarities in gut microbiota composition, showed significant differences between obese and lean; this also agrees with most available studies. Thus, the microbiota in the obese group presented fewer bacterial taxa, and lean samples showed a more diverse gut microbiota profile than obese samples based on Shannon index results. Controversy regarding relative abundance at genus and phylum level in individuals with obesity, compared with lean subjects, was observed.

Moreover, higher genera in the obese group correlated positively with BMI and FM (*Acidaminococcus*) and WHtR (*Lachnospira*). The exception was *Akkermansia* which was more prevalent in the obese group but was negatively associated with WHtR. This is in contrast to other studies (Gao X. et al., 2018; Jinatham et al., 2018), in different populations. On the other hand, genera higher in the lean group correlated negatively with adiposity (BMI, WC, WHtR, and FM).

The structure, function, and diversity of the gut microbiota in subjects with obesity differ from those of lean people (Cheng et al., 2019). In general, people with obesity show lower richness and biodiversity (Turnbaugh et al., 2009; Cotillard et al., 2013; Le Chatelier et al., 2013; Isolauri, 2017) similar to our findings, while Kocełak et al. (2013) and Kasai et al. (2015) found greater diversity richness in individuals with obesity. Le Chatelier et al. reported that subjects with obesity who have low

bacterial richness present more overall adiposity, dyslipidemia, insulin resistance, and higher inflammation compared with obese individuals who have an elevated gut bacterial richness (Le Chatelier et al., 2013; Crovesy et al., 2020). In line with the literature, the present study revealed that Firmicutes and Bacteroidetes were the two most abundant bacterial phyla in the gut of obese and lean subjects without significant differences noted at the level of Firmicutes, Bacteroidetes (Pinart et al., 2021) nor F/B ratio (Castaner et al., 2018; Jinatham et al., 2018) between the two groups. It is well known that Firmicutes and Bacteroidetes predominate the gut microbiome globally (Castaner et al., 2018). Scarce data on the gut microbiota of people in the Arabian Peninsula describe the dominance of Firmicutes and Actinobacteria as phyla in individuals from Saudi Arabia and the preponderance of either Firmicutes or Bacteroidetes in individuals from Kuwait (Plummer et al., 2020).

Of interest, it was believed in early reports that the ratio of Firmicutes and Bacteroidetes differs between lean and obese people, with a high ratio observed in the US (Plummer et al., 2020). However, this was later refuted, and the majority of evidence does not show significant differences in the relative abundance of Firmicutes (Pinart et al., 2021), whereas contradictory findings in the relative abundance of Bacteroidetes persist (Crovesy et al., 2020; Pinart et al., 2021).

The usefulness of a high F/B ratio as an indicator of obesity is still debatable and more complicated than a mere difference in the relative abundance between phyla (Turnbaugh and Gordon, 2009; Venema, 2010; Jinatham et al., 2018). The critical impact of some bacteria on human metabolism may be due to the number of less abundant bacteria or the higher abundance of other ones (Sonnenburg and Backhed, 2016). Gut microbiota geared towards the production of SCFA, rather than a simple increase in F/B ratio, may be associated with an increased energy harvest from ‘one’s diet leading to obesity. Investigating the association between energy harvest related to bacterial SCFA production and obesity is warranted (Venema, 2010; Jinatham et al., 2018). Furthermore, the F/B ratio may be strongly associated with metabolic markers of obesity, such as insulin resistance and metabolic syndrome, instead of obesity (Louis et al., 2016). Based on our results, a high F/B ratio may not be a valid global biomarker of obesity (Houtman et al., 2022). It is more likely that differences at the genus (and even species) level, compared with the phylum level, could be related to changes in metabolic function (Bauer et al., 2016). While significantly higher Lentisphaerae in lean individuals and Saccharibacteria and Verrucomicrobia in the obese group were reported, no differences in the relative abundance of Fusobacteria, Actinobacteria, and

Proteobacteria are observed. The issue of differences between phyla in obese and lean individuals remains controversial in the literature (Pinart et al., 2021).

Similarly, differences between the obese and lean groups at the genus level remain controversial (Crovesy et al., 2020). Interestingly, in our study, the genus Lachnospiraceae NK4A136 was significantly higher in the lean group. Studies in mice suggest that this genus has a protective and anti-inflammatory effect being a potential butyrate producer (Companys et al., 2021). Furthermore, Companys et al. (2021) first identified the genus Lachnospiraceae NK4A136 as a biomarker of leanness in humans. Furthermore, in our study, as shown elsewhere (Gao R. et al., 2018), butyrate-producing Ruminococcus was higher in the lean group, denoting a more diverse microbiome profile.

Moreover, Christensenellaceae.group.7 (Firmicutes phylum) was significantly higher in the lean group. It is usually associated with a low BMI (Castaner et al., 2018), and when transplanted to mice, it promotes a lean host phenotype and positively impacts the diversity of the community (Aguirre and Venema, 2015). The abundance of *Alistipes* was higher in the lean group; this new genus is significantly elevated in high-fat-diet-fed mice than in controls (Yang et al., 2022); individuals with obesity have a higher abundance of *Alistipes* (Crovesy et al., 2020). This aberrant finding may be related to the fact that Emirate adults could have a distinct gut microbiota composition given their varying dietary factors and lifestyle. In UAE, there is a transition towards energy-dense diets high in animal protein, total and saturated fatty acids, and simple sugars (Cheikh Ismail et al., 2020). High-fat diets are linked to considerable changes in the gut microbiota composition at the phylum and genus levels (Rosenbaum et al., 2015).

Our finding of a negative association between the genus *Lachnospiraceae* and PBF and BMI is also reported by Lippert et al. in older adults in Austria (Lippert et al., 2017), but not in a study with human stool from Ghanaian volunteers (Dugas et al., 2018). The negative correlation between bacterial taxa that were dominant in the lean group and the adiposity markers (BMI, WC, WHtR, FM, PBF) is unexpected, considering that most of these taxa belong to the Firmicutes phylum.

In contrast, genera that were higher in obese subjects positively correlated with BMI and FM (*Acidaminococcus*) as well as WHtR (*Lachnospira*), suggesting them as potential microbiota biomarkers of obesity (Companys et al., 2021). In addition, levels of *Acidamonicoccus* positively correlated with type 2 diabetes in the Saudi population (Al-Muhanna et al., 2022). Contrary to our results, a study in overweight adults showed that reduced *Lachnospira* abundance was associated with weight gain (Companys et al., 2021). These conflicting findings may have been

attained because the two genera comprise various species whose role in obesity has not been thoroughly studied; such issues are still debatable (Aguirre and Venema, 2015).

Some of the identified microbial taxa correlated with adiposity but not other biochemical parameters, i.e., glucose and lipid homeostasis markers. It is tempting to assume that taxa showing negative correlations with adiposity are appropriate markers of metabolic health. Nevertheless, larger studies are required to ascertain such relationships (Palmas et al., 2021).

The presence of divergent results between this study and other studies in the literature might be attributed to the geographical location of the studies, given dietary and environmental variations known to affect gut microbiota (Al-Muhanna et al., 2022) or to many other factors, such as the population under study, gender, physical activity, drugs, ethnicity, and the season, as well as methods used to analyze the gut microbiota, such as different DNA extraction techniques, different areas of the 16S rRNA gene sequenced and primers used. The composition of the gut microbiota can be easily influenced, and all factors that affect it are difficult to control (Crovesy et al., 2020). The majority of available studies did not evaluate factors that can affect the gut microbiota, such as diet, physical activity, smoking, stress, and sleep, which might explain the possible differences found between studies (Rosenbaum et al., 2015; Aljazairy et al., 2022). Amongst these, the diet is likely to greatly impact the gut microbiota composition (Crovesy et al., 2020).

4.1. Strengths and limitations

This study provides meaningful insight into the relationship between gut microbiota and obesity, specifically in Emirati adults, and is a useful addition to the international microbiome reference dataset. Yet, this study is limited by its relatively small sample size. Furthermore, we did not adjust for a potential confounding factor such as dietary intake, hindering our ability to link unique gut microbiota profiles with specific diets. Finally, our results should be interpreted cautiously as they are based on observational data.

5. Conclusion

We revealed significant differences in microbiota between obese and lean subjects at phylum and genus levels. Remarkably, our study showed no significant differences in Firmicutes and Bacteroidetes or F/B ratio, suggesting that F/B cannot be used as a universal predictor biomarker for obesity in adults. Genera that were higher in obese subjects correlated positively with BMI and FM (Acidaminococcus) as well as WHtR (Lachnospira) and are genera that might serve as microbiota biomarkers of obesity in Emerati. In contrast, genera higher in the lean group correlated negatively with adiposity. Future studies are needed to confirm our results and to understand better the interplay between diet, lifestyle, gut microbiota, and health. Whether changes in the gut microbial composition are a cause or a consequence of obesity remains an open question.

Data availability statement

The raw sequences and corresponding metadata have been archived in the Sequence Read Archive (SRA) repository at the NCBI under accession number PRJNA962831: http://www.ncbi.nlm.nih.gov/bioproject/962831.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical approval was granted by the Research Ethics Committee of the Ministry of Health and Prevention of UAE (MOHP/DXB-REC-52/2018), the Dubai Health Care Regulatory Research Ethics Committee (DHCR-REC), and the Zayed University Ethical Committee Board (ZU19_51_F). The study followed the Declaration of Helsinki. Written informed consent was collected from all study subjects. The patients/participants provided their written informed consent to participate in this study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MA, MK, and KV: conceptualization, methodology, and data curation. MA and KV: software and supervision. MK, KV, and CM: validation. MA: formal analysis, investigation, and writing – original draft preparation. MK, KV, CM, GW, and TM: resources and writing – review and editing. MA, MK, KV, CM, GW, and TM:

visualization. MK and KV: project administration. CA and KV: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2023.1182460/full#supplementary-material

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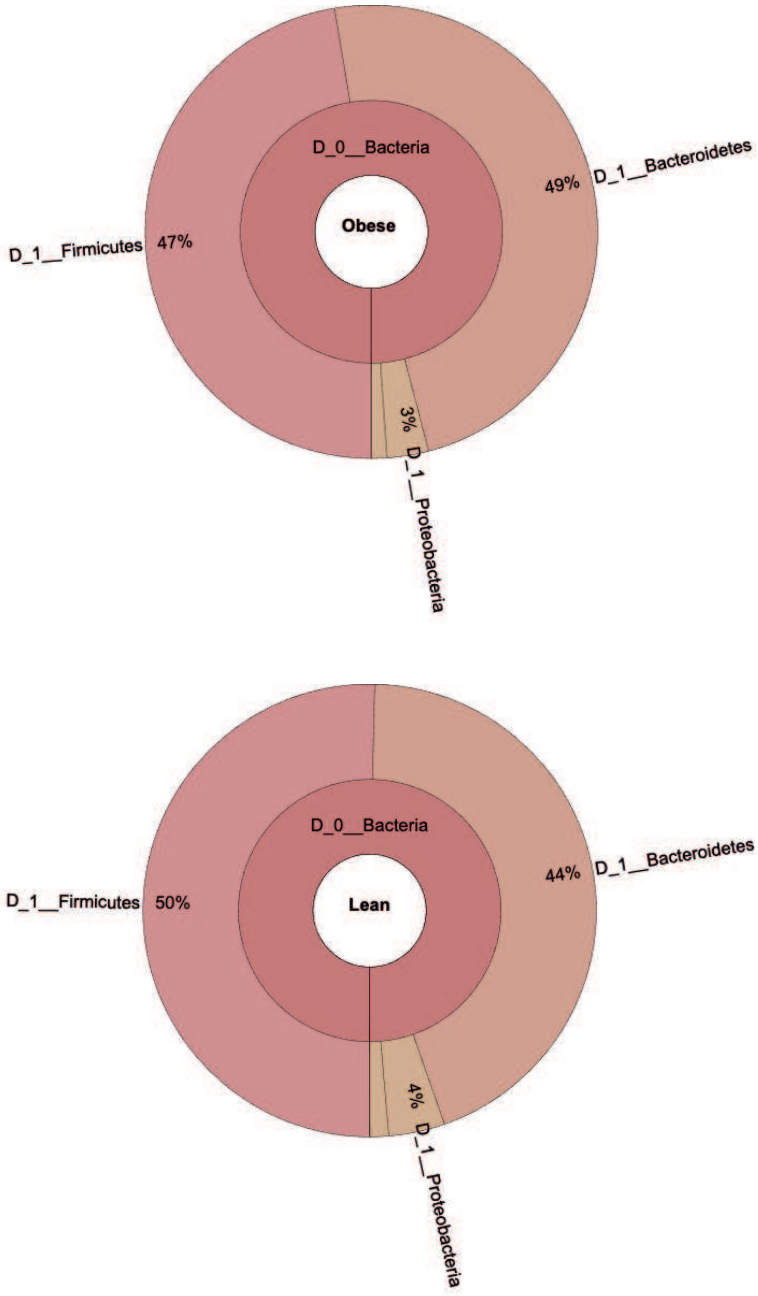
Supplementary Materials

Supplementary Table 1. Lifestyle factors for obese and lean participants

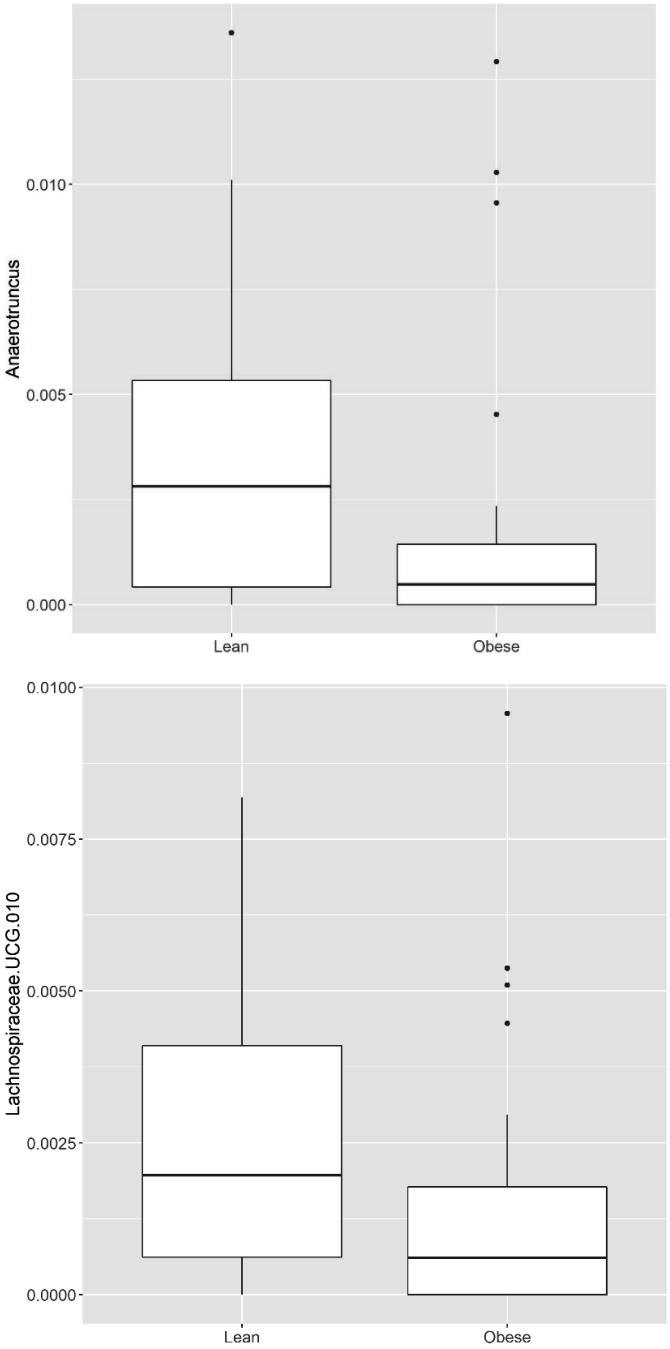
Lifestyle factors	Lean (n=31)	Obese (n=43)	p-value
Probiotic Supplement - Yes, n (%)	1 (3.2)	0 (0)	0.236
Fiber Supplement - Yes, n (%)	0 (0)	2 (4.7)	0.223
Probiotic Food Consumption - Yes, n (%)	24 (77.4)	29 (67.4)	0.348
Probiotic Food Consumption Frequency- n (%)			0.138
None	5 (16.1)	15 (34.9)	
2 or less/per week	16 (51.6)	13 (30.2)	
3 to 6/week	9 (29)	11 (25.6)	
7 or more/week	1 (3.2)	4 (9.3)	
Prebiotic Supplement - Yes, n (%)	1 (3.2)	0 (0)	0.236
Smoker - Yes, n (%)	3 (9.7)	12 (27.9)	0.054
Alcohol consumption - Yes, n (%)	0 (0)	2 (4.7)	0.223
Physical activity level			<0.001*
Sedentary	0 (0)	6 (14)	
Light	12 (38.7)	31 (72.1)	
Moderate	1 (3.2)	2 (4.7)	
High	18 (58.1)	4 (9.3)	

Supplementary Table 2. Spearman correlation coefficient (rho) for the taxa showing significant correlations with clinical data

	BMI	WC	WHtR	PBF	FM
Genus	**Rho**	**Rho**	**rho**	**rho**	**Rho**
uncharacterized Rhodospirillaceae	-0.44	-0.35	-0.38	-0.43	-0.40
Victivallis	-0.39	-0.42	-0.42		
uncharacterized *Ruminococcaceae*	-0.38	-0.37	-0.36		-0.34
uncharacterized *Erysipelotrichaceae*	-0.37	-0.37	-0.38		-0.35
Lachnospiraceae.UCG.010	-0.37	-			-0.34
uncharacterized *Clostridiales.vadinBB60. group*	-0.36	-0.37	-0.37	-0.38	-0.38
Anaerotruncus	-0.36	-	-0.33	-	-0.34
Acidaminococcus	0.36	-		-	0.34
Christensenellaceae.R.7.group	-0.36	-	-0.33	-	-0.33
Ruminococcaceae.UCG.005	-0.35	-	-0.33	-	-0.37
Ruminococcaceae.UCG.014	-0.35	-	-0.36	-0.38	-0.36
Family.XIII.UCG.001	-0.33	-		-0.36	-0.36
Ruminococcaceae.UCG.010	-0.33	-	-0.31	-	-0.32
Ruminococcaceae.UCG.002	-	-	-0.32	-	-
Akkermansia	-	-	-0.36	-	-
Lachnospira	-	-	0.34	-	-



Supplementary Figure 1: (A) Average phylum distribution of gut microbiota of obese participants. (B) Average phylum distribution of gut microbiota of lean participants.



Supplementary Figure 2. (A) Comparison of relative abundance of *Anaerotruncus* (genus level); (B) Comparison of relative abundance of *Lachnospiraceae.UCG.010* (genus level) between lean and obese participants. *q < 0.05

4

Chapter 4

Changes in energy homeostasis, gut peptides, and gut microbiota in Emiratis with obesity after bariatric surgery

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Abstract

Background

Obesity is a growing health concern worldwide, including United Arab Emirates. Bariatric surgery is an effective treatment option, with to date unclear weight loss mechanisms. In this prospective study, we explored post-bariatric surgery changes in energy homeostasis, gut peptides, hormones, and gut microbiota.

Method

We recruited 19 Emirati adults who were planning to undergo sleeve gastrectomy (SG). We assessed the energy requirements using 24-hour diet recalls, indirect calorimetry for resting energy expenditure (REE), and a questionnaire for appetite.

Anthropometrics included body mass index (BMI), waist circumference, waist-to-height ratio, fat mass, fat-free mass, and percentage of body fat. Gut peptides, including peptide YY (PYY), glucagon-like peptide-1/2 (GLP-1/2), ghrelin (GHR), cholecystokinin (CCK), insulin, and leptin, were quantified using ELISA. Gut microbiota composition at phylum and genus levels, including the Firmicutes/Bacteroidetes (F/B) ratio and alpha (α) and beta (β) diversity, was determined by sequencing amplicons of the V3-V4 region of the 16S rRNA at baseline and three months post-surgery. Comparisons used paired sample T-test, Wilcoxon, and McNemar test. QIIME 2 was used to identify taxa and their relative abundance; subsequent analyses were done in R for (α) and (β) diversity (package qiime2R) and Wilcoxon signed-rank test in R for differences in microbiota at phylum and genus levels. We conducted Spearman correlation analyses between genera and energy homeostasis, appetite, anthropometrics, hormones, and gut peptides.

Results

At three months post-SG, energy intake, appetite, all anthropometric indices, insulin, leptin, and GLP-1 significantly decreased; PYY and GHR significantly increased, and REE was stable. β-diversity of the gut microbiota and its composition at phylum and genus levels significantly changed post-surgery, yet F/B remained constant. Energy intake, BMI, and appetite negatively correlated with several taxa that significantly increased post-SG.

Conclusion

Gut peptides, hormones, and microbiota change partly account for bariatric surgery's weight-loss benefits. Understanding these alterations can inform personalized interventions targeting obesity.

Introduction

Obesity rates have dramatically increased over the last two decades [1]. By 2023, it is anticipated that more than one billion individuals globally will be affected by this trend [2]. The situation is not different in the Arabian Gulf countries such as the United Arab Emirates (UAE), where obesity prevalence is believed to have at least doubled between 1989 and 2017 [3], reaching 24% among males and 40% among females [4].

In addition to diet, lifestyle, and genetics, gut microbiota has surfaced as a potential factor influencing obesity and related metabolic disturbances [5,6]. Proposed mechanisms involve the gut microbiota's impact on gut peptides, appetite, energy balance, and fat storage [7–12] through a bidirectional signaling axis known as the "microbiota-gut-brain axis" [10,13].

Given the rising prevalence of obesity and the challenges of adhering to lifestyle, dietary, and pharmacotherapy interventions [14], bariatric surgery has gained recognition as an effective long-term adjunct for managing obesity and its associated comorbidities [15,16]. Bariatric surgery can be restrictive or malabsorptive [17]. Sleeve gastrectomy (SG) is a restrictive surgery. The precise mechanisms responsible for weight loss and metabolic alterations associated with SG have not been entirely clarified. Nonetheless, potential factors that may play a role include changes in food preferences, decreased food intake, heightened satiety, improved gastric emptying, reduced nutrient absorption, and increased energy expenditure [18–22]. These mechanisms may, in part, be a result of post-bariatric surgery alterations in gut peptides such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) [23–27], and, as mentioned above, these could be influenced by the gut microbiota. Recent findings indicate a substantial modification in the composition and diversity of the gut microbiota after bariatric surgery. Key reported changes encompass increased levels of Proteobacteria [new nomenclature Pseudomonadota] and Bacteroidetes [Bacteroidota] [28–30], reduced levels of *Clostridium* and the overall Firmicutes [Bacillota] phylum [29,31,32], and variations in *Bacteroides* and *Prevotella* based on the consumed diet [33–36]. The composition and diversity of the gut microbiota are thought to play a significant role in weight regulation [37]. Specifically, a higher Firmicutes to Bacteroidetes ratio (F/B), referring to the relative abundance or proportion of the two major phyla of bacteria in the human gut microbiota, has been linked to obesity [38], although there is no consensus on the use of this ratio [39,40]. Ethnicity

greatly influences microbiota composition and diversity [41,42], making it crucial to conduct ethnic-specific research. In this context, we embarked on a prospective study to explore the effect of SG on energy homeostasis, gut peptides, hormones, and gut microbiota in a sample of Emiratis with obesity. We aim to understand the unique mechanisms relevant to weight loss following SG, beyond the restrictive effect of the surgery on food intake. Through an in-depth exploration of these mechanisms, we aspire to lay the groundwork for formulating less invasive anti-obesogenic treatment strategies.

Materials and methods

As illustrated in the supporting information (S1 Flow Chart).

Study design

The study design involved a three-month prospective, pre-post investigation.

We recruited Emiratis with obesity undergoing SG from two hospitals in the UAE, one in Sharjah and one in Dubai, between October 27, 2019, and March 26, 2021.

The study was registered in ClinicalTrials.gov (ID: NCT04200521)

Sample size calculation

The sample size was determined by the F/B ratio, which is the principal consequence of this research. By employing traditional calculations based on normal distributions and the findings of Damms-Machado et al., in which the mean (SD) fecal F/B changed significantly from 5.9 (2.1) to 10.4 (1.4) in the three months after bariatric surgery [29], it was determined that a sample size of two patients would be sufficient to achieve 80% power at a two-sided 5% significance level to identify an effect of comparable magnitude. Considering the anticipated high dropout rate, the minimal sample size was multiplied by 15. Thus, we targeted thirty adult Emiratis with obesity of both sexes and resided in the UAE intending to undergo SG. A total of 43 eligible participants were recruited; however, only 19 of them underwent SG and were subsequently included in the study.

Informed consent

Information for participants. We provided each participant with an information sheet that detailed the purpose, duration, procedures, and protocols involved,

potential risks and benefits, and their rights as participants, including the right to withdraw at any time without penalty.

Consent process. The consent process involved training the research staff, explaining the study in detail, answering any questions, and ensuring that participants fully understood the information provided. We conducted this interaction in the participants' preferred language to ensure their comprehension.

Documentation. Participants who agreed to take part in the study signed a written informed consent form. We securely stored these forms to ensure confidentiality and adhere to ethical standards.

Ethical considerations

The Dubai Health Care Regulatory Research Ethics Committee (DHCR-REC), the Research Ethics Committee of the Ministry of Health and Prevention of the UAE (MOHP/DXB-REC-52/2018), and the Zayed University Ethical Committee Board (ZU19_51_F) granted ethical approvals for the study. Before enrollment, written informed consent was obtained from all patients. In studies involving human subjects, every procedure was conducted in adherence to the ethical principles set forth by the relevant national and institutional research committees, in addition to the 1964 Helsinki Declaration.

Inclusivity in global research

Additional information regarding the ethical, cultural, and scientific considerations specific to inclusivity in global research is included in the Supporting Information (S1 Checklist).

Inclusion criteria

Patients determined to undergo sleeve gastrectomy (SG) by the multidisciplinary team at the partner hospitals were evaluated for their eligibility for the study by the research team. Inclusion criteria entailed Emirati participants residing in the UAE, with stable body weight for the past three months and free of antibiotics for at least three months, aged between 18 to 60 years, of either sex, with a body mass index (BMI) of ≥ 35 kg/m2, and consenting to participate in the study.

Exclusion criteria

The study excluded individuals who were either pregnant or nursing during that period.

Additionally, we excluded individuals who had used antibiotics within the

previous three months due to potential alterations in gut microbiota composition that could influence study results. We also excluded participants who experienced significant weight loss of 5% or more in the three months before surgery, as this could potentially impact baseline metabolic parameters.

Moreover, individuals with excessive alcohol consumption, defined as exceeding two standard drinks per day for males and one standard drink per day for females, were excluded from the study [43].

Study variables

General demographics and medical history. The subsequent information was gathered: age, sex, comorbidities (including hypertension, dyslipidemia, diabetes mellitus type 2 (T2DM), and cardiovascular disease), surgical history within the previous five years, weight loss of at least 5% over the previous three months, present medication usage (including antibiotic consumption), prebiotic and probiotic supplement consumption, nutritional supplement intake, and level of physical activity.

We analyzed physical activity levels using two questions from the initial screening questionnaire. “Do you integrate physical activity into your daily routine?” and “Do you incorporate any exercise program?” required a “yes” or “no” response. Sedentary was defined as “no” to both questions, light physical activity as “yes” to the first question, moderate physical activity as “yes” to the second question, and high physical activity as “yes” to both.

Nutritional assessment. Anthropometrics: The participant’s body weight was determined to the nearest kilogram using a portable Seca 762 scale (Vogel & Halke, Hamburg, Germany) while fasting and wearing lightweight apparel, and removing their footwear. Height was determined to the nearest millimeter using a portable Seca stadiometer while they were shoeless. BMI was calculated as weight (kg)/ height (m2). Using measuring tapes (Seca 201- Ergonomic circumference measuring tape), the waist circumference (WC) was determined at the midpoint, halfway between the right iliac crest and the lower costal region, with an accuracy of 0.1 cm [44]. The WC was then, classified and categorized as appropriate or increased based on the cut-off points of < 94 cm and ≥ 94 cm for males and < 80 and ≥ 80 cm for females, respectively [45]. Waist-to-height ratio (WHtR) was determined by dividing WC by height in centimeters; abdominal obesity was defined as a WHtR value of 0.5; a WHtR value below 0.5 was regarded as normal [46].

Body composition: Percentage body fat (PBF), fat mass (FM), and fat-free mass (FFM) were evaluated using a bioelectrical impedance analyzer (BC-420 MA, Tanita Corporation, Tokyo, Japan), following the manufacturer's instructions. We defined elevated PBF among males and females using cut-offs of ≥ 25% and ≥ 35%, respectively [47].

Resting energy expenditure (REE): Resting energy expenditure was assessed using a portable indirect calorimeter (Metabolic Analyser-Indirect Calorimetry; Breezing, Halberstadt, Germany). We conducted this measurement under resting conditions, requiring participants to refrain from eating or drinking for a minimum of 2 hours before the analysis.

Before each measurement, the breezing device was calibrated according to the manufacturer's instructions. Calibration involved setting up the device to accurately measure oxygen (VO2) and carbon dioxide (VCO2) levels. Participants were instructed to wear a mouthpiece provided with the calorimeter. A nose clip was utilized to ensure that participants breathed exclusively through the mouth, minimizing the risk of air leakage and optimizing measurement accuracy. Participants stayed in a comfortable position to minimize movement. The device continuously records gas exchange data during a designated period of normal breathing (3 minutes). Finally, the collected data is analyzed by the device's software to determine participants' REE by analyzing the oxygen and carbon dioxide content of breath. This process provides a reliable assessment of their resting metabolic rate [48].

Food intake: Was assessed using three 24-hour dietary recalls, during which the patient described and quantified the foods and beverages over the past 24 hours for three consecutive days, including two weekdays and one weekend day. During the interview, the dietitian probed the participants more than once to cover forgotten eating occasions and foods and assisted the participant in estimating portion size to provide comprehensive information about the intake. Daily energy (Kcal) and fiber intakes (g/1000 Kcal) were calculated using the food composition database of the Nutritics software (using the Middle Eastern version of their software program).

Appetite: The assessment was conducted using the Simplified Nutritional Appetite Questionnaire (SNAQ) [49]. SNAQ is a quick and easy-to-administer self-assessment screening tool composed of four items (1, 2, 4, and 6) of the Council

on Nutrition Appetite Questionnaire (CNAQ). These items assess appetite, satiety, the taste of food, and the number of meals per day, whereby each question has five letter answer options ranging from a to e, which respectively stand for a = 1; b = 2; c = 3; d = 4, and e = 5. The sum of these items constitutes the SNAQ score, which ranges from 4 to 20, with higher scores indicating better appetite and a lower risk of malnutrition. A cut-off of fourteen indicates a risk of malnutrition and predicts a significant risk of at least 5% weight loss within six months.
We translated the questionnaire into Arabic according to international procedures [50].

Two independent translators first translated it both forward and backward, compared the two versions, and made necessary adjustments to the Arabic version.

Postoperative bariatric diet meal planning (S1 File**):** Participants start with clear liquids (Stage 1) and advance to full liquids (Stage 2) within several days post-surgery, ensuring at least 60 ounces (1,800 cc) of fluid intake daily to avoid dehydration. They then progress through pureed foods (Stage 3), soft foods (Stage 4), and finally all solids (Stage 5) throughout 4 to 6 weeks, with typical daily caloric intake increasing from 400 kcal/day initially to 1,200– 1,500 kcal/day several months post-surgery [51].

Biochemical evaluation

Gut peptides (total GLP-1, GLP-2, PYY, CCK, GHR) and hormones (insulin and leptin). A total of 3 vacutainers of ethylenediaminetetraacetic acid (EDTA) tubes of venous blood samples were collected after a 12-hour overnight fast by a registered nurse/phlebotomist using a 22-gauge needle. We immediately stored the collected blood in EDTA-coated tubes on ice and centrifuged it at 3000 rpm for 15 minutes at a refrigerated temperature. Then, plasma was collected and stored at –20 ºC for later analysis at the Research Institute for Medical and Health Sciences (RIMHS), Sharjah University. Total GLP-1, GLP-2, PYY, GHR, insulin, and leptin were measured using sandwich-based enzyme-linked immunosorbent assay (ELISA) kits (Diametra Millipore, St. Louis, Missouri, USA). We measured CCK using a competitive ELISA kit from ABclonal Technology (Wuhan, China), adhering to the manufacturer's instructions. The minimum detectable concentrations of these assays are 1.5 pm; 0.3 ng/ml; 6.5 pg/mL; 50 pg/mL; 2 μ U/mL; 0.2 ng/mL, 4.93 pg/ml for GLP-1, GLP-2, PYY, GHR, insulin, leptin, and CCK, respectively.

The measurement of fasting plasma glucose (FPG) levels was conducted following the manufacturer's instructions using a portable Lux Metre Blood Test (Biochemical Systems International, S.p.A.; Arezzo, Italy). In addition, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was computed by multiplying fasting serum insulin (mU/mL) by FPG (mg/dL) and dividing the result by 405 [52]. HOMA-IR values exceeding 1.8 were regarded as suggestive of insulin resistance [53].

Gut microbiota

Stool sample collection. Stool samples were self-collected into Zymo (DNA/RNA) Shield™ fecal collection tubes and stored at room temperature without refrigeration. From each participant, two samples were obtained: one was subjected to analysis, and the other one was retained to verify accuracy. Collection of samples adhered to established protocols. To collect 1 gram of feces, a spoon was affixed to the cap of each collection tube, which was pre-filled with 9 ml of DNA/RNA Shield™. We collected sixty-two stool samples from the 43 eligible subjects three days pre-surgery and from the 19 included participants three months post-operatively. The analysis included paired samples from the nineteen participants who underwent SG.

DNA isolation and sequencing of amplicons of the V3–V4 region of the 16S rRNA gene. The DNA isolation and sequencing of the barcoded amplicons of the V3-V4 region of the 16S rRNA gene were performed by the established protocols supplied by Illumina (Illumina, Eindhoven, The Netherlands) [54]. The steps taken were as follows: the sequencing procedure was executed utilizing the Illumina MiSeq system (San Diego, CA, USA), employing barcodes, and the 2x300 bp protocol. The software Quantitative Insights Into Microbial Ecology (QIIME 2) (https://qiime2.org) software [55] was utilized to analyze the raw sequences. The latter were classified utilizing the Silva database (version 132) as the reference database for the 16S rRNA gene.

We filtered the reads and took only those included in at least 20% of the samples. We use the old nomenclature for phyla, providing new names in brackets in the text for proper comparison with previous literature.

Diversity analysis. α Diversity indices: The following diversity indices (Observed Operational Taxonomic Units (OTUs), Chao1 index, Phylogenetic diversity (Faith's PD), Pielou's evenness, and Shannon diversity index) were calculated with QIIME 2

and displayed in R Studio using the R software (4.1.x) (R Core Team, http://www.R-project.org): We created boxplots using the ggplot2 package for R. We set the depth of rarefication at 3800.

β Diversity indices: Principal Coordinate Analysis (PCoA) was performed using QIIME2 software to visualize dissimilarities in β-diversity. The analysis utilized Unweighted UniFrac, Weighted UniFrac, Bray-Curtis dissimilarity, and Jaccard similarity matrices and were converted to 2D-plots in R using the phyloseq package. Eigenvalues were computed to determine the variance explained by each principal coordinate.

We used Permutational Multivariate Analysis of Variance (PERMANOVA) [56] to assess the statistically significant differences in β diversity between the two groups.

When there were more than two categories, we used the non-parametric Kruskal-Wallis method to calculate the p-value in pairwise comparisons for the diversity between each category.

The non-parametric Wilcoxon signed-rank test for paired samples corrected with the Benjamini–Hochberg false discovery rate (FDR) for multiple comparisons was used in R to analyze differences in microbiota in participants pre- and post-surgery (at phylum and genus levels). The composition of the two groups was visualized using the Krona tool (https://github. com/marbl/Krona/wiki/KronaTools). We calculated the F/B ratio by dividing the relative abundances of Firmicutes and Bacteroidetes.

We investigated the microbial taxa with differential abundances between pre- and post-surgery using linear discriminant analysis (LDA) effect size (LEfSe) (version 1.0 http://huttenhower.sph.harvard.edu/galaxy/). Taxa in each group were deemed enriched if their absolute log10 LDA scores were greater than 2.

A Spearman correlation analysis, for non-parametric data, as is usual for microbiota analyses, was carried out between genera and continuous variables (BMI, WC, WHtR, PBF, REE, energy intake, fiber intake/1000 kcal, appetite, insulin, leptin, GLP1, GLP2, PYY, CCK, and GHR) to pinpoint the microorganisms that correlated positively or negatively with surgical results. The Spearman rho ranges between values of | 0.20 | and | 0.39 | ; | 0.4 | and | 0.69 | ; | 0.70 | and | 0.89; | 0.90 | and | 1.00 | denote a weak, moderate, strong, and very strong correlation, respectively [57]. At a cut-off of < 0.05 for q-values (adjusted p-values after the False Discovery Rate (FDR) correction), were considered significantly different. We generated a Spearman correlation analysis heatmap in R software using the corrplot package.

Statistical analysis

The general characteristics of the participants were analyzed utilizing version 21 of the Statistical Package for the Social Sciences software (SPSS Inc. Chicago, IL, USA). The normality of the data was assessed using the Shapiro-Wilk test before selecting the appropriate statistical analyses. The Shapiro-Wilk test evaluates the null hypothesis (H_0) that the data follows a normal distribution. A P-value greater than 0.05 indicates that we fail to reject the null hypothesis, suggesting that the data does not significantly deviate from normality and can be considered normally distributed (weight (W = 0.94; p = 0.32), BMI (W = 0.95; p = 0.44), WC (W = 0.96; p = 0.58), WHtR (W = 0.97; p = 0.84), fat mass (FM) (W = 0.9; p = 0.06), fat-free mass (FFM) (W = 0.92; p = 0.15), PBF (W = 0.96; p = 0.61), REE (W = 0.95; p = 0.48), EI (W = 0.95; p = 0.44), Fiber intake (W = 0.94; p = 0.29), Fiber/1000Kcal (W = 0.94; p = 0.27), appetite score (W = 0.94; p = 0.32), HOMA-IR (W = 0.92; p = 0.14), GLP1 (W = 0.95; p = 0.54), GLP2 (W = 0.94; p = 0.3), CCK (W = 0.92; p = 0.15), leptin (W = 0.92; p = 0.16), insulin (W = 0.95; p = 0.52), and GHR (W = 0.94; p = 0.36)). Conversely, a P-value less than 0.05 means we reject the null hypothesis, indicating that the data significantly deviates from normality and should be considered non-normally distributed (FPG (W = 0.54; p < 0.001) and PYY (W = 0.9; p = 0.001)).

Continuous variables are presented as mean ± standard error (SE) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. Within-subject changes after bariatric surgery were evaluated by a paired sample T-test for normally distributed continuous variables, the Wilcoxon signed-rank test (NPT) for non- normally distributed data, and the McNemar test for categorical variables. A two-tailed p-value less than 0.05 was deemed to indicate statistical significance.

Results

Effects of bariatric surgery on anthropometrics and plasma levels of gut hormones

The baseline characteristics of the participants are detailed in Table 1 along with the study variables comparing the conditions before and after bariatric surgery.

Table 1. Demographics, anthropometrics, and biochemical parameters between pre- and post-bariatric surgery (n = 19).

Variable	Pre-surgery	Post-surgery	Std. error mean and 95%confidence interval of the difference (CI lower, upper %)	p-value	Statistical test (t/Z)
Age (years) (M ±SE)	29.78 ± 2.2	–	–	–	–
Sex n (%)					
Female	12 (63.2)	–	–	–	–
Male	7 (36.8)	–	–	–	–
Weight (kg) (M ± SE)	120.33 ± 7.37	98.38 ± 6.57	1.3 (19.21, 24.67)	<0.001[a]	t = 16.87
Height (cm) (M ± SE)	166 ± 2.31	–	–	–	–
BMI (kg/m^2) (M ± SE)	43 ± 1.98 (10)	35 ± 1.83	0.38 (6.98, 8.59)	<0.001[a]	t = 20.36
WC (cm) (M ± SE)	126 ± 4.84	111 ± 4.94	1.46 (12, 18)	<0.001[a]	t = 9.97
WHtR (M ± SE)	0.75 ± 0.02	0.66 ± 0.02	0.009 (0.06, 0.10)	<0.001[a]	t = 9.53
FM (kg) (M ± SE)	54 ± 3.92	38 ± 3.58	1.65 (12.5, 19.5)	<0.001[a]	t = 9.69
FFM (kg) (M ± SE)	61 ±2.83	56 ± 2.64	0.99 (3.3, 7.5)	<0.001[a]	t = 5.43
PBF (%) (M ± SE)	46 ± 1.42	40 ± 1.86	1.22 (4, 9)	<0.001[a]	t = 5.44
REE (Kcal) (M ± SE)	1679 ± 82.96	1805 ± 53.92	−75.1 (−284, 32)	0.110	t = −1.68
Energy Intake (kcal) (M ± SE)	2454 ± 171.7	756 ± 67.6	155.27 (1372, 2024)	<0.001[a]	t = 10.93
Fiber Intake (g) (M ± SE)	12 ± 1.43	5.9 ± 0.86	0.85 (4.2, 7.8)	<0.001[a]	t = 7.04
Fiber g/ 1000 Kcal (M ± SE)	5 ± 0.51	7.5 ± 0.71	0.71 (−4.1, −1.1)	0.002[a]	t = −3.65
Appetite (M ± SE)	16.58 ±0.37	11.74 ± 0.5	0.61 (3.5, 6.1)	<0.001[a]	t = 7.83
FPG (mg/dl) (Mdn (IQR))	98 (12.88)	98.5 (16.25)	–	0.896	Z = −0.13
HOMA-IR (M ± SE)	7 ± 1.12	2.5 ± 0.5	0.75 (2.9, 6.06)	<0.001[a]	t = 5.91
Insulin (mU/mL) (M ± SE)	25 ± 2.91	9 ± 1.59	2.32 (11.01, 20.8)	<0.001[a]	t = 6.83
Leptin (ng/mL) (M ± SE)	45 ± 2.77	28 ± 2.91	1.57 (13.54, 20.14)	<0.001[a]	t = 10.71
GLP1 (pM) (M ± SE)	25 ± 2.67	12 ± 1.23	2.27 (8.18, 17.74)	<0.001[a]	t = 5.7
GLP2 (ng/mL) (M ± SE)	2.6 ± 0.24	1.96 ± 0.2	0.123 (0.36, 0.88)	<0.001[a]	t = 5.07
PYY (pg/mL) (Mdn (IQR))	48 (17.01)	116 (22.1)		<0.001[a]	Z = −3.54
CCK (pg/mL) (M ± SE)	69.5 ± 6.71	54.86 ± 3.38	6.07 (2, 27.5)	0.026[a]	t = 2.42
GHR (pg/mL) (M ± SE)	568 ± 15.01	693 ± 41.98	42.26 (−215, −37)	0.008 [a]	t = −2.97

[a]Denotes statistical significance between the two groups ($p < 0.05$); The statistical significance was evaluated by Paired sample T-test for normally distributed continuous variables (t test); Wilcoxon signed-rank test (NPT) for non-normally distributed variables (Z test). BMI: Body mass index, WC: Waist circumference, WHtR: Waist-to-height ratio, FM: Fat mass, FFM: Fat-free mass, PBF: Percentage body fat, REE: Resting energy expenditure, FPG: Fasting plasma glucose; HOMA-IR: Homeostatic model assessment of insulin resistance, GLP-1, GLP-2: Glucagon-like peptides 1 and 2, PYY: Peptide YY, CCK: Cholecystokinin, GHR: ghrelin.

Ultimately, 19 subjects were included pre- and post-surgery: mean age of 29.78 ± 2.29; included 7 males (36.8%) and 12 females (63.2%). Among the nineteen participants enrolled in the study, n = 1 had hypertension, and n = 1 had dyslipidemia; however, none were diagnosed with T2DM or cardiovascular disease. Regarding surgical history, two participants had undergone cholecystectomy, one had a history of appendectomy, and one had a prior caesarean section. Preoperative medication regimens included one participant being prescribed antihypertensive medication, another receiving antacid therapy, and a third utilizing antihistamine medication. Additionally, one participant was taking multivitamins before surgery.

Following surgery, the majority of participants received multivitamins and iron supplements, while one continued antacid therapy, another continued antihypertensive medication, and a third continued antihistamine therapy. Notably, none of the participants reported the use of prebiotics, probiotics, or fiber supplements either before or after the surgical intervention. There were no significant differences in the level of physical activity observed between the pre- and post-surgery groups. Furthermore, no one consumed alcohol, and there was no difference in smoking habits. (S1 Table). Additionally, none of the study participants had postoperative complications. Three months post-surgery, the mean BMI fell from 43 to 35 kg/ m2 ($t = 20.36$; $p < 0.001$); similarly, waist circumference ($t = 9.97$; $p < 0.001$), waist-to-height ratio ($t = 9.53$; $p < 0.001$), and PBF ($t = 5.44$; $p < 0.001$) showed significant improvements. Appetite reduced significantly post-surgery. Participants reduced their total daily energy intake from (245 4*Kcal*± 171) pre-surgery to (75 6*Kcal*± 67.6) ($t = 10.93$; $p < 0.001$) at three months post-surgery. We noted no significant differences regarding REE and FPG.

Post-operatively, the HOMA-IR displayed a significant reduction; however, it remained above 1.8. Moreover, fasting levels of insulin ($t = 6.83$; $p < 0.001$), leptin ($t = 10.71$; $p < 0.001$), GLP-1 ($t = 5.7$; $p < 0.001$), GLP-2 ($t = 5.07$; $P < 0.001$), and CCK

(t = 2.42; P = 0.026) decreased significantly, and GHR (t = −2.97; p = 0.008) and PYY (Z = −3.54; p < 0.001) levels significantly increased.

α- and β-diversity (microbial diversity and richness, microbial dissimilarities)

α-Diversity. The α-diversity of the pre-and post-surgery samples (Fig 1) was calculated using Kruskall-Wallis for five different metrics, including Shannon diversity (Fig 1A; pre (Mean (SEM) = 6.47 ± 0.14, post = 6.73 ± 0.10; p = 0.21), Chao1 (Fig 1B; pre = 213.2 ± 16.14, post = 241.16 ± 16.83; p = 0.23), Pielou's evenness (Fig 1C; pre = 0.85 ± 0.009, post = 0.87 ± 0.008; p = 0.31), observed OTUs (Fig 1D; pre = 199.31 ± 14.7, post = 222.05 ± 13.74; p = 0.28) and Faith's PD (Fig 1E, pre = 13.2 ± 0.71, post = 14.58 ± 0.93; p = 0.28). We noted no statistically significant differences in the five-diversity metrics between pre- and post-surgery.

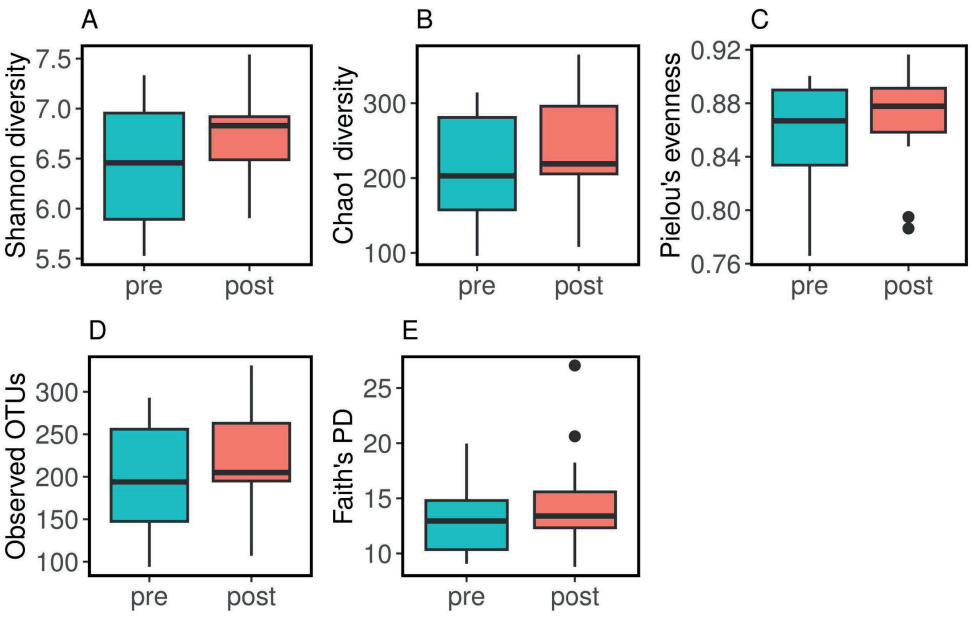


Fig 1. α-diversity pre- and post-SG-surgery. (A) Shannon; (B) Chao1; (C) Pielou's evenness; (D) Observed OTUs; (E) Faith's PD.

β-diversity. Regarding β-diversity (Fig 2), no significant differences were observed for Unweighted UniFrac and Bray-Curtis dissimilarity metrics. However, significant differences were identified for Weighted UniFrac and Jaccard metrics between pre-and post-surgery ((Fig 2B; p = 0.012; (Eigenheim-values PC1: 0.80, PC2: 0.22 and Fig 2D; p = 0.006; Eigenheim-values PC1: 0.82, PC2: 0.74, respectively). All p values were calculated with the statistic test PERMANOVA.

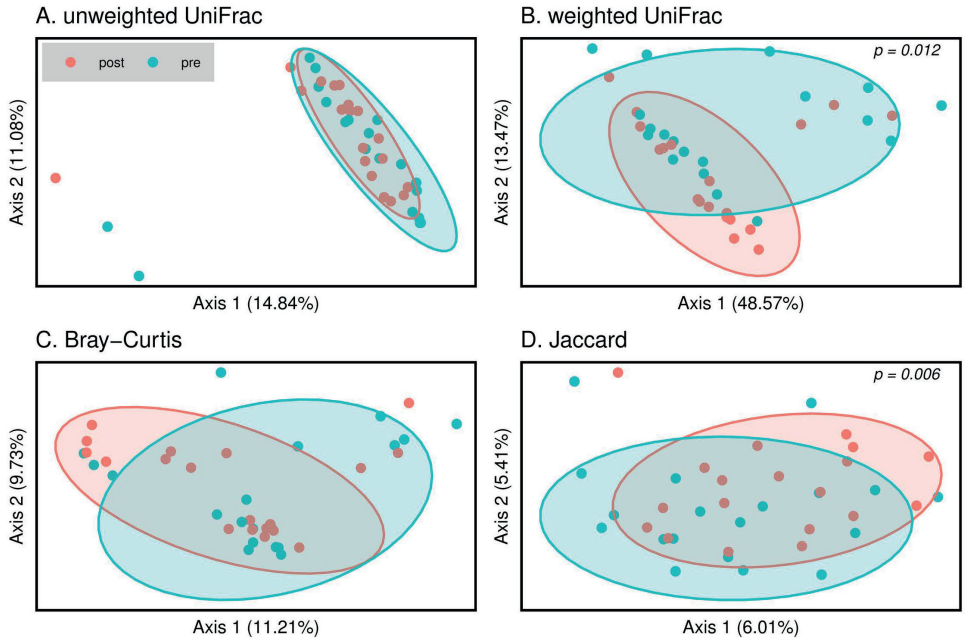


Fig 2. Principal Coordinate Analysis (PCoA) based on (A) Unweighted UniFrac, (B) Weighted UniFrac, (C) Bray-Curtis dissimilarity, and (D) Jaccard similarity. The total variance explained by the first two components is displayed on the PC1 and PC2 axes, respectively. Eigenvalues for the first five axes (PC1 to PC5) are provided in S3 Table. Pre-surgery (blue spheres) and post-surgery (red spheres).

Pseudo-F for PERMANOVA for the different analyses were as follows: Unweighted UniFrac: F = 1.960337; Weighted Uni: F = 1.691676; Bray: F = 1.272821 and Jacc: F = 1.314021. Eigenheim values for the first five principal coordinates are detailed in S3 Table.

Relative abundance at the phylum level

Bacteroidetes [Bacteroidota], Firmicutes [Bacillota], and Proteobacteria [Pseudomonadota] dominated the microbiome composition of obese Emirati participants pre- and post-surgery (S1A and S1B Fig). The detailed proportions of the top 7 phyla in the pre-and post-surgery samples are provided in (Table 2). Proteobacteria [Pseudomonadota] and Saccharibacteria [Saccharimonadota] exhibited a statistically significant increase in their proportion post-surgery (Z = −1.9; q = 0.013 and Z = −2.4; q = 0.027, respectively). No changes were noted regarding the relative abundance of Firmicutes and Bacteroidetes nor the F/B ratio between pre- and post-surgery samples.

Table 2. Comparison of gut microbial composition at the phylum level pre- and post-surgery.

Phylum	Pre-surgery (Mdn (IQR))	Post-surgery (Mdn (IQR))	q-value	Statistical test (Z)
Firmicutes [Bacillota]	0.49 (0.16)	0.44 (0.13)	0.3	−0.88
Bacteroidetes [Bacteroidota]	0.46 (0.15)	0.47 (0.15)	0.7	−0.12
Proteobacteria [Pseudomonadota]	0.028 (0.017)	0.04 (0.025)	0.013a	−1.9
Actinobacteria [Actinomycetota]	0.005 (0.006)	0.005 (0.007)	0.65	−0.08
Lentisphaerae [Lentisphaerota]	0 (0)	0 (0)	0.3	−0.88
Fusobacteria [Fusobacteriota]	0 (0)	0 (0.0001)	0.1	−1.7
Saccharibacteria [Saccharimonadota]	0 (0.00008) (	0.0001 (0.0004)	0.027[a]	−2.4
F/B ratio	1.14 (0.65)	0.95 (0.65)	0.084	−0.4

[a]q-value equal to or less than 0.05 was considered statistically significant for Wilcoxon Signed-Rank test with FDR correction. Mdn (IQR), median (interquartile range).

Relative abundance at the genus level

A total of 28 genera showed differences in abundance between pre- and post-surgery with absolute LDA scores > 2, using LefSe (Fig 3A). In this case, of the twenty-eight genera, the same five genera significantly decreased post-surgery as for the Wilcoxon signed-rank test (Table 3 and Fig 3B–I), while 11 genera that were significantly increased by the Wilcoxon signed-rank test also increased post-surgery as identified by LEfSe.

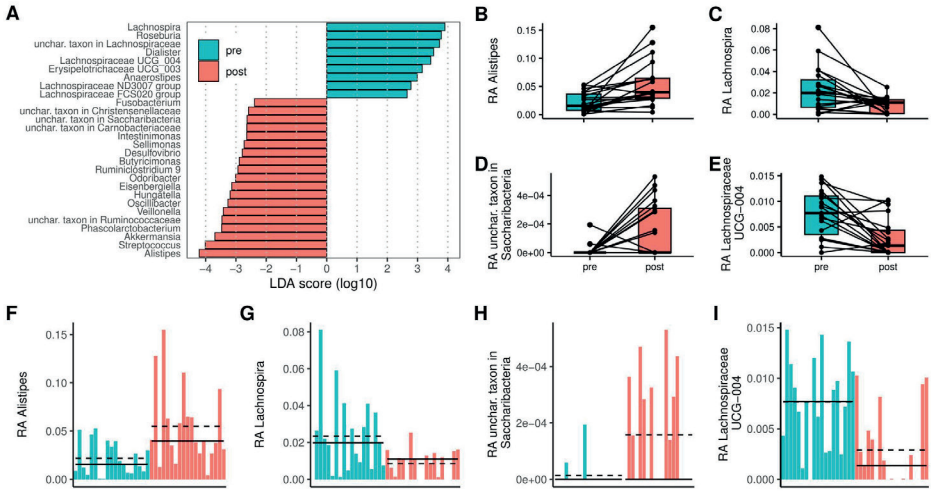


Fig 3. Boxplots display the median (as the central tendency) and the interquartile range (25th to 75th percentiles) as the bottom and top edges of the box. The whiskers extend to the most extreme data points not considered outliers (1.5 times the interquartile range), and the outliers are plotted individually. (A) LefSe discriminative analysis between pre- and obese post-surgery samples (absolute LDA score > 2). The LDA score (log10) for the more prevalent genera in the pre-surgery is represented on a positive scale (green), and the LDA score for the more prevalent genera in the post-surgery is defined on a negative scale (red). (B) Paired boxplots of Alistipes in pre- and post-surgery samples. (C) Paired boxplots of Lachnospira in pre- and post-surgery samples. (D) Paired boxplots of Saccharibacteria in pre- and post-surgery samples. (E) Paired boxplots of Lachnospiraceae UCG 004 in pre- and post-surgery samples. (F) Relative abundance of Alistipes in pre- and post-surgery samples. Means (straight line) and medians (dotted line) are shown for both groups. (G) Relative abundance of Lachnospira in pre- and post-surgery samples. Means (straight line) and medians (dotted line) are shown for both groups. (H) Relative abundance of Saccharibacteria in pre- and post-surgery samples. Means (straight line) and medians (dotted line) are shown for both groups. (I) Relative abundance of Lachnospiraceae UCG 004 in pre- and post-surgery samples. Means (straight line) and medians (dotted line) are shown for both groups.

Table 3. Changes in gut microbial taxa (Genus level)pre- and post-surgery.

Genus	Pre-surgery (Mdn (IQR))	Post-surgery (Mdn (IQR))	q-value	Statistical test (Z)
Decreased in post-surgery				
***Lachnospiraceae* UCG-004**	0.007 (0.008)	0.001 (0.004)	0.001[a,b]	−3.18
Lachnospira	0.02 (0.03)	0.01 (0.01)	0.027[a,b]	−2.45
***Erysipelotrichaceae* UCG-003**	0.0008 (0.004)	0 (0)	0.021[a,b]	−2.62
Dialister	0.0086 (0.014)	0.0006 (0.008)	0.038[a,b]	−2.33
***Lachnospiraceae* FCS020 group**	0.0007 (0.001)	0 (0.00008)	0.049[a,b]	−2.27
Lachnospiraceae	0.027 (0.024)	0.019 (0.013)	0.056[b]	−2.17
***Lachnospiraceae* ND3007 group**	0.0005 (0.001)	0 (0.0007)	0.06[b]	−2.13
Roseburia	0.022 (0.026)	0.012 (0.018)	0.05[b]	−2.21
Anaerostipes	0.004 (0.005)	0.001 (0.003)	0.07[b]	−2.07
Increased in post-surgery				
Streptococcus	0.001 (0.001)	0.013 (0.013)	0.000009[a,b]	−3.82
Alistipes	0.015 (0.03)	0.039 (0.038)	0.0006[a,b]	−3.34
Desulfovibrio	0 (0)	0.0004 (0.003)	0.006[a,b]	−3.06
Carnobacteriaceae	0 (0)	0.0003 (0.0006)	0.008[a,b]	−2.97
Eisenbergiella	0 (0)	0.0005 (0.003)	0.009[a,b]	−2.93
Hungatella	0 (0)	0.0007 (0.002)	0.009[a,b]	−2.93
Uncharacterized genus in *Ruminococcaceae*	0.002 (0.001)	0.005 (0.005)	0.009[a,b]	−2.89
Sellimonas	0 (0)	0 (0.001)	0.02[a,b]	−2.66
Butyricimonas	0.0005 (0.002)	0.002 (0.003)	0.027[a,b]	−2.53
Saccharibacteria	0 (0)	0 (0.0003)	0.031[a,b]	−2.49
Oscillibacter	0.0017 (0.004)	0.004 (0.007)	0.038[a,b]	−2.33
Fusobacterium	0 (0)	0 (0.0002)	0.21[b]	−1.54
Intestinimonas	0 (0.0005)	0.0005 (0.0015)	0.05[b]	−2.27
Uncharacterized genus in *Christensenellaceae*	0 (0.00008)	0.00009 (0.0009)	0.08[b]	−1.99
Ruminiclostridium 9	0.0017 (0.004)	0.0035 (0.005)	0.05[b]	−2.21
Odoribacter	0.0035 (0.005)	0.007 (0.006)	0.06[b]	−2.09
Veillonella	0.0006 (0.0016)	0.003 (0.007)	0.06[b]	−2.13
Phascolarctobacterium	0.0005 (0.009)	0.008 (0.017)	0.06[b]	−2.11
Akkermansia	0 (0.0002)	0.0008 (0.015)	0.11[b]	−1.87
Clostridiales	0 (0)	0 (0.0003)	0.043[a]	−2.38
Haemophilus	0 (0.0009)	0.0005 (0.01)	0.049[a]	−2.29
Uncharacterized genus in *Coriobacteriaceae*	0 (0)	0 (0.0005)	0.049[a]	−2.31

[a]q-value equal to or less than 0.05 was considered statistically significant with FDR correction. The non-parametric Wilcoxon signed-rank test was used.

[b]Taxa that were different as identified by LEfSe with an LDA effect score >2

Changes noted at the level of the following genera were only statistically significant using LEfSe, including *(Lachnospiraceae* and *Lachnospiraceae* ND3007 group*, Roseburia, Anaerostipes* (pre-surgery); *Fusobacterium, Intestinimonas,* an uncharacterized genus in *Christensenellaceae, Ruminiclostridium* 9*, Odoribacter, Veillonella, Phascolarctobacterium, Akkermansia* (post-surgery).

Using the non-parametric Wilcoxon signed-rank test (for paired samples), 19 genera significantly changed between pre-and post-surgery, as depicted in (Table 3 and Fig 3B–I). Of the 19 genera, five decreased post-operatively (*Lachnospiraceae* UCG-004, *Lachnospira, Erysipelotrichaceae* UCG-003, *Dialister,* and *Lachnospiraceae* FCS020 group), while the remaining 14 increased post-surgery.

Correlations between microbial taxa and clinical parameters

The taxa that show statistically significant correlations with clinical parameters are provided in the S2 Table and S2 Fig, along with the correlation coefficients (rho).

Several taxa that significantly increased post-surgery (uncharacterized genera in *Ruminococcaceae*, *Desulfovibrio*, *Akkermansia, Carnobacteriaceae*, *Streptococcus, and Sellimona*s) were negatively correlated with energy intake, BMI, and appetite. *Roseburia*, which decreased post-surgery, was positively correlated with appetite, while PYY was positively correlated with genera that increased post-surgery (*Carnobacteriaceae*, *Streptococcus, Eisenbergiella, Hungatella, Veillonella*) and negatively correlated with *Dialister* that decreased post-surgery. Lachnoclostridium and Flavonifractor showed a negative correlation with leptin. Hungetella and Eisenbergiella, which were significantly higher post-surgery, showed a positive correlation with GHR.

There were no observed correlations among the gut microbiota at the genus level and the subsequent anthropometric and dietary variables (WC, WHtR, PBF) REE, fiber/ 1000 kcal; or biochemical variables (insulin, GLP1, GLP2, and CCK).

Discussion

There is a growing body of evidence linking the gut microbiota to obesity; however, the impact of bariatric surgery on the gut microbiota and the mechanism of action is understudied. Moreover, the integrated communication between the gut microbiota and the metabolic and neuroendocrine systems, along with its connection to obesity, remains to be uncovered. Some of the significant determinants of gut microbiota composition are geography, ethnicity, and cultural practices; thus, gut bacteria composition must be studied in several areas of the globe. We explored the impact of bariatric surgery on the gut microbiota and the factors that influence it, such as energy balance, gut peptides, and hormones, in a sample of Emiratis with obesity. Participants achieved significant weight loss post-surgery, with significant differences in the gut microbiota composition.

Obesity is associated with dysbiosis and less bacterial α-diversity. Post-surgery, our sample experiences an increase in α-diversity without reaching statistical significance. This was consistent with the literature, where patients' post-surgery, α-diversity, and metabolic profiles improved [58]. However, the published data on the matter is inconsistent. While some research indicated a significant increase [59–63], others found no change or even a decrease [32,42,58,64] post-surgery on gut bacteria. According to Palleja et al. [65], Roux-en-Y gastric bypass leads to an increase in microbial diversity, which remains stable even one year postoperatively. Another comparative study between RYGB and sleeve gastrectomy (SG) also reported greater microbial diversity in the RYGB group, whereas no significant changes were observed in microbial diversity before and after SG in obese individuals [66]. The discrepancies may be the result of many factors, such as the type of surgery conducted [58,66], the sample characteristics at baseline, and the diets followed post-surgery. Therefore, changes in α-diversity appear not to be a reliable indicator of the effectiveness of bariatric surgery in humans [67]. Additionally, the alterations in gut microbiota following RYGB, including specific taxonomic shifts (e.g., greater abundances of Escherichia, Bacteroides, and Veillonella), may play a role in the differing metabolic outcomes between the two procedures [68].

Most literature pinpoints a major change in the microbial community after bariatric surgery, suggesting that the latter significantly impacts the gut microbiota, facilitates weight loss, and ameliorates metabolic profile [59,67]. We observed significant changes in β-diversity post-surgery, denoting a heterogeneous

microbiota [69]. However, not all four metrics were significant, with the weighted UniFrac (which considers abundance) being significant, but also Jaccard similarity (which does not take abundance into account). Therefore, we also looked at which taxa were differentially abundant after SG surgery.

We observed significant differences in the relative abundance of several bacterial taxa. In pre-and post-surgery, Bacteroidetes and Firmicutes dominated the microbiome composition, with Proteobacteria the third most phylum, but trailing by an order of magnitude. The other phyla were even less abundant. Post-surgery, Proteobacteria, and Saccharibacteria significantly increased. The rise in Proteobacteria is consistent with earlier findings [30,63,70–72]. Increases in luminal acidity and dissolved oxygen following SG favor the growth of these microbes [30]. A rise in Proteobacteria after bariatric surgery is associated with favorable outcomes, including weight loss [73], enhanced glucose homeostasis, and reduced systemic inflammation [74], even though this phylum is also known to harbor (potential) pathogenic species.

Despite some previous reports that obesity is associated with a higher F/B ratio that decreases after surgery [18,75], F/B remained constant post-surgery in our study. F/B may not be associated with weight loss or predict the outcome post-surgery [39,72,76]. Instead, obesity may be caused by an enhanced energy harvest from one's diet, not just by a simple rise in F/B ratio but also by gut bacteria tuned towards creating SCFA. Therefore, looking into the connection between energy harvest associated with bacterial SCFA synthesis and obesity is warranted [77]. In line with the literature, we observed significant decreases in several genera, including *Lachnospiraceae* [78]*, Dialister*, *Roseburia*, *Anaeostipes, and Eryspelotrichaceae* [18]. Noteworthy, increased appetite positively correlated with *Roseburia* in our study. This is in line with previous findings showing that this genus predominated in the microbiota pre-surgery and decreased post-surgery which could explain the decrease in appetite noted post-surgery [18,71]. Furthermore, bariatric surgery induced an increase in the relative abundance of *Butyricimonas,* which has been linked to decreased appetite [79]. As expected, *Akkermansia*, which is usually low in obesity, increased post-surgery [72] approximately 6-fold (not significant in the Wilcoxon test, but an LDA of −3.5 in LEfSe). The mucin-degrading properties of *Akkermansia* reduce inflammation and alterations in adipose tissue, and this bacterium has been strongly linked to favorable metabolic outcomes and a decline in body weight [67,80]. There is a significant correlation between an increase in *Akkermansia abundance* and a reduction in the taste of energy-dense foods [32]. This is consistent with the hypothesis that *Akkermansia* prefers an environment

with lower food intake, as in our context, where it negatively correlates with energy intake. *Akkermansia* enrichment is a potential therapy for obesity management. Indeed, a randomized clinical trial showed that short-term oral administration of pasteurized *Akkermensia* to overweight and obese participants led to weight loss and improved insulin sensitivity [81].

Several studies [18,71] reported increased *Alistipes* (phylum Bacteroidetes), *Veilonella*, and *Streptococcus* post-surgery. We found similar results. Increases in these strains are usually associated with metabolic improvements and more significant weight loss [18,71]. Furthermore, we found a positive correlation between PYY (the satiety hormone) and *Veilonella* and *Streptococcus* in our study. Specifically, greater abundances of *Veillonella* and *Streptococcus* have been associated with T2DM remission following Roux-en-Y gastric bypass (RYGB) [82].

The gut-brain axis (GBA), which controls hunger and food intake, and the intestinal microbiota consist of bidirectional communication [83]. Some bacterial strains can affect the production of gut hormones, such as PYY, GLP-1, leptin, and GHR, that control hunger and satiety in the brain [83,84] and regulate energy and glucose homeostasis [75,85]. Most evidence refers to increased GLP-1 post-surgery [86]. Interestingly, we observed a decrease in fasting GLP-1, as also shown in some studies [75,87], suggesting that enhanced insulin sensitivity may lead to the downregulation of GLP-1. Methodological differences might explain this discrepancy, i.e., assessing fasting post-prandial GLP-1 response vs. testing a metabolite or the active form of GLP-1. Therefore, it remains challenging to draw firm conclusions about GLP-1 post-SG [87]. Our participants also showed increased plasma PYY post-surgery, as demonstrated elsewhere [24,75,85], partially attributed to weight loss and enhanced satiety. PYY is a neuropeptide that has satiating and reducing effects on body weight and adiposity [88]. Conversely, GHR promotes food intake and attenuates the anorectic effect of PYY and GLP-1 [89]. Gastric cells primarily. Removing part of the stomach may lower GHR, as shown in most SG studies [85]. Yet, we unexpectedly found that GHR increased. A possible explanation is that the majority of GHR-producing cells are located in the stomach's fundus, whereas circulating acyl GHR may come primarily from the duodenum, which remains intact in SG, leading to a compensatory upregulation of duodenal GHR production [88]. In GHR-deficient mice, SG was similarly effective in inducing weight loss, raising the question of whether this hormone is a crucial facilitator of weight reduction [87], especially since weight loss post-surgery is independent of GHR [90].

The considerable reduction in insulin levels in our study is one of the most

significant outcomes of bariatric surgery [91]. Similarly, post-surgery, there was a significant decrease in HOMA-IR levels [92]. Enhanced insulin sensitivity promotes weight loss and decreased appetite [90]. Similarly, leptin resistance improved post-surgery. Leptin stimulates anorexigenic neurons and reduces appetite [84]. As discussed above, changes in the colonic microbiome post-surgery correlate with variations in appetite. Sanmiguel et al. [32] found a link between having higher levels of certain types of colonic bacterial species and losing your appetite after SG. These bacteria included *Odoribacter*. We report a similar finding, where appetite also dropped significantly post-surgery, associated with an increase in *Roseburia* and *Butyricimonas*. Future studies should explore causal processes linking the effects of increasing these bacteria on appetite.

Energy intake, BMI, and appetite negatively correlated with several taxa that significantly increased post-surgery were with. Among them were *Streptococcus, Akkermansia*, a genus in *Carnobacteriaceae,* and a genus in *Ruminococcaceae*. It has been demonstrated that dietary fiber affects hunger, body weight, and gut microbiota composition [93]. Participants consumed more fiber/1000 kcal post-SG, which could play a role. However, they did not meet the recommended daily level. Interestingly, although we detected several significant gut microbiota correlations with clinical parameters, none were reported for resting energy expenditure [94,95].

The question of whether the changes noticed post-bariatric surgery are permanent or reversible remains debatable and potentially surgery-specific [96]. The most extensive modifications in the composition of the gut microbiota are usually present post-RYGB [42]. SG induces less drastic alterations in the diversity of the adaptive gut microbiota than RYGB because it does not alter the gut's anatomical structure [42,79]. Apart from the type of surgical intervention [30,97], the inconsistencies in the impact of bariatric surgery on the gut microbiota are partly due to the differences in participant characteristics, such as geographic location [98], ethnicity, sex, age, initial BMI, initial microbial composition, gastrointestinal comorbidities, medication use, prebiotics/probiotics use, differences in diet, as well as study design, sampling time, sample storage method, sequencing methodology, bioinformatics and statistical software used [42], all of which can change gut microbial composition.

Strengths and limitations

To the best of our knowledge, this is the only study that has examined the effect of bariatric surgery on the following gut peptides (GHR, GLP-1, GLP-2, CCK, PYY) and hormones including insulin, and leptin, on Emiratis with obesity post-SG-surgery. Furthermore, this study's strengths include a novel research question targeting ethnic-specific research, a clear data-extraction process, well-defined inclusion and exclusion criteria, and a wide range of parameters assessed through valid methods. On the other hand, our results are limited by the small number of patients and the limited follow-up period, although small samples are common in such studies [29,33,97,99]. Furthermore, changes in these subjects' gut microbiota are evident. According to studies using several follow-up time points, most microbiome alterations occur within three months post-surgery, followed by a steady microbiome for the next year [100]. We did not measure the post-prandial secretion of gut hormones in response to a standardized meal test. Additionally, other gut hormones such as the appetite reducing GIP-oxyntomodulin hybrid peptide were not measured, which could provide further insights into metabolic changes post-surgery [101]. Another limitation is that we did not account for diet, a flaw that is present in the majority, if not all, of human bariatric studies. Diet following bariatric surgery may alter significantly over time, which could impact the gut microbiota and should be investigated. Furthermore, our study did not include other bariatric surgery techniques, such as Roux-en-Y gastric bypass (RYGB), limiting the opportunity to investigate consistency or potential variations between diverse bariatric surgery procedures [34]. Despite the observational study design's inability to establish causality for changes reported post-surgery, it allows for the formulation of several hypotheses. Another limitation of this study is the potential lack of generalizability of the findings. The study exclusively focused on the Emirati population, which was chosen due to the scarcity of gut microbiota data in the GCC region and the unique ethnic influences that could impact microbiota composition. Although this population provides valuable insights into how gut microbiota and bariatric surgery outcomes interact in a largely understudied region, the results may not be directly applicable to other ethnic or regional populations with different genetic, dietary, and lifestyle factors. Future studies are recommended to explore these associations across diverse ethnic groups and geographic regions to enhance the generalizability of the findings and to determine if region-specific factors or genetic predispositions contribute to the observed effects.

Practical implications

Understanding changes post-bariatric surgery in gut peptides, hormones, and gut microbiota and the interplay between these factors can lead to non-invasive, anti-obesogenic personalized interventions, including targeted probiotics, prebiotics, dietary, and pharmacological interventions. Based on our results, we suggest interventions to reduce *Roseburia* levels and/ or increase *Butrycimonas*, ultimately influencing appetite. Furthermore, the administration of probiotics rich in *Akkermensia* to treat obesity appears promising and warrants empirical research.

Conclusion

We discovered that bariatric surgery significantly alters the plasma levels of gut peptides and hormones, as well as the composition of the gut microbiota. We speculate that the microbiota modifications could, at least in part, be responsible for the positive outcomes of bariatric surgery, including weight loss. Most importantly, we could not confirm the association between obesity and an increased F/B ratio [102,103]. Further research is necessary to understand the interplay between the gut microbiota and changes in gut peptides, hormones, human metabolism, and energy homeostasis following bariatric surgery.

Supporting information

S1 Flow Chart. Overview of the study process.
S1 Fig. Krona plot of the intestinal bacterial communities pre (A) and post-surgery (B) at the phylum level. The _ in both plots indicates “uncharacterized.”
S2 Fig. Heatmap of Spearman correlation analysis between gut microbiota (at genus level) and anthropometrics and clinical variables. The asterisk (*) denotes statistical significance at a cut-off of < 0.05 for q-values (adjusted p-values after the False Discovery Rate (FDR) correction) and the negative and positive values are the rho (= correlation factor), which can be positive for positive correlations and negative for negative correlations.
S1 Table. Lifestyle factors for pre-and post-bariatric surgery.
S2 Table. Spearman correlation coefficient (rho) for the taxa showing significant negative and positive correlations with clinical data according to the heatmap (S2 Fig).
S3 Table. Eigenvalues of principal coordinates (PCs) for different beta diversity metrics.
S1 File. Postoperative bariatric diet meal planning.
S1 Checklist. Inclusivity in global research.

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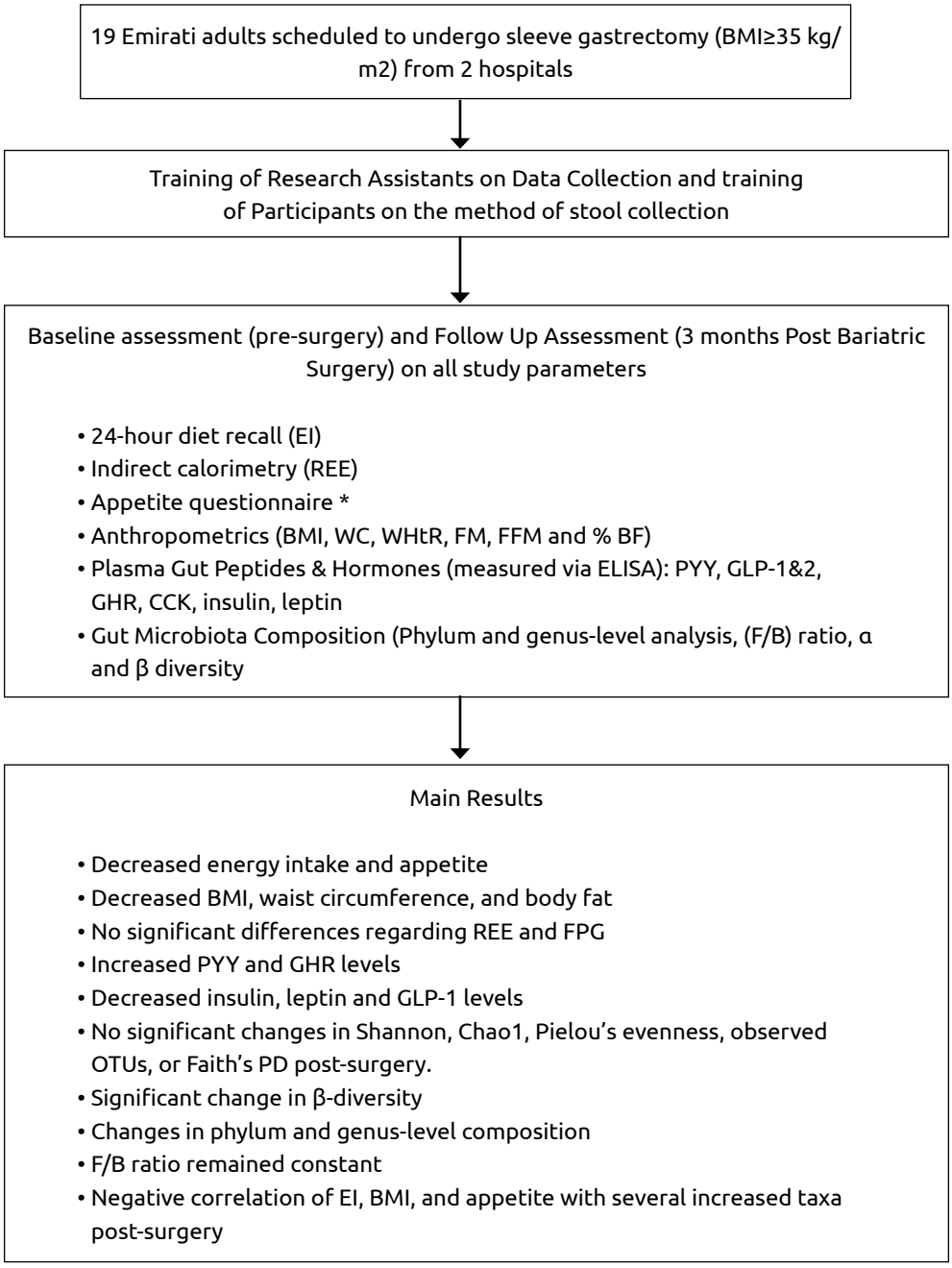
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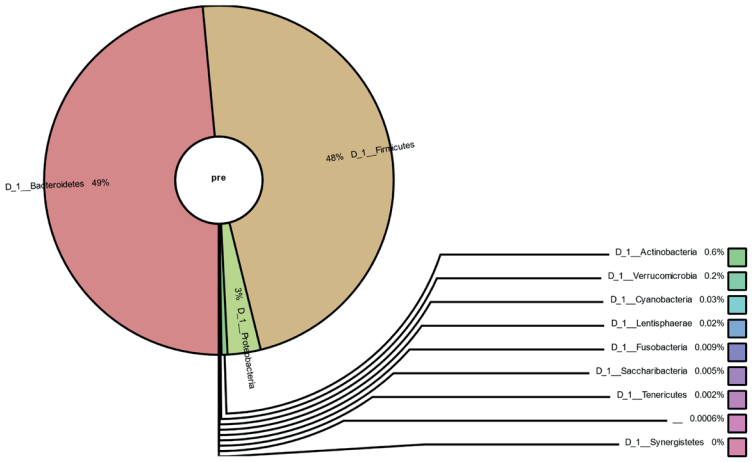
Supplementary Materials

S1 Flow chart. Overview of the study process

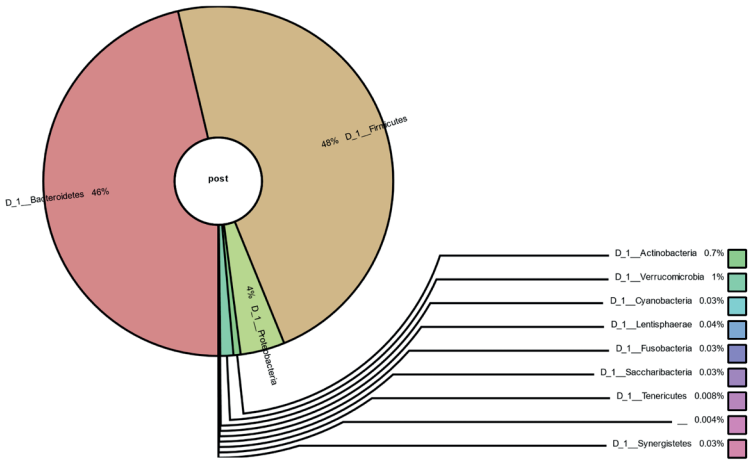


Abbreviations: BMI: Body mass index, EI: Energy intake, REE: Resting energy expenditure, FPG: Fasting plasma glucose, WC: Waist circumference,WHtR: Waist-to-height ratio, FM: Fat mass, FFM: Fat-free mass, PBF: Percentage body fat, PYY: Peptide YY, GLP-1, GLP-2: Glucagon-like peptides, 1 and 2, GHR: ghrelin, CCK: Cholecystokinin, F/B: Firmicutes/ Bacteroidetes ratio.

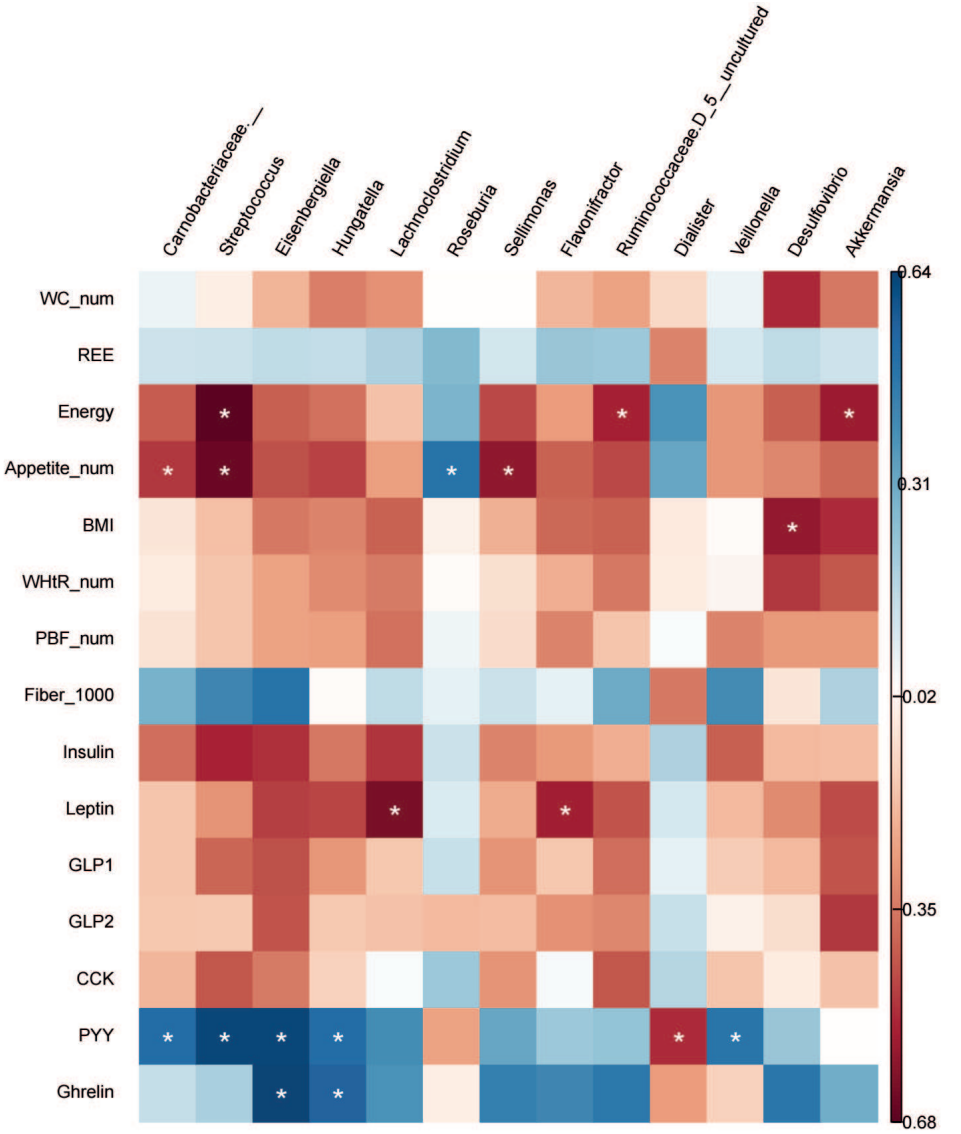
S1A Fig.



S1B Fig.



S1 Fig. Krona plot of the intestinal bacterial communities pre (A) and post-surgery (B) at the phylum level. The _ in both plots indicates "uncharacterized



S2 Fig. Heatmap of Spearman correlation analysis between gut microbiota (at genus level) and anthropometrics and clinical variables. The asterisk (*) denotes statistical significance at a cut-off of <0.05 for q-values (adjusted p-values after the False Discovery Rate (FDR) correction) and the negative and positive values are the rho (= correlation factor), which can be positive for positive correlations and negative for negative correlations.

S1 Table. Lifestyle factors for pre- and post-bariatric surgery (n=19).

Lifestyle factors	Pre-surgery	Post-Surgery	p-value
Probiotic Supplement - Yes, n (%)	0 (0)	0 (0)	-
Fiber Supplement - Yes, n (%)	0 (0)	0 (0)	-
Prebiotic Supplement - Yes, n (%)	0 (0)	0 (0)	-
Medication use - Yes, n (%)	3 (15.8)	3 (15.8)	1
Nutritional Supplements -Yes n (%)	1 (5.3)	16 (84.2)	<0.001[a]
Smoking -Yes n (%)	3 (15.8)	4 (21.1)	0.33
Alcohol consumption- Yes n (%)	0 (0)	0 (0)	-
Physical activity level			0.163
Sedentary	2 (10.5)	3 (15.8)	
Light	16 (84.2)	11 (57.9)	
Moderate	1 (5.3)	1 (5.3)	
High	0 (0)	4 (21.1)	

[a]Denotes statistical significance between the two groups ($p<0.05$); The statistical significance was evaluated for categorical variables by the McNemar test.

S2 Table. Spearman correlation coefficient (rho) for the taxa showing correlations with clinical data according to the heatmap (S2 Fig).

BMI		EI	Appetite	Leptin	GHR	PYY
Genus						
An uncharacterized taxon within *Carnobacteriaceae*	-	-	-0.49	-	-	+0.52
Streptococcus	-	-0.68	-0.64	-	-	+0.62
Eisenbergiella	-	-	-	-	+0.6	+0.62
Hungatella	-	-	-	-	+0.55	+0.52
Lachnoclostridium	-	-	-	-0.62	-	-
Roseburia	-	-	+0.49	-	-	-
Sellimonas	-	-	-0.58	-	-	-
Flavonifractor	-	-	-	-0.54	-	-
An uncharacterized taxon within *Ruminococcaceae*	-	-0.54	-	-	-	-
Dialister	-	-	-	-	-	-0.51
Veillonella	-	-	-	-	-	+0.48
Desulfovibrio	-0.57	-	-	-	-	-
Akkermansia	-	-0.56	-	-	-	-

The negative and positive Spearman rho ranges between values of |0.20| and |0.39|; |0.4| and |0.69|; |0.70| and |0.89; |0.90| and |1.00| denote a weak, moderate, strong, and very strong correlation, respectively. Only statistically significant correlations are presented in the table at a cut-off of <0.05 for q-values (adjusted p-values after the False Discovery Rate (FDR) correction).

Supplementary Table 3: Eigenvalues of Principal Coordinates (PCs) for Different

Beta Diversity Metric	PC1 Eigenvalue	PC2 Eigenvalue	PC3 Eigenvalue	PC4 Eigenvalue	PC5 Eigenvalue
Unweighted UniFrac	0.7899	0.5899	0.5899	0.5899	0.5899
Weighted UniFrac	0.7997	0.2218	0.2218	0.2218	0.2218
Bray-Curtis	1.3166	1.1431	1.1431	1.1431	1.1431
Jaccard	0.8177	0.7357	0.7357	0.7357	0.7357

S1 File: Postoperative Bariatric Diet Meal Planning (Mechanick et al., 2019)

Stage 1: Bariatric Clear Liquids (1 to 3 days after surgery)

☐ Provide six to eight small feedings of clear liquid foods. Begin with sips of water, and then add bouillon or clear broth, unsweetened juices (apple, cranberry, or grape juices), diet gelatin, and herbal tea like anise, or chamomile. Generally, it should be low in calories and sugar and free of caffeine, carbonation, and alcohol.

☐ If tolerated well, progress to Bariatric Full Liquids

Stage 2: Bariatric Full Liquids (10 to 14 days after surgery)

☐ Provide six to eight small feedings per day. Begin with high protein liquids/ shakes/ soups or specialized high protein (low fat, low sugar-free, high protein drinks).

The combined volume of the six to eight small feedings plus water intake should be at least 48 to 64 oz/day (6-8 cups) to meet hydration needs.

Stage 3: Bariatric Pureed Diet (10 to 14 days)

If tolerated well, advance to a pureed diet (stage 3).

-Puree diet is food blended or liquefied with adequate fluid, eaten without chewing, and the consistency and texture should progress gradually.

☐ Provide four to six small feedings of pureed foods. Use high-quality protein foods such as scrambled eggs, low-fat or cottage cheese, or blenderized lean meats such as tuna, fish, and chicken. Strained baby foods are a convenient option. Integrate high-quality protein food with each meal or snack.

☐ Portion: 2 to 4 oz (4 to 8 tbsp) at a time of solid foods.

☐ Consume protein food first, vegetables and fruit second, and starch foods last to help ensure adequate protein consumption.
☐ Alternate fluid intake with food intake. Avoid consuming fluids with meals. Wait at least 30 minutes after consumption of solid foods or meals to drink fluids.
☐ Avoid chewing gum. If swallowed, gum can block the stomach opening.
☐ Avoid drinking from straws because the air swallowing can cause bloating and stretch the pouch.
☐ Behavior techniques must be applied and reinforced (e.g., eating small amounts, eating slowly, and chewing food thoroughly before swallowing).

Stage 4: Bariatric soft Diet (1 to 2 weeks)
☐ If intake is improving, advance to soft foods.
Textured-modified: To limit stage-4 foods to those that can be mashed or do not require excessive chewing (chopped or ground foods).
☐ Behavior techniques must be applied and reinforced (e.g., eating small amounts, eating slowly, and chewing food thoroughly before swallowing).

Stage 5: Bariatric Diet (regular consistency)
After 1 or 2 weeks on soft foods, start introducing some solid food and progress to all solids as tolerated (stage 5), generally 4 to 6 weeks after surgery.
☐ Provide four to six small feedings of regular consistency food. Use high-quality protein foods such as scrambled egg, low-fat cheese or cottage cheese, or lean meats such as tuna fish, chicken,
☐ Alternate fluid intake with food intake. Consume fluids at least 30 minutes before or after solid foods.
☐ Should keep a food record to document food intake and eating behavior, including foods tolerated or not tolerated, to discuss with the dietitian during follow-up visits.
If patients do not progress through these stages of their diet in the appropriate periods due to nausea, vomiting, or dysphagia, careful evaluation of nutrition should be performed, and the surgeon should consider investigating potential causes

5

Chapter 5

Obesity and the gut microbiota in the Middle East: a cross-cultural study of Lebanese and Emirati adults

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Abstract

Obesity is a growing public health concern in the Middle East and North Africa (MENA) region, yet limited research has explored how gut microbiota varies between Arab populations. This study compared the gut microbiota composition and diversity of Emirati and Lebanese adults with obesity and assessed the role of age and nationality in shaping microbial variation. A total of 43 Emirati and 30 Lebanese individuals with obesity (body mass index (BMI) ≥35 kg/m^2) were recruited. Participants provided anthropometric and biochemical data, dietary records, and stool samples for 16S rRNA sequencing. The analysis revealed significantly higher BMI, weight, and fat mass in Emirati participants, while Lebanese individuals reported higher fibre intake. Taxonomic profiling showed higher relative abundances of *Pseudomonadota*, *Mycoplasmatota*, *Cyanobacteriota*, and *Lentisphaerota* in the Lebanese group, whereas *Bacteroidota* wasmore abundant among Emiratis. Lebanese participants also exhibited significantly greater microbial alpha-diversity. Beta-diversity analysis confirmed clear distinctions in microbial community structure between the two groups. Linear Discriminant Analysis Effect Size (LefSe) (LDA score >^{10}log2) and regression models ($P < 0.05$) identified specific bacterial genera associated with nationality, although these associations were attenuated after adjusting for age. These findings suggest that gut microbiota in Arab populations is influenced by demographic, dietary, and environmental factors, emphasising the need for culturally tailored microbiota-based strategies to manage obesity and related metabolic conditions.

Keywords: gut microbiota – 16S rRNA–microbial diversity – ethnicity – anthropometrics

1 Introduction

Obesity has emerged as one of the most pressing global health challenges of the 21st century. According to the World Health Organization (2024), more than one billion people – approximately one in eight worldwide – are currently living with obesity (WHO, 2024). The World Obesity Federation (2025) projects that by 2030, adult obesity prevalence will have increased by over 115% compared with 2010, reaching roughly 1.13 billion individuals globally. Furthermore, long-term forecasts from the Global Burden of Disease (GBD) BMI Collaborators (2025) suggest that by 2050, around 60% of adults (nearly 3.8 billion people) and one-third of children and adolescents (≈ 746 million) will be overweight or obese worldwide (IHME, 2025). These trends are particularly concerning in the Middle East and North Africa, where obesity rates are among the fastest rising. Obesity rates have been steadily rising in Gulf countries, with prevalence increasing from 6.5% in 1975 to 20% in 2016 (Ritchie, 2017; WHO, 2016). According to the United Arab Emirates (UAE)'s 2017–2018 National Health Survey, obesity affected 27.8% of the UAE population, while in Lebanon, the prevalence was 30.8% as reported by the World Health Organization in 2016 (WHO, 2016). Without effective prevention and policy interventions, obesity-related diseases – including type 2 diabetes, cardiovascular disease, and other metabolic complications – are expected to increase substantially, especially in low- and middle-income settings (GBD 2021 Adult BMI Collaborators, 2025; IHME, 2025;WHO, 2024; World Obesity Federation, 2025).

Genetic predisposition, lifestyle and environmental factors contribute to obesity, whilst emerging evidence highlights the gut microbiota as a key regulator of in particular, environmental and diet-related effects on metabolism and energy homeostasis (Patrone *et al.*, 2016; Turnbaugh *et al.*, 2006). The gut microbiota comprises not only bacterial phyla but also fungi, archaea, viruses, and protozoa, with its bacterial component being primarily composed of *Bacillota*, *Bacteroidota*, *Actinomycetota*, *Pseudomonadota*, *Fusobacteriota*, and *Verrucomicrobiota* (Oren and Garrity, 2021), with *Bacillota* and *Bacteroidota* accounting for nearly 90% of microbial communities (Arumugam *et al.*, 2011; Rinninella *et al.*, 2019).

An imbalance in gut microbiota, commonly referred to as dysbiosis, remains a debated concept, as microbial composition varies considerably among individuals, making it difficult to establish universal criteria for distinguishing a dysbiotic state from a healthy profile. Nevertheless, variations in gut microbiota have been linked

to several metabolic and inflammatory disorders, including obesity, diabetes, and allergies (Gupta *et al.*, 2017). Early animal studies suggested a strong relationship between the *Bacillota*/*Bacteroidota* ratio and obesity (Turnbaugh *et al.*, 2006), but subsequent findings in humans have been inconsistent (Magne *et al.*, 2020; Sze and Schloss, 2016). Beyond this ratio, specific bacterial phyla and genera have also been associated with obesity (OB) (Crovesy *et al.*, 2020). Individuals with obesity, insulin resistance (IR), and type 2 diabetes mellitus (T2DM) frequently exhibit altered gut microbiota compared to lean counterparts, characterised by reduced microbial richness and diversity as well as lower levels of butyrate-producing bacteria, changes that have been linked to metabolic impairments (Jardon *et al.*, 2022). Increasingly, researchers emphasise that definitions of dysbiosis should account not only for taxonomic shifts but also for functional consequences on host metabolism and health.

The composition of gut microbiota varies among individuals and across populations, influenced by lifestyle, genetics, age, diet, medication use, geography, ethnicity, and environment (Crovesy *et al.*, 2020; Deschasaux *et al.*, 2018; Gupta *et al.*, 2017; Jardon *et al.*, 2022; Pinart *et al.*, 2021). Advances in high-throughput sequencing technology have enhanced our understanding of population-specific differences in gut microbiota (Yasir *et al.*, 2015).

While the Lebanese and Emirati populations share some environmental and cultural similarities, variations in dietary patterns, lifestyle habits, and genetic backgrounds may shape distinct gut microbiota profiles. These differences raise concerns about the universality of microbiome-based therapies, emphasising the need for geographically tailored, community-specific approaches to microbiome research (Gupta *et al.*, 2017).

Although multiple studies have explored the relationship between gut microbiota and obesity in different populations (Escobar *et al.*, 2014; Jain *et al.*, 2018), comparative research in Middle Eastern populations remains scarce (Yasir *et al.*, 2015). Furthermore, data on ethnicity-driven gut microbiota differences in Arab populations remain inconsistent (Brooks *et al.*, 2018).

This study aims to bridge this research gap by analysing gut microbiota composition and diversity in Lebanese and Emirati individuals with OB using high throughput 16S ribosomal RNA (rRNA) gene amplicon sequencing and assessing whether age or other factors contribute to these observed variations. Identifying population-specific microbiota signatures associated with OB will provide valuable insights for developing targeted interventions to manage and prevent obesity-related complications in the Middle East, where research remains limited.

2 Materials and methods

Study design

We conducted a cross-sectional design among Lebanese and Emirati subjects with OB living in the UAE and Lebanon, respectively. The present study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Middle East Institute of Health University Hospital (MEIHUH) in Lebanon (AL-04-02/2018-IRB/MEIH) and by the Research Ethics Committee of the Ministry of Health and Prevention of UAE (MOHP/DXB-REC-52/2018), the Dubai Health Care Regulatory Research Ethics Committee (DHCR-REC), and the Zayed University Ethical Committee Board (ZU19_51_F) in UAE.

Study population

Recruitment took place from October 2019 until April 2021. Sample size was determined by following standard calculations based on normal distributions. The current study utilised data from a mother study designed to investigate gut microbiota profiles in Lebanese andEmirati participants, both with OB and of normal weight, as well as changes following bariatric surgery. The present analysis was restricted to obese participants from these larger cross-sectional studies that included both obese and normal-weight adults from Lebanon and the UAE. The current manuscript focuses solely on the obese subgroup to assess ethnicity-related microbial differences within obesity. In the mother study, the primary outcomewas the change in the *Bacillota* /*Bacteriodota* ratio. Sample size calculation was based on expected changes in this ratio before and after bariatric surgery, referencing findings from Damms-Machado *et al.* (2015), which reported a significant increase in the faecal *Bacillota* /*Bacteriodota* ratio from5.9 (SD2.1) to 10.4 (SD1.4) three months post-surgery. Based on these values, aminimum of two participants was required to achieve 80% power at a two-sided 5% significance level (Ali Ahmad *et al.*, 2025). To account for protocol deviations and anticipated reductions in effect size (~30%), researchers conservatively multiplied the required sample by a factor of 15. This adjustment yielded a final target of 30 participants per group. Accordingly, we aimed to recruit 30 Emirati and 30 Lebanese adults with OB, including both sexes, residing in the UAE and Lebanon, respectively.

Inclusion and exclusion criteria

Participants were eligible if they were adults between 18 and 60 years of age, had a body mass index (BMI) ≥ 35 kg/m2, and had maintained stable body weight (no fluctuation greater than 5%) during the three months prior to recruitment. Eligibility was restricted to Emirati and Lebanese nationals with both parents of the same nationality. Additional requirements included absence of antibiotic use in the previous three months and willingness to complete a 3-day 24-hour food diary (two weekdays and one weekend) to assess habitual energy and fibre intake. For Emirati participants, dietary intake was analysed using the Middle Eastern food composition database available in the Nutritics software, whereas for Lebanese participants, food reference tables from *Understanding Nutrition* (Whitney and Rolfes, 2002) were used. All participants provided written informed consent before enrolment. Eligibility was assessed through a structured screening questionnaire (Supplementary Materials and methods S1), which captured information on general health, weight history, alcohol intake, physical activity, smoking, medication use, and supplement intake (including probiotics, fibre, and prebiotics).

Participants were excluded if they had experienced weight loss ≥5% within the last three months, were pregnant, reported excessive alcohol consumption (>1/2 ounce/day for females; >1 ounce/day for males) (Snetselaar *et al.*, 2021), or were unwilling or unable to provide informed consent.

Recruitment

Lebanese participants with obesity were recruited from the weight-loss program at the Middle East Institute of Health University Hospital (MEIH-UH), while Emirati participants with obesity were recruited from hospitals in Dubai and Sharjah. Recruitment took place between October 2019 and April 2021.

Anthropometric measurements

Eligible subjects were asked to arrive at the testing site after a 12 h fast and were asked to avoid alcohol and caffeine consumption, as well as any unusual strenuous exercise 24 h prior to the screening.While subjects wore light clothes and no shoes, height andweight weremeasured using the 'SECA 700' balance and BMI was calculated as the ratio of weight (kg) to height (m) squared (kg/m^2).Waist circumference (WC) (cm) was measured to the nearest 0.1 cm using a flexible, non-stretchable measuring tape at the umbilicus level midway between the lower ribs and the upper iliac crest while standing (Alberti *et al.*, 2006). WC was defined as normal or 'at risk' according to the International Diabetes Federation (IDF) using

Europids cutoff values for normal of <94 cm for males and <80 cm for females (Alberti *et al.*, 2006). Waist-to-height ratio (WtHR) was calculated as the ratio of the waist circumference divided by height (both in cm). A cut-off of 0.5 was used to define abdominal obesity, whereby aWtHR <0.5 was considered normal (Gibson and Ashwell, 2020).

The percentage of body fat (PBF) wasmeasured using a bioelectrical impedance analyzer 200 (BC-420 MA, Tanita Corporation, Tokyo, Japan) for Emiratis and an InBody composition analyzer 720 (InBody Co., Ltd., Seoul, Korea) for Lebanese participants, according to the manufacturer's instructions. Cutoffs of ≥25% and ≥35% were used to define elevated PBF among males and females, respectively (Nuttall, 2015).

Biochemical analyses

After a 12 h fast, on-site, venous blood samples were collected by a registered nurse for the analyses of fasting blood glucose (FBG, mg/dl), total cholesterol (TC, mg/dl), low-density lipoprotein cholesterol (LDLC, mg/dl), high-density lipoprotein cholesterol (HDL-C, mg/dl), and triglyceride (TG, mg/dl) that were analysed via an enzymatic colorimetric method using the Roche/Hitachi Cobas® 6000 analyzer (Roche, Basel, Switzerland) and insulin via the Enzyme-Linked Immunosorbent Assay (ELISA) principle using the Elecsys insulin kit (Roche) for Lebanese participants. As for Emirates, the former were measured via the portable Lux Meter Blood Test (Biochemical Systems International, S.p.A; Arezzo, Italy) following the manufacturer's instructions. As for insulin: one 5 ml venous blood sample was drawn into an ethylenediaminetetraacetic acid (EDTA) tube and analysed by using ELISA kits (Diametra Millipore, St. Louis, MO, USA).

Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMAIR), defined as (fasting immunoreactive insulin (μU/ml) × fasting plasma glucose (mg/dL))/ 405 (Vaccaro *et al.*, 2004). HOMA-IR values exceeding 1.8 for Emirati participants (Esteghamati *et al.*, 2009) and 2.32 for Lebanese participants (Chedid *et al.*, 2009) were considered indicative of insulin resistance.

Stool collection

Stool was collected using a faecal specimen collector along with the Zymo DNA/RNA Shield™ Faecal Collection tube which was pre-filled with DNA/RNA Shield™ (9 ml) (Zymo Research Corp., Irvine, CA, USA). Subjects were asked to follow the instructions by the developer of the tubes, where two samples were collected from

each participant, one of which was analysed, and the second was held for accurate verification. Collection tubes had a spoon attached to the cap for collecting 1 g of faeces. The nucleic acids (DNA & RNA) in the samples were preserved by DNA/RNA Shield™ at room temperature (DNA > 1 year, RNA up to 1 month).

DNA isolation and sequencing of the V3–V4 region of the 16S rRNA gene

DNA isolation and sequencing of the barcoded amplicons of the V3–V4 region of the 16S rRNA gene were performed according to the Illumina protocols (Illumina, Eindhoven, the Netherlands) which involved PCR amplification using region-specific primers, followed by indexing, purification, and paired-end library preparation (Surono *et al.*, 2022). Sequencing was conducted on the Illumina MiSeq platform(San Diego, CA, USA) using barcodes and the paired end 2 × 300 bp protocol. Raw reads were processed and demultiplexed using (QIIME 2, version 2023.2) (Bolyen *et al.*, 2019), and taxonomic classification was performed using the SILVA 16S rRNA gene reference database, version 132 (Quast *et al.*, 2013; Yilmaz *et al.*, 2014).

Diversity analyses

The alpha-diversity metrics used in this study included Faith's phylogenetic diversity (PD) (Faith, 1992), observed features (DeSantis *et al.*, 2006), Chao1 index (Chao, 1984), Pielou's evenness (Pielou, 1966) and Shannon's indices (Shannon andWeaver, 1949). These indices were calculated usingQIIME 2 and visualised in RStudio (version 4.2.1) using the phyloseq and ggplot2 packages (Wickham, 2016). Rarefaction curves were also generated using the ggplot2 package, with rarefication depth set at 3800. Beta-diversity was assessed using Bray–Curtis dissimilarity (Bray and Curtis, 1957), Jaccard similarity (Jaccard, 1908), unweighted UniFrac, and weighted UniFrac (Lozupone and Knight, 2005) and visualised through Principal Coordinate Analysis (PCoA) plots using the vegan and phyloseq packages in R.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 20 (SPSS Inc. Chicago, IL, USA) and software package R (4.2.1) (R Core Team, http://www.R-project.org) in RStudio. The normality of data using SPSS was tested using the skewness and kurtosis. Normally distributed data is expressed as mean (M) ± standard deviation (SD), and skewed data as

median (Mdn) and interquartile range (IQR). Depending on the data distribution, differences between the groups were assessed using an independent samples t-test for normally distributed continuous variables or a nonparametric test using the Mann– Whitney U-test for skewed continuous variables and chi-square for categorical values. The value of $P < 0.05$ was used to denote statistical significance.

Comparisons of relative abundances at the phylum and genus levels were performed using the nonparametric Kruskal–Wallis H-test corrected with the Benjamini–Hochberg false discovery rate (FDR) for multiple comparisons by using the software package R in RStudio. Although only two groups were compared, the Kruskal–Wallis test was retained for themicrobiota data to maintain consistency with the LEfSe workflow and because its distribution-free properties are well suited to highly skewed genus-level abundance data. In contrast, Mann–Whitney U-tests were used for clinical variables, as this is the standard non-parametricmethod for two-group comparisons. Spearman's rank correlation coefficient was used to evaluate associations between microbial taxa and clinical variables. In addition, linear regressionmodels were applied to examine the relationship between microbial composition and nationality, with age assessed as a potential confounder. Both unadjusted and age-adjusted models were reported. For each genus-level analysis, the relative abundance of the bacterial genus was used as the dependent variable in separate linear regressionmodels, and nationality (Lebanese *vs.* Emirati) served as the main independent variable (coded 1 and 0, respectively). Relative abundances were analysed as proportional values without transformation (e.g. no log, arcsine-square-root, or CLR transformation), as exploratory inspection indicated that model residuals met acceptable assumptions for linear regression. Zero values were retained as observed without imputation. Age was added as a covariate in adjusted models to assess confounding, applying a ≥10% change-in-estimate criterion for identifying meaningful confounding effects (Skelly *et al.*, 2012). Model assumptions – including linearity, homoscedasticity, multicollinearity, and normality of residuals – were evaluated using residual plots and diagnostic checks. No additional covariates met criteria for inclusion.

Taxonomic composition was summarised using stacked bar plots at the phylum and genus levels, illustrating the relative abundance of dominant microbial taxa across study groups.

The statistical significance of beta-diversity between the two groups with OB (Emirati *vs.* Lebanese) was determined using Permutational Multivariate Analysis of Variance (PERMANOVA) using the software package R in RStudio.

Linear discriminant analysis (LDA) effect size (LEfSe) was done using the R

software in RStudio to explore microbial taxa with differential abundance between Lebanese and Emirati individuals with OB. Genera enriched in each group with an LDA score >^{10}log2 at a value of $P < 0.05$ were considered (Segata *et al.*, 2011).

3 Results

Participant characteristics

The participant characteristics are presented in Table 1.

Table 1 Demographic, anthropometric, and biochemical parameters between Lebanese and Emirati individuals with obesity

Variable[1]	Emirati n = 43	Lebanese n = 30	P-value[2]
Age (years)	29.9 ± 9.1	41.0 ± 10.7	<0.001*
Female (n (%))	27 (62.8)	20 (66.7)	0.807
Weight (kg)	119.0 (98.8 –133.2)	101.1 (98.4-112.0)	0.015*
Height (cm)	165.2 ± 9.8	164.06 ± 8.07	0.062
BMI (kg/m^2)	42.8 (37.8-46.1)	38.4 (35.7-41.7)	0.002*
WC (cm)	123.3 ± 17.8	118.7 ± 8.5	0.149
WtHR	0.74 ± 0.08	0.63 ± 0.07	<0.001*
PBF (%)	46.1 ± 5.3	45.4 ± 5.79	0.596
FM (kg)	53.8 ± 13.3	47.4 ± 7.3	<0.011*
EI (Kcal)	2075± 738	1822 ± 746	0.157
Fibre (g)	10 (7.8-13.8)	17.3 (13.1-21)	<0.001*
Fibre (g)/1000 Kcal	4.9 (4.0-7.3)	10.5 (6.4-14.3)	<0.001*
FBG (mg/dL)	97 (93.6-104.0)	98.5 (95.0-107.3)	0.346
Insulin	22.0 ± 14.0	20.9 ± 10.3	0.716
HOMA-IR	4.78 (3.08-7.59)	5.24 (3.47-6.73)	0.771
HDL-C (mg/dl)	41.7 ± 11.1	44.6 ± 11.3	0.279
LDL-C (mg/dl) (Mdn (IQR))	93 (75-118)	109 (81-136)	0.115
TG (mg/dl) (M ± SD)	128.5 ± 62.1	149.7 ± 50.2	0.127
TC (mg/dl) (Mdn (IQR))	161.6 (143.0-181.7)	177.0 (159.3-218.3)	0.020*
Lifestyle factors	Yes, n (%)	Yes, n (%)	
Probiotic supplement	0 (0)	0 (0)	–
Fiber supplement	2 (4.7)	0 (0)	0.509
Probiotic food consumption	29 (67.4)	8 (26.7)	0.001*
Probiotic food consumption frequency			
None	15 (34.9)	22 (73.3)	<0.001*
2 or less/week	13 (30.2)	7 (23.3)	
3 to 6/week	11 (25.6)	1(3.3)	
7 or more/week	4 (9.3)	1 (3.3)	
Prebiotic supplement	0 (0)	0 (0)	–
Smoker	12 (27.9)	14 (46.7)	0.137
Alcohol consumption	2 (4.7)	12 (40)	<0.001*
Diabetes	0 (0)	2 (6.7)	0.166

Variable[1]	Emirati n = 43	Lebanese n = 30	P-value[2]
Cardiovascular disease	0 (0)	3 (10)	0.065
Dyslipidaemia	1 (2.3)	6 (20)	0.017*
Hypertension	5 (11.6)	8 (26.7)	0.125
Irritable bowel syndrome	0 (0)	3 (10)	0.065
Cancer	0 (0)	0 (0)	–

[1] BMI: body mass index, WC: waist circumference, PBF: percentage body fat, FM: fat mass, WtHR: waist-to-height ratio, FBG: fasting blood glucose, HOMA-IR: homeostaticmodel assessment for insulin resistance, HDL-C: high- density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides, TC: total cholesterol, M ± SD: Mean ± standard deviation, Mdn (IQR): median (interquartile range).

[2] Statistical significance * (P <0.05) between groups. Independent-sample t-test was used for normally distributed continuous variables with mean, and SD (Age, Height, WC, WtHR, PBF, FM, EI, insulin, HDL-C, TG), Mann-Whitney U-test for skewed continuous variables (Weight, BMI, Fiber, Fiber/ 1000 kcal; FBG, HOMA-IR, LDL-C and TC) with medians and IQR, and Chi-square test was used for categorical variables.

A total of 43 Emirati and 30 Lebanese individuals with OB (BMI ≥35 kg/m^2) were enrolled in the study. The difference in sample sizes between the two groups was mainly due to recruitment challenges in Lebanon.While the broader study initially aimed to enrol participants undergoing bariatric surgery fromboth countries, enrolment in Lebanon was hindered by financial constraints and disruptions caused by the COVID-19 pandemic.

Most of the subjects were females including 62.8 and 66.7% of the Emirati and Lebanese participants, respectively (P = 0.807). Anthropometricmeasurements showed that weight (P = 0.015), BMI (P = 0.002),WtHR (P < 0.001), fat mass (FM) (P < 0.011), and probiotic food consumption (P = 0.001) were significantly higher in the Emirati group. As for fibre intake (P < 0.001), total cholesterol (P = 0.02), dyslipidaemia (P = 0.017), and alcohol consumption (P < 0.001), these were significantly higher in the Lebanese subjects. There was no significant difference between the two groups with respect to WC, PBF, energy intake (EI), FBG, insulin, HOMA-IR, HDL-C, LDL-C, TG, fibre supplement, smoking, diabetes, cardiovascular disease, irritable bowel syndrome, hypertension, and cancer. None of the participants were on probiotic or prebiotic supplements. Lebanese participants were significantly older than Emirati participants (41.0 ± 10.7 vs 29.9 ± 9.1 years, P < 0.001; Table 1).

Alpha- and beta-diversity

According to the alpha-diversity metrics (Figure 1), Lebanese adults with OB showed significantly higher diversity (Shannon index, P = 0.015), coinciding with the higher observed operational taxonomic unit (OTU) (P = 0.007), higher Chao1 richness (p = 0.006), and higher Faith's phylogenetic diversity (PD) (P = 0.007) compared to the Emirati group, but no statistically significant difference in evenness (Pielou's evenness, P = 0.964). Microbial composition as reflected by the beta-diversity measures including unweighted UniFrac, weightedUniFrac, Bray–Curtis dissimilarity, and Jaccard similarity showed a marked separation between the gut microbiota community of Lebanese and Emirati with OB. Pairwise PERMANOVA analysis indicated a significant difference in beta-diversity between the two groups (Figure 2); (P = 0.001; P = 0.008; P = 0.001; P = 0.001, respectively).

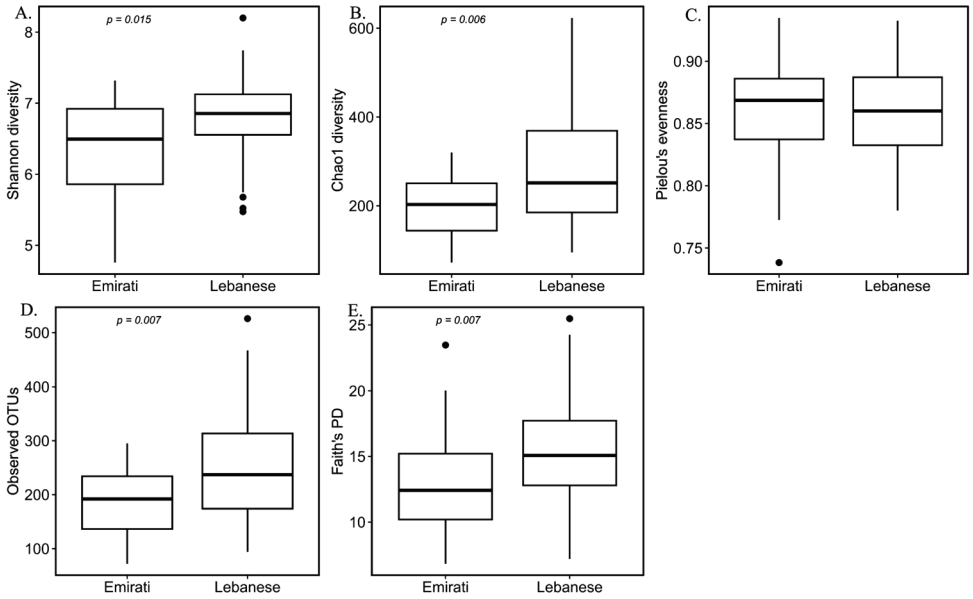


Figure 1 Alpha-diversity of Lebanese and Emirati individuals with obesity. Alpha-diversity boxplot showing Shannon diversity (A), Chao1 diversity (B), Pielou's evenness (C), Observed operational taxonomic unit (OTU)(D), and Faith's Phylogenetic Diversity (PD) (E) of Lebanese and Emirati individuals with obesity. For each sample, the alpha-diversity indices are shown on the y-axis, and the groups (Emirati or Lebanese) are on the x-axis. Boxes denote the interquartile range (IQR) between the first and third quartiles, and the horizontal line defines the median. Whiskers represent the smallest (ymin) and largest (ymax) values. Outliers are indicated by black circles. KruskalWallis test was performed. A P-value <0.05 denotes a significant difference between Lebanese and Emirati individuals with obesity.

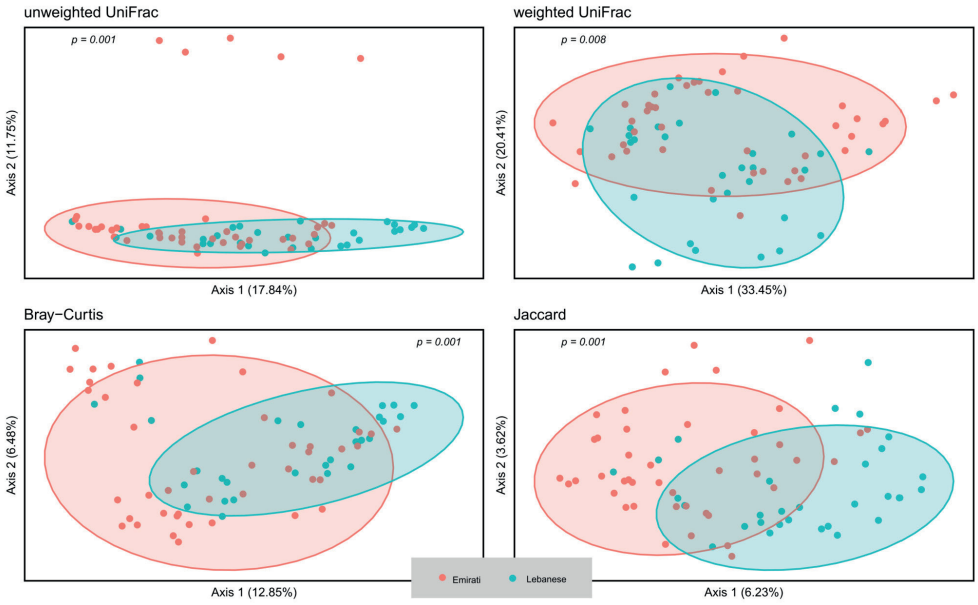


Figure 2 Beta-diversity of Lebanese and Emirati individuals with obesity. Principal coordinate analysis (PCoA) plot of unweighted Unifrac, weighted Unifrac, Bray-Curtis dissimilarity, and Jaccard similarity index between Lebanese (blue) and Emirati individuals (red) with OB. A *P*-value <0.05 denotes a significant difference between the two groups.

Taxonomic analysis

Taxonomic profiling of the gut microbiota was conducted and visualised using stacked bar plots. At the phylum level (Figure 3A), the microbial communities of both Lebanese and Emirati participants with obesity were dominated by *Bacillota* and *Bacteroidota*, which together accounted for nearly 90% of the total bacterial abundance. In the Lebanese group, *Bacillota* represented approximately 49% of the community, followed by *Bacteroidota* (41%), while *Pseudomonadota* (about 9%) and *Verrucomicrobiota* (<1%) were detected in lower proportions. Similarly, in the Emirati group, *Bacillota* (47%) and *Bacteroidota* (49%) were themost abundant phyla, with smaller contributions from *Pseudomonadota* (3%) and other phyla such as *Actinomycetota*, *Mycoplasmatota*, *Cyanobacteriota*, and *Lentisphaerota*, each present at very low levels.

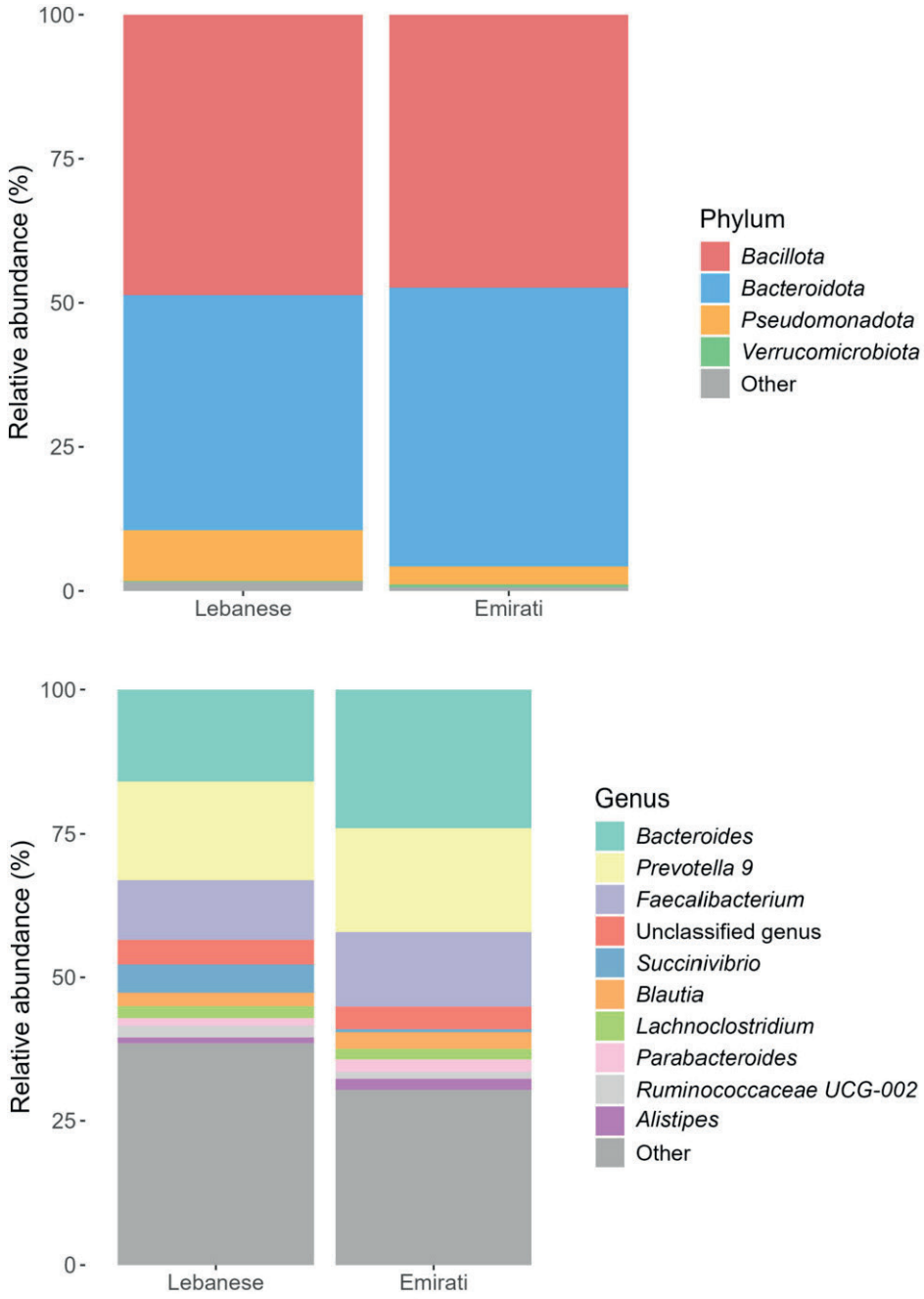


Figure 3 Stacked bar plots. (Top) Stacked bar plots of phylumlevel and (Bottom) at genus level composition detected in datasets of Lebanese *vs.* Emirati individuals with obesity. Relative abundances (percentages) of the phyla are displayed.

At the genus level (Figure 3B), the gut microbiota composition included a range of taxa commonly reported in obese populations. The most represented genera included *Bacteroides*, *Prevotella*, *Faecalibacterium*, *Ruminococcus*, *Lachnospira*, *Blautia*, and *Alloprevotella*, reflecting their contribution to carbohydrate fermentation and short-chain fatty acid production. Additional taxa such as *Collinsella*, *Paraprevotella*, *Dialister*, *Eubacterium ruminantium* group, *Intestinimonas*, and *Caproiciproducens* were also present, alongside multiple low-abundance genera distributed across individuals.

It is noteworthy that several taxa were completely absent in one group but present in the other at phylum (Figure 4A) and genus level (data not shown). For example, *Allisonella*, *Howardella*, *Intestinimonas*, and *Caproiciproducens*were detected in the Lebanese cohort but absent in Emiratis, whereas other genera such as *Bacteroides* and *Parabacteroides* were enriched in Emiratis but nearly absent in Lebanese participants.

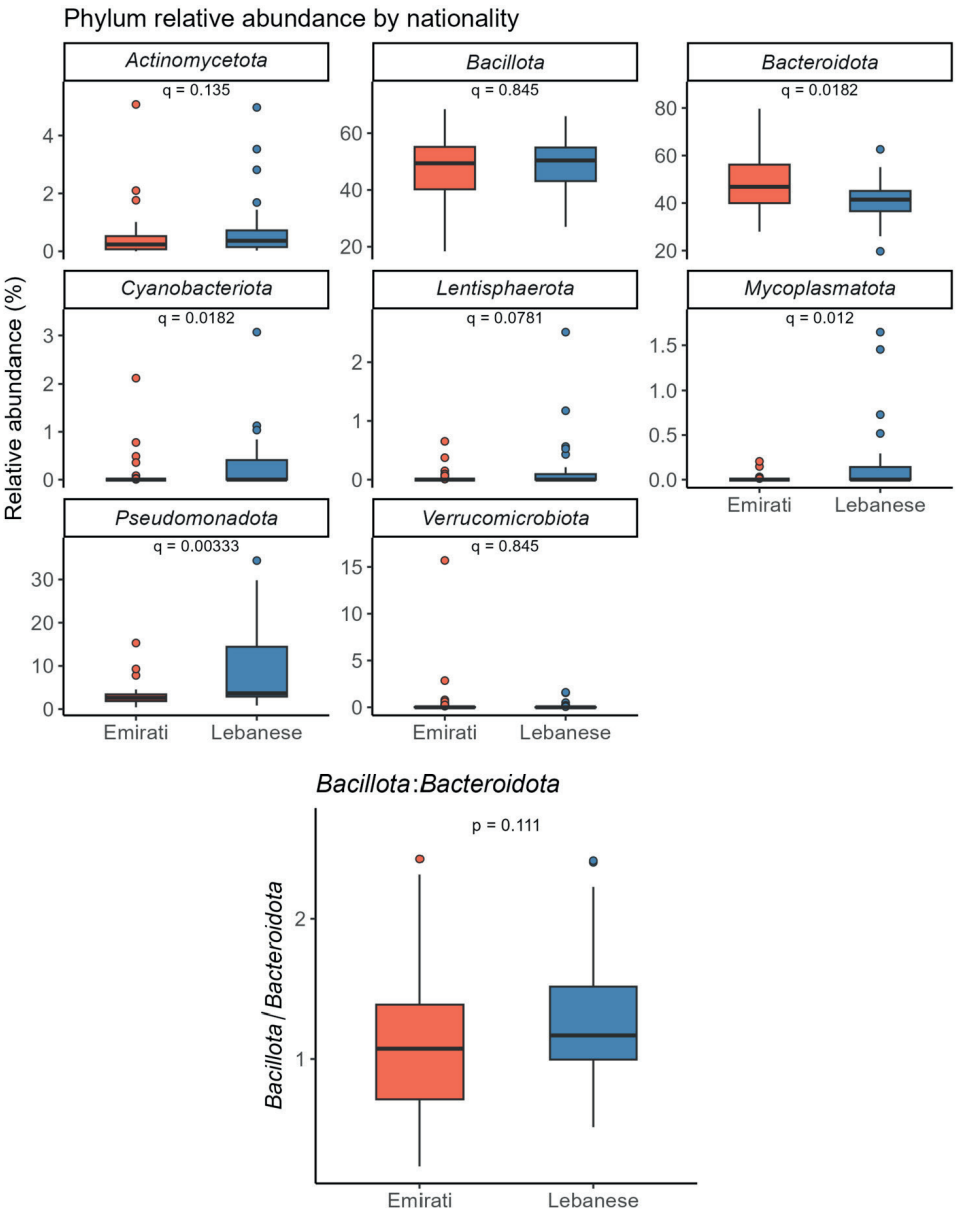


Figure 4 Comparative relative abundance of selected bacterial phyla and *Bacillota/Bacteroidota* ratio in Lebanese and Emirate participants with obesity. (Top panels) Boxplots showing relative abundance (%) of selected phyla, stratified by nationality with q-values. (Bottom panel) Boxplot of *Bacillota/Bacteroidota* ratio stratified by nationality. Differences between groups were assessed using the Kruskal-Wallis test followed by false discovery rate (FDR). Adjusted *q*-values are indicated where applicable. A *q*-value of ≤ 0.05 was considered statistically significant, as determined by the Kruskal-Wallis test with FDR correction.

Taken together, these findings indicate that the gut microbiota in both Lebanese and Emirati individuals with obesity was shaped by a limited number of dominant phyla and genera, complemented by a broad range of low-abundance taxa that added to inter-individual variability within each population.

Differences in gut microbial genera between Lebanese and Emirati individuals with obesity

Based on the relative abundances of the gut microbiota in the Lebanese *vs.* Emirati individuals with OB, LEfSe identified several genera that differed significantly between Lebanese and Emirati individuals, with only taxa exceeding the LDA threshold ($>^{10}$log2) and $P < 0.05$ reported.

In the Emirati group, *Bacteroides*, *Parabacteroides* (both of the *Bacteroidota* phylum), *Blautia*, *Acidaminococcus*, *Subdoligranulum*, *Phascolarctobacterium*, and *Lachnospiraceae UCG-004* (all *Bacillota* phylum) were enriched. In contrast, Lebanese participants showed higher abundances of 22 bacterial genera: *Unchar. taxon Clostridiales vadinBB60* group 1, *Tyzzerella*, *Streptococcus*, *Anaerotruncus*, *Erysipelotrichaceae UCG-003*, *Ruminiclostridium 6*, *Ruminococcaceae NK4A214* group, *Ruminococcaceae UCG-010*, *Eubacterium ruminantium* group, *Ruminococcaceae UCG-005*, *Christensenellaceae R-7* group, *Dialister*, *Ruminococcaceae UCG-002*, *Lachnospiraceae NK4A136* group (all *Bacillota* phylum); *Rikenellaceae RC9* gut group, *Paraprrevotella*, *Prevotellaceae NK3B31* group, *Unchar. taxon in Prevotellaceae*, and *Alloprevotella* (all *Bacteroidota* phylum); *Desulfovibrio*, *Sutterella*, and *Succinivibrio* (all *Pseudomonadota* phylum) (Figure 5).

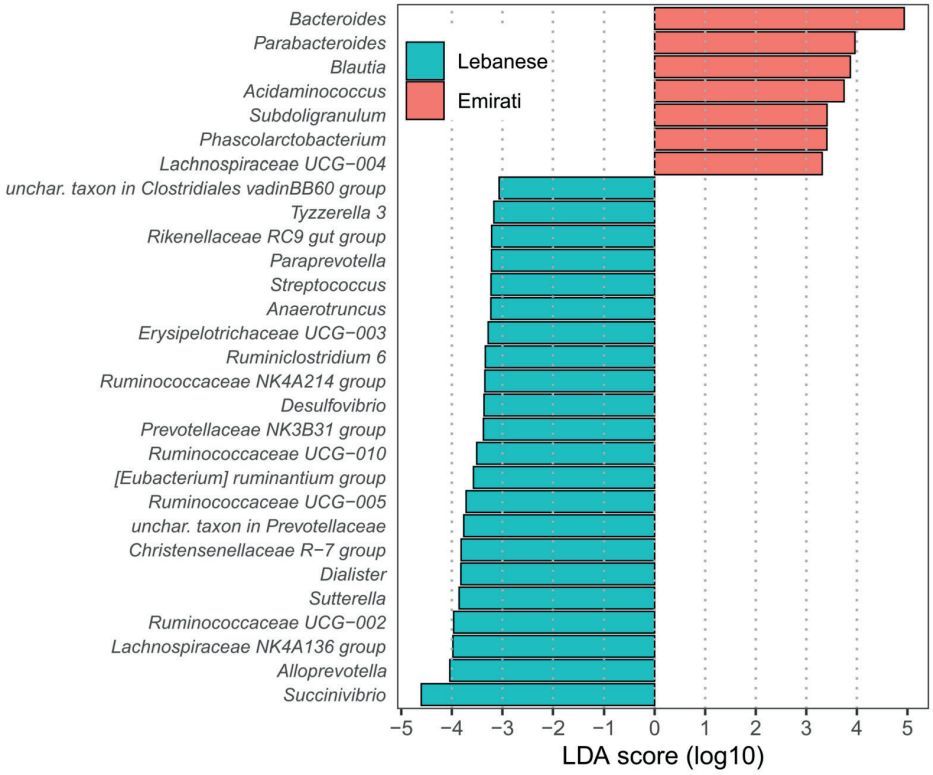


Figure 5 Linear discriminant analysis effect size (LEfSe) plot. The genera enriched in Lebanese and Emirati individuals with OB are coloured by blue and red, respectively. Histogram of the LDA scores computed for features differentially abundant among Lebanese and Emirati individuals with obesity. Only class meetings with an LDA significant threshold $>^{10}$log2 and $P < 0.05$ are shown.

According to the Kruskal-Wallis analysis with Benjamini–Hochberg correction at the genus level, as seen in Figure 6, there is an overlap with some of the results from the LEfSe. For the Lebanese group with OB, in accordance with the LEfSe results, there is an increased relative abundance of 14 out of the 22 microbial taxa, which are *Alloprevotella* (q <0.001), *Lachnospiraceae* NK4A136 group (q <0.001), *Ruminococcaceae* UCG-005 (q = 0.002), *Eubacterium ruminantium* group (q = 0.003), *Sutterella* (q = 0.006), *Ruminococcaceae* UCG-002 (q = 0.010), *Unchar. taxon Clostridiales vadin* BB60 group 1 (q = 0.013), *Paraprevotella* (q = 0.016), *Dialister* (q = 0.020), *Ruminiclostridium* 6 (q = 0.021), *Rikenellaceae* RC9 gut group (q = 0.022), *Anaerotruncus* (q = 0.029), *Erysipelotrichaceae* UCG- 003 (q = 0.035), and *Christensenellaceae* R-7 group (q = 0.037). None of the results for LEfSe and Kruskal-Wallis overlapped for the Emirati subjects.

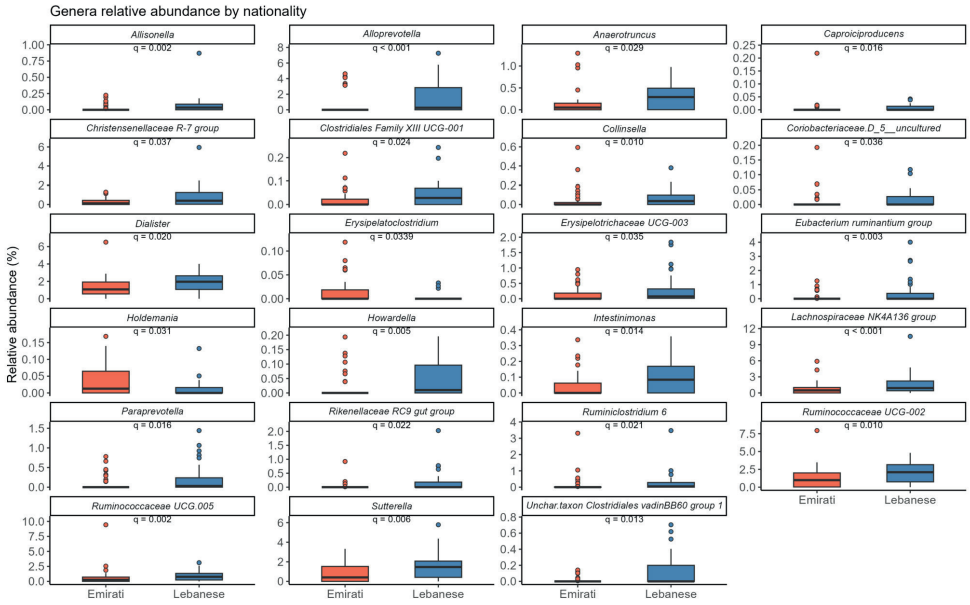


Figure 6 Relative abundance of selected gut bacterial genera by nationality. Boxplots depict the relative abundance (%) of selected bacterial genera in Lebanese and Emirati participants with obesity. Group comparisons were performed using the Kruskal–Wallis test, with false discovery rate (FDR) correction applied to account for multiple testing. Adjusted q-values are displayed for each genus.

Spearman correlation between gut microbiota and age in Lebanese and Emirati individuals with obesity

There was on average more than 10-year difference between Lebanese and Emirati participants (Table 1). Spearman correlation analysiswith FDR correction (Figure 7 and Table 2) identified several bacteria that were significantly positively associated with age ($q < 0.01$). The most pronounced correlation was observed for *Ruminococcaceae* NK4A214 (rho = 0.397, $q = 0.0014$), followed by *Prevotellaceae D_5* uncultured (rho = 0.386, $q = 0.002$), *Ruminococcaceae* UCG-005 (rho = 0.364, $q = 0.004$), and *Anaerotruncus* (rho = 0.359, $q = 0.005$). Additional significant associations were found for *Alloprevotella* (rho = 0.358, $q = 0.005$), *Ruminococcaceae* UCG-002 (rho = 0.358, $q = 0.005$), *Clostridiales vadin BB60* group (rho = 0.354, $q = 0.005$), and *Ruminococcaceae* UCG-010 (rho = 0.347, $q = 0.006$). Among all clinical and demographic variables assessed, age was the only factor significantly correlated with specific bacterial genera after FDR correction (Figure 7). Collectively, these findings indicate that age plays a substantial role in shaping gut microbiota

composition, particularly influencing members of the *Ruminococcaceae* family and other bacteria such as *Prevotellaceae D_5* uncultured and *Anaerotruncus*. The uniformity of positive associations suggests a gradual, age-related enrichment of these bacteria. None of the other clinical parameters were significantly correlated with any of the taxa.

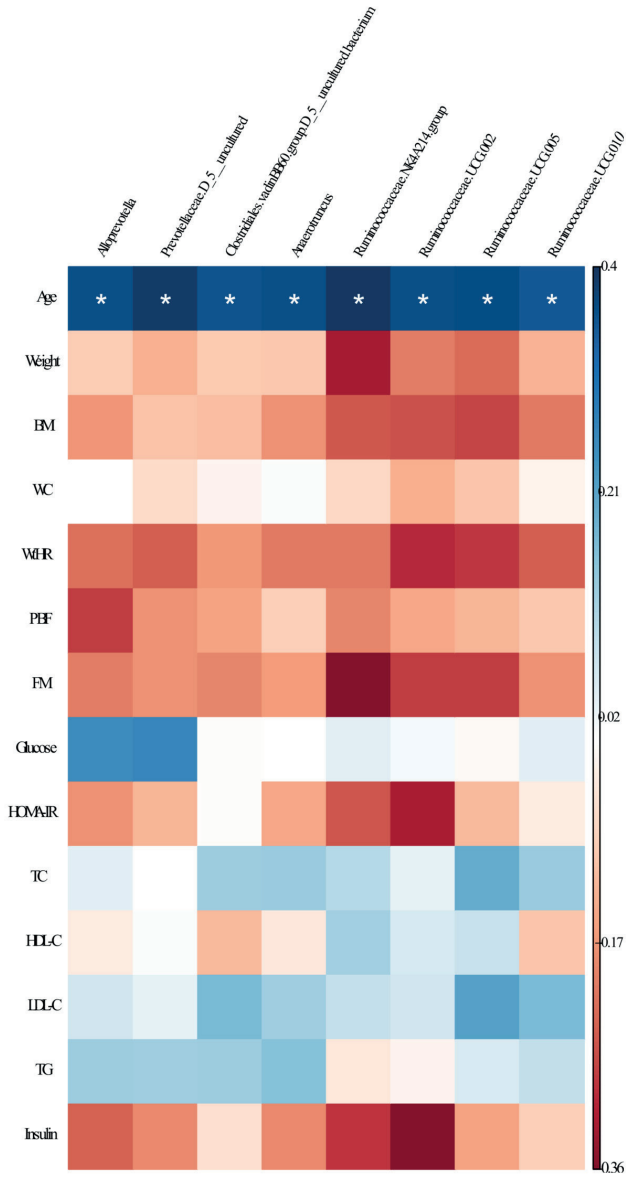


Figure 7 Spearman correlation analysis between gut microbiota and clinical variables in Lebanese and Emirati individuals with obesity. In the heatmap, blue squares indicate significant positive correlations, and red squares indicate significant negative correlations. * Significant correlation at q <0.05 (FDR-correction). Only age showed significant correlations with gut microbial taxa after FDR correction. Abbreviations: BMI: Body mass index;WC: waist circumference; WtHR: waist to height ratio, PBF: percent body fat; FM: fat mass; HOMA-IR: homeostatic model assessment for insulin resistance LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol; TG: triglyceride.

Table 2 Correlation analysis between gut microbiota and age in Lebanese and Emirati individuals with obesity

Bacteria	q-value[1]	rho
Ruminococcaceae.NK4A214.group	*0.*0014*	0.397
Prevotellaceae.D_5__uncultured	*0.*0022*	0.386
Ruminococcaceae.UCG.005	*0.*0040*	0.364
Anaerotruncus	*0.*0046*	0.359
Alloprevotella	*0.*0046*	0.358
Ruminococcaceae.UCG.002	*0.*0046*	0.358
Clostridiales.vadinBB60. group. D_5__uncultured. bacterium	*0.*0052*	0.354
Ruminococcaceae.UCG.010	*0.*0064*	0.3467

[1] Indicates significant correlation * $q < 0.05$ for Spearman correlation analysis with FDR correction.

Linear regression analysis

The relationship between microbial composition and nationality was subsequently examined, comparing Lebanese and Emirati individuals with OB, while accounting for age as a potential confounder. Linear regression models were used (Table 3) to assess these associations, with both unadjusted and adjusted models reported. A change-in-estimate criterion with a cut-off of 10%was used to identify the confounder (Skelly *et al.*, 2012).

Table 3 Linear regression analysis between gut microbiota and age among Lebanese and Emirati individuals with obesity.[1]

Gut microbiota	Model	Intercept estimate	Nationality (Lebanese) estimate	Age estimate	R^2 (Adj.)	*P*-value (Nationality)	*P*-value (Age)	Confounding (%)
	Unadj.	5.00 × 10−3	1.09 × 10−2	–	0.085	0.007 **	–	–
Alloprevotella	Adj.	−1.30 × 10−3	8.40 × 10−3	2.2 × 10-4	0.089	0.067	0.263	22.9
	Unadj.	8.00 × 10−4	5.70 × 10−3	–	0.074	0.012 *		–
Prevotellaceae D_5	Adj.	−1.00 × 10−5	5.50 × 10−3	3 × 10-5	0.061	0.037 *	0.821	5.0
	Unadj.	1.00 × 10−4	1.20 × 10−3	–	0.147	<0.001*	–	–
Clostridiales vadinBB60	Adj.	−1.10 × 10−3	7.00 × 10−4	4 × 10-5	0.213	0.047 *	0.011*	38.9
	Unadj.	1.50 × 10−3	1.50 × 10−3	–	0.048	0.036 *	–	–
Anaerotruncus	Adj.	6.00 × 10−5	9.7 × 10-4	5.0 × 10-5	0.059	0.229	0.181	35.3
	Unadj.	3.30 × 10−3	1.90 × 10−3	–	0.031	0.073	–	–
Ruminococcaceae NK4A214	Adj.	−3.00 × 10−4	6.0 × 10-4	1.2 × 10-4	0.059	0.613	0.0247 *	–
	Unadj.	1.25× 10−2	7.90 × 10−3	–	0.052	0.030 *	–	–
Ruminococcaceae UCG-002	Adj.	2.40 × 10−3	4.20 × 10−3	3.3 × 10-4	0.085	0.301	0.0637	46.97
	Unadj.	6.40 × 10−3	3.30 × 10−3	–	0.002	0.284	–	–
Ruminococcaceae UCG-005	Adj.	2.50 × 10−3	1.80 × 10−3	1.3 × 10-4	−0.0019	0.599	0.404	43.81
	Unadj.	5.00 × 10−4	2.97 × 10-3	–	0.140	<0.001*	–	–
Ruminococcaceae UCG-010	Adj.	−1.30 × 10−3	2.3 × 10-3	6.0 × 10-5	0.153	0.018 *	0.1530	22.73

[1] Indicates significant correlation * $P < 0.05$ for linear regression analysis.

In the unadjusted model, Lebanese individuals had a significantly higher relative abundance of *Alloprevotella* compared to Emiratis (β = 0.0109, $P = 0.007$). However, after adjusting for age, the effect size decreased (β = 0.0084) and was no longer statistically significant ($P = 0.067$), with a 22.9% reduction in effect size, suggesting that age may be a confounder.

For *Prevotellaceae D_5*, Lebanese nationality remained significantly associated with higher bacterial abundance in both unadjusted (β = 0.0057, $P = 0.012$) and adjusted models (β = 0.0055, $P = 0.037$). The 5% reduction in effect size suggests that age had minimal confounding influence.

In *Clostridiales vadin BB60*, a strong association was observed in the unadjusted

model (β = 0.0012, $P < 0.001$). After adjusting for age, the effect size decreased by 38.9% (β = 0.0007, $P = 0.047$), indicating that age played a significant role as a confounder. Additionally age was a significant predictor of bacterial abundance ($P = 0.011$).

For *Anaerotruncus*, Lebanese nationality was significantly associatedwith bacterial abundance in the unadjusted model (β = 0.0015, $P = 0.036$). However, after adjusting for age, the effect size declined by 35.3% (β = 0.00097) and was no longer significant ($P = 0.229$), further indicating confounding by age.

The unadjusted model for *Ruminococcaceae NK4A214* showed a weak association (β = 0.0019, $P = 0.073$), and in the adjusted model, the effect size further decreased (β = 0.0006, $P = 0.613$), indicating that age largely explained the observed relationship.

For *Ruminococcaceae UCG* – 002, Lebanese individuals exhibited significantly higher levels in the unadjusted model (β = 0.0079, $P = 0.030$). However, after adjustment, the effect size decreased by 46.97% (β = 0.0042) and lost statistical significance ($P = 0.301$), suggesting that age was a strong confounder.

No significant association was found for *Ruminococcaceae UCG* – 005 in either the unadjusted ($P = 0.284$) or adjusted model ($P = 0.599$).

Finally, for *Ruminococcaceae UCG* – 010, the unadjusted model showed a strong association (β = 0.00297, $P < 0.001$). After adjusting for age, the effect size decreased by 22.73% but remained statistically significant (β = 0.0023, $P = 0.018$), indicating that the association persisted but was partially influenced by age.

Overall, the regression analyses revealed a consistent pattern across taxa: several nationality–microbiota associations observed in the unadjusted models were attenuated after controlling for age, indicating that age acted as a meaningful confounder for many genera. However, a subset of taxa – including *Prevotellaceae D_5*, *Clostridiales vadinBB60*, and *Ruminococcaceae UCG-010*– remained significantly associated with nationality even after adjustment, suggesting a robust nationality-linked microbial signature. In addition, age itself showed positive associations with several genera, reinforcing its influential role in shaping gut microbial composition within this cohort.

4 Discussion

This study contributes to the growing body of research exploring how geography, culture, and ethnicity shape gut microbiota and its relationshipwith obesity. By comparing obese individuals from two Arab nationalities – Lebanese and Emirati residing in their respective countries, we highlight distinct microbial patterns potentially driven by regional dietary and lifestyle habits. Existing studies, such as comparisons between French and Saudi individuals, have shown that dietary and cultural factors can significantly influence microbial composition (Yasir *et al.*, 2015). Despite global interest in ethnic differences inmicrobiota composition, data from Middle Eastern populations remain limited. Our findings emphasise the need for more inclusive studies in this region to better understand how cultural and environmental factors influence metabolic health and to inform tailored intervention strategies.

The comparison of Lebanese and Emirati individuals with OB provides a meaningful framework to explore how cultural norms shape gut microbiota and potentially affect metabolic outcomes. The predominance of female participants 62.8 to 66.7% reflects a broader regional trend of higher obesity prevalence among ciswomen in the Middle East and North Africa (MENA), a phenomenon attributed to sociocultural perceptions associating larger body size with beauty and affluence (Mallat *et al.*, 2016; Naja *et al.*, 2011; Sibai *et al.*, 2003). These findings suggest that public health strategies targeting obesity in MENA countries should consider the cultural contexts influencing body image and dietary behaviours, alongside biological factors such as the gut microbiota.

Despite overall dietary similarities, Lebanese participants reported significantly higher fibre intake. While no direct correlations between fibre intake and microbial taxa were observed after FDR correction, fibre's known role in modulating gut microbiota may partly explain the distinct microbial profiles observed. In contrast, Emirati individuals exhibited higher anthropometric measures – including weight, BMI, WtHR, and fat mass – although these were not significantly associated with specific bacterial genera in our dataset. These differences align with previous studies linking higher fibre intake to greater gut microbial diversity and improved metabolic health (Nasreddine *et al.*, 2012, 2014). Comparable patterns have been observed in other cross-cultural comparisons, such as between French and Saudi populations, where differences in fibre consumption and traditional *versus*Westernised diets influenced microbial composition (Yasir *et al.*, 2015).

Another important demographic difference in our cohort was age, with Lebanese participants being on average more than 10 years older than Emiratis (Table 1). Since age is a well-recognised determinant of gut microbiota composition, this imbalance needed to be considered when interpreting our findings.

Our findings revealed that Lebanese adults with OB exhibit significantly greater gut microbial diversity compared to their Emirati counterparts. This is supported by multiple alpha-diversity indices, including the Shannon index, observed features, Chao1 richness, and Faith's PD. Greater microbial diversity may indicate a more complex and versatile ecosystem, potentially conferring resilience to metabolic diseases, as various studies have associated increased gut microbiota diversity with improved metabolic profiles in both humans and mice (Astbury *et al.*, 2020; Cotillard *et al.*, 2013; Le Chatelier *et al.*, 2013; Meyer and Bennett, 2016). Additionally, although a meta-analysis found that obesity is linked to alterations in gut microbial composition, including changes in richness and diversity, significant discrepancies were observed across different cohorts (Chanda and De, 2024). For instance, high BMI has been associated with decreased gut microbial diversity, and certain taxa, such as *Christensenellaceae*, have been linked to BMI variations across ethnicities (Balakrishnan *et al.*, 2021).

In terms of beta-diversity, PCoAwas used to visualise differences between the Lebanese and Emirati populations, and these were confirmed as statistically significant by pairwise PERMANOVA analyses, indicating marked differentiation inmicrobial community composition. This suggests that nationality – and by extension, environmental and dietary exposures – may play a critical role in shaping gut microbiota profiles (Parizadeh and Arrieta, 2023; Yasir *et al.*, 2015).

Taxonomic analysis of gut microbiota revealed both shared and distinct features. While both groups exhibited comparable proportions of the dominant phyla *Bacillota* and *Bacteroidota* – consistent with established gut microbiota compositions (Chen *et al.*, 2021; Zhang *et al.*, 2023) – notable differences emerged in less abundant but potentially influential taxa. The Lebanese group displayed significantly higher levels of *Pseudomonadota* (9% vs 3% in Emiratis), *Mycoplasmatota* (q = 0.003), *Cyanobacteriota* (q = 0.009), and *Lentisphaerota* (q = 0.049), whereas the Emirati group exhibited a greater abundance of *Bacteroidota* (q = 0.009). Elevated levels of *Mycoplasmatota* in the dietary components, such as high fat and sugar intake, which have been associated with increased obesity risk (Konstantinidis *et al.*, 2020; Napoli *et al.*, 2024). Although the *Bacillota/ Bacteroidota* ratio has historically been linked to obesity-related microbiota changes (Boulange *et al.*, 2016; Compare *et al.*, 2016; John *et al.*, 2018; Turnbaugh

et al., 2008), our results underscore the limitations of using this ratio as a universal marker of obesity. In our study, Lebanese individuals with OB exhibited a higher, but not significant, *Bacillota/ Bacteroidota* ratio than obese Emiratis, despite the latter presenting with higher overall obesity levels. This discrepancy aligns with recent research questioning the reliability of the *Bacillota/Bacteroidota* ratio across ethnically and geographically diverse populations (Magne *et al.*, 2020). While some studies have observed elevated *Bacillota/Bacteroidota* ratios in obese individuals (Koliada *et al.*, 2017), others report inconsistent or population-specific patterns (Kim *et al.*, 2019). These findings highlight the need to move beyond broad phylum-level comparisons and instead investigate specific microbial genera and their functional contributions to host metabolism (Bauer *et al.*, 2016).

Geographic, ethnic, and cultural factors are welldocumented determinants of gut microbiota composition (Yatsunenko *et al.*, 2012). As previous studies show, Americans, Japanese, Koreans, and Chinese individuals each harbour distinct microbial profiles, with varying proportions of *Bacillota*, *Actinomycetota*, and *Bacteroidota*, respectively (Brooks *et al.*, 2018). At the genus level, variations are similarly pronounced, with *Bacteroides* enriched in Chinese populations, *Prevotella* in Indians, and *Ruminococcus* in the Dutch (Brooks *et al.*, 2018). Our findings reflect these ethnically stratified patterns. Emiratis – characterised by higher BMI – had increased levels of *Bacteroides* and *Parabacteroides*, which are associated with high-fat, high-sugar diets and enhanced energy harvest. Conversely, Lebanese participants had higher abundances of *Alloprevotella* and *Paraprevotella*, linked to high-fibre intake and improved metabolic profiles (Christensen *et al.*, 2018). These results bolster the existing evidence linking *Bacteroides*- dominant microbiota to increased adiposity, while leaner individuals often harbour *Prevotella*-rich communities (Lee *et al.*, 2024). Supporting this, studies comparing French and Saudi populations (Yasir *et al.*, 2015), as well as investigations among Emiratis (Ahmad *et al.*, 2023) and Lebanese (Abou-Samra *et al.*, 2025) have highlighted gut microbiota differences shaped by diet, lifestyle, and cultural practices.

LEfSe analysis further identified taxa that discriminate between the two populations. Emirati individuals showed enrichment in *Bacteroides*, while Lebanese participants had higher levels of *Lachnospiraceae*. Both genera have been previously implicated in metabolic functions related to energy harvest, lipid metabolism, and fat storage (Wu *et al.*, 2024; Yang *et al.*, 2022). However, interpretation of these differences must consider the significant age gap between the groups. Spearman correlation analysis confirmed that age significantly correlated with several taxa, and linear regression models showed that some between-group differences –

particularly at the genus level – were attenuated or lost after adjusting for age. This underscores the role of age as a confounding factor in microbiota studies, as also reported in previous research (Chen *et al.*, 2021; De la Cuesta-Zuluaga *et al.*, 2019; Odamaki *et al.*, 2016).

Age-related changes in the gut microbiome have been extensively documented across the human lifespan. Research spanning from infancy to old age has identified key transitions in microbial composition – particularly during early development and later life stages (Odamaki *et al.*, 2016). Some studies report minimal age-related differences (Takagi *et al.*, 2019), while others identify significant associations between age and microbial composition (De la Cuesta-Zuluaga *et al.*, 2019). These inconsistencies indicate that age can act as a confounder in microbiome studies and must be carefully considered. In our cohort, although age explained part of the between-group variation, several taxa – including *Prevotellaceae D_5*, *Clostridiales vadinBB60*, and *Ruminococcaceae UCG-010* – remained significantly associated with Lebanese nationality after adjustment. This suggests that nationality-related dietary and environmental factors continue to influence gut microbiota composition independently of age, consistent with evidence that distinct microbial signatures persist across populations even when controlling for demographic variables (Brooks *et al.*, 2018; Yatsunenko *et al.*, 2012).

Each of these taxa has known links to healthpromoting microbial functions. *Prevotellaceae* D_5 is associated with fibre-rich diets and improved glycaemic control (Kovatcheva-Datchary *et al.*, 2015); *Clostridiales vadinBB60* has been found in metabolically healthy individuals and centenarians and is implicated in lipid metabolism and anti-inflammatory effects (Zhang *et al.*, 2019). *Ruminococcaceae UCG-010* plays a role in fibre degradation and short-chain fatty acid production, which support gut health and are linked to GLP-1 release, satiety, and protection against type 2 diabetes (Gryaznova *et al.*, 2022; Mancabelli *et al.*, 2017; Tims *et al.*, 2013; Tsai *et al.*, 2020; Wei *et al.*, 2018). The persistence of these associations despite age adjustment highlights the key role of cultural and environmental influences tied to nationality in shaping the gut microbiota.

Although ethnicity was not found to have a significant correlation with microbiota composition in a Middle Eastern population, lifestyle and environmental influences exhibited a greater degree of homogeneity compared to the ethnic, sociocultural, economic, and dietary diversity observed within the United States (Brooks *et al.*, 2018). Importantly, our study controlled for methodological consistency – using identical DNA extraction and sequencing protocols – yet still observed significant differences between groups. This reinforces the notion that

factors such as diet (Asnicar *et al.*, 2021), genetics (Goodrich *et al.*, 2014), physical activity, and medication use (Heiman and Greenway, 2016) contribute meaningfully to microbiota variation.

Strengths and limitations

This study provides novel comparative insights into how regional and ethnic factors may shape gut microbiota composition in the context of obesity, focusing on two Arab populations living in the MENA region. The use of standardised microbiota sequencing protocols across sites minimised methodological variability, while comprehensive data collection – including anthropometric, biochemical, and selected dietary variables – facilitated robust analysis. The application of linear regression models adjusted for age, along with rigorous participant selection and harmonised methodologies, further strengthened the reliability and interpretability of the findings. Nonetheless, several limitations should be considered. The cross-sectional design limits the ability to infer causality, suggesting that there must be longitudinal research to examinemicrobiota dynamics over time. The relatively small sample size may constrain the generalisability of the results. This study also focused exclusively on obese participants froma larger cross-sectional dataset that also included normal-weight adults. As such, comparisons with normal-weight controls were beyond the scope of the current analysis but will be explored in a separate study using the same parent cohort. Another notable limitation is the significant age difference between the Lebanese and Emirati participants, which could independently influence gut microbiota composition. While we addressed this through correlation and regression analyses, which confirmed age as a confounding factor, residual confounding cannot be fully excluded. Although age differences between the 2 samples were accounted for, other relevant factors – such as physical activity, medication use, psychosocial stress, socioeconomic status, and genetic background– were not assessed and may have influenced gut microbiota composition. Additionally, dietary assessment was limited to fibre and probiotic intake, omitting other potentially significant dietary components (e.g. fat and protein intake). Variability in laboratory assays between countries may have introduced inconsistencies in biochemicalmeasurements, and the lack of functional microbiota profiling restricted insights into microbial metabolic potential. Additionally, the use of different bioelectric impedance analysis devices across study sites (Tanita in the UAE and InBody in Lebanon) may introduce inter-device variability and measurement bias, which could affect the comparability of body composition data between the two populations.

5 Conclusions

This study highlights significant gut microbiota differences between Lebanese and Emirati adults with OB, shaped by cultural, dietary, and geographic factors. Emiratis exhibited a higher abundance of *Bacteroides* and *Parabacteroides*, bacteria commonly linked to highfat, low-fibre diets and greater energy harvest. In contrast, Lebanese individuals showed greater microbial diversity and elevated levels of *Alloprevotella*, *Paraprevotella*, and *Mycoplasmatota*, reflecting higher fibre intake. Furthermore, this study reveals that dietary patterns rooted in cultural and geographic context strongly influence the composition of gut microbiota. The study also identified age as key confounder, which significantly influenced the associations between nationality and microbial profiles. These findings highlight the importance of incorporating both age – and ethnicityspecific microbiome signatures when designing targeted obesity interventions. Notably, microbial differences such as higher abundances of *Prevotellaceae D_5*, *Clostridiales vadinBB60*, and *Ruminococcaceae UCG- 010* in Lebanese individuals remained significant after adjusting for age, emphasising the potential for culturally driven, microbiota-informed strategies. Ultimately, the gut microbiota may serve as both a biomarker of lifestyle and a modifiable factor in the management of obesity and its metabolic consequences within Arab populations living in the MENA region. Future research should adopt longitudinal designs to elucidate the causalmechanisms linking gut microbiota to obesity and metabolic health, particularly in response to dietary and lifestyle interventions. Including non-obese control groups and diverse Arab populations will enhance generalisability and provide insights into ethnicity-specific microbial variations. Integrating functional metagenomics, metabolomic profiling, and detailed dietary, lifestyle, and genetic data will deepen our understanding of microbial activity and itsmetabolic impact. Additionally, culturally tailored dietary interventions and investigations into age-related microbial shifts across life stages are warranted to inform effective, personalised strategies for weight management in the MENA region.

Supplementary materials

Data is available on https://doi.org/10.1163/18762891-bja00111 under Supplementary Materials.

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Authors' contribution

Conceptualization, M.A.S., M.A.A., M.K. and K.V.; methodology, M.A.S., M.A.A., M.K. and K.V.; software, M.A.S., M.A.A., and K.V.; validation, M.K. and K.V.; formal analysis, M.A.S. and M.A.A.; investigation, M.A.S. and M.A.A.; resources, M.K., K.V. and C.A.M.; data curation, M.A.S., M.A.A., M.K. and K.V.; writing – original draft preparation, M.A.S. and M.A.A.; writing – review and editing, M.K., K.V., E.B and C.A.M.; visualization, M.A.S., M.A.A., M.K. and K.V.; supervision, M.K., K.V., and E.B.; project administration, M.K. and K.V.; funding acquisition, C.A.M. and K.V. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

KV is editor in chief of Beneficial Microbes, but has not been involved in the review and decision process of this article. The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Supplementary Materials

Appendix A – Screening Questionnaire

Name: _____
Date: _____
Nationality/Origin:_____
Mother's Nationality/Origin: _____
Father's Nationality/Origin: _____
Age:_____
Gender: ☐ Male ☐ Female
Height: _____
Weight: _____
BMI: _____

1. If you are a female, are you currently pregnant or breastfeeding or planning to become pregnant or menopausal?

☐ Yes ☐ No

2. Do you suffer from the following?
   a) Diabetes
   b) Heart disease
   c) Dyslipidemia
   d) Hypertension
   e) IBS
   f) Cancer
   g) Other:_____

3. Did you undergo any surgery in the last 5 years?

☐ No ☐ Yes (specify):_____
_____

4. Did you lose more than 5% of your weight in the last 3 months

☐ No ☐ Yes

5. Are you currently on any medication?

☐ No ☐ Yes (specify):_____
_____

6. Are you currently taking any probiotic supplements?
☐ No ☐ Yes (specify brand and how many per day):_____

7. Are you currently taking any fiber supplements?
☐ No ☐ Yes (specify brand and how many per day):_____

8. Do you generally consume probiotic food such as yogurt/ayran/activia/actimel/ yakult?
☐ No ☐ Yes
If yes ☐ 2 or less/week* ☐ 3-6/per week*
☐ 7 or more/week*
**The portion is considered 1 cup (250ml)*

9. Are you currently taking any prebiotic supplements?
☐ No ☐ Yes (specify brand / how many per day/ for how long):_____

10. Are you currently taking any nutritional supplements?
☐ No ☐ Yes (specify): _____
_____

11. Are you currently taking any antibiotics?
☐ No ☐ Yes (specify, and for how long):_____
_____

12. When was your last course of antibiotics taken?
☐ Less than a month ☐ 1 – 3 months ago ☐ 6 -9 months ago ☐ 9-12 months ago ☐ >12 months ago

13. Are you a smoker?
☐ No ☐ Yes (specify number of cigarettes per day/ years of smoking):_____

14. Do you drink alcohol?
☐ No ☐ Yes (specify average number of drinks/week)_
_____

15. Have you been dependent on the use of drugs in the past 5 years?

☐ No ☐ Yes

16. Do you integrate physical activity in your daily routine?

☐ Walk to work
☐ Walk in a mall
☐ Walk outdoors
☐ Bike to go to places
☐ Take the stairs

Frequency: ☐ 2-3 x/week ☐ 3-5x/week ☐ Every Day

Duration: ☐ 10-30 min/day ☐ 30-45 min/day ☐ more than 60 minutes/ day

17. Do you incorporate any exercise program?

☐ No ☐ Yes

if yes ☐ 2-3 x/week ☐ 3-5x/week ☐ Every Day

☐ 30 min/session ☐ 30-45 min/session ☐ more than 60 minutes

☐ Resistance Training ☐ Cardiovascular Training

SUBJECT NUMBER:

Investigator Comments:_____

6

Chapter 6

General Discussion

Overview

Obesity is a significant public health concern in the United Arab Emirates (UAE), with a national prevalence of 27.8% among adults, according to the National Health Survey 2017–2018 (Ministry of Health and Prevention, 2018). This prevalence is notably higher among women (30.6%) compared to men (25.1%) (Ministry of Health and Prevention, 2024). The health implications of obesity are profound, increasing the risk of chronic conditions such as stroke, heart disease, high blood cholesterol, hypertension, fatty liver disease, pregnancy complications, osteoporosis, and type 2 diabetes (Ministry of Health and Prevention, 2024; World Health Organization, 2021).

Gut microbiota composition has been associated with metabolic health, yet its specific contribution to obesity appears heterogeneous rather than uniform across populations (Lynch & Pedersen, 2016; Turnbaugh et al., 2006). Bariatric surgery has emerged as an effective intervention for severe obesity. In the UAE, more than 5,000 bariatric procedures were performed annually before the COVID-19 pandemic, with sleeve gastrectomy being the most common procedure (Angrisani et al., 2018; Haskins, 2022). However, the influence of bariatric surgery on gut microbiota composition and gut-derived peptide profiles within the Emirati population remains underexplored.

Investigating postoperative changes in microbiota and peptide hormones alongside metabolic outcomes may provide insight into biological pathways relevant to obesity management in the region.

The present thesis evaluates coordinated associations between microbial, hormonal, and metabolic parameters and does not infer causal directionality.

This dissertation examines relationships between gut microbiota composition, gut-derived peptide hormones, obesity, and metabolic health in Arab populations, primarily Emirati adults, and explores changes observed following bariatric surgery.

In addition, the dissertation characterizes differences in fasting gut-derived peptide hormone profiles between lean Emirati adults and Emirati adults with

obesity and evaluates their associations with markers of adiposity and insulin resistance.

The research characterizes fecal microbiota differences between lean Emirati adults and Emirati adults with obesity at the genus level and relates these patterns to metabolic markers rather than relying on the Firmicutes/Bacteroidetes ratio.

The dissertation further examines coordinated postoperative changes in microbiota and gut-derived peptide hormones and compares microbiota composition between Emirati and Lebanese adults with obesity.

Across the studies included in this dissertation, a consistent theme emerges: hormonal profiles, microbial community structure, and clinical metabolic markers change in parallel, but their interpretation depends on physiological and population context (e.g., Emirati versus Lebanese background; pre- versus post-bariatric surgery).

Integrative Synthesis: What the Studies Collectively Teach Us

The combined evidence from this dissertation supports several observations across hormonal, microbial, and clinical domains.

First, gut-derived peptide hormone profiles and gut microbiota composition were associated with metabolic risk, but not always in patterns similar to the ones consistently reported in Western cohorts. In particular, fasting GLP-1 concentrations were higher in Emirati adults with obesity compared to lean counterparts and showed a positive association with insulin resistance. Several Western studies have reported reduced or unchanged fasting GLP-1 concentrations in obesity (Færch et al., 2015; Steinert et al., 2017), although findings across cohorts are not fully consistent (Kubota & Yabe, 2021). These differences likely reflect heterogeneity in metabolic phenotype, study design, and population characteristics rather than a single universal endocrine pattern. Second, bariatric surgery was accompanied by concurrent improvements in BMI, insulin resistance, gut peptide profiles, and microbiota diversity. These parallel shifts indicate coordinated physiological adaptation and a more beneficial microbial and metabolic profile in the postoperative state.

Third, the ethnic context influenced the interpretation of microbiota composition. Lebanese participants demonstrated higher microbial diversity and enrichment of fibre-associated genera despite persistent obesity. Although these characteristics are frequently regarded as metabolically favorable, the present findings suggest that microbiota composition alone may not fully reflect metabolic status within this population. Rather, microbial patterns appear to be shaped by dietary habits and population-specific host factors. These observations underscore the importance of interpreting microbiota data within ethnic, dietary, and physiological contexts rather than in isolation.

Collectively, these findings demonstrate that obesity in Arab populations is characterized by interconnected but context-dependent relationships between gut peptides, microbiota, and metabolic outcomes. The contribution of this thesis, therefore, lies not in identifying a single biomarker, but in showing that

obesity-related biological signals vary according to population background and clinical state. This informs the interpretation of obesity studies in the Middle East.

Gut-derived peptide hormones and metabolic dysregulation in obesity

Fasting concentrations of multiple gut-derived peptide hormones differed significantly between Emirati adults with obesity and lean counterparts, highlighting obesity-associated alterations of enteroendocrine hormones in this population.

Fasting GLP-1 concentrations were significantly higher in individuals with obesity and showed a strong positive association with insulin resistance, as measured by HOMA-IR, even after adjustment for BMI. These observations suggest that fasting GLP-1 in this cohort may reflect compensatory signalling or underlying metabolic dysregulation rather than effective satiety signalling. (Müller et al., 2019). However, the present study design does not allow for the determination of the underlying mechanisms.

Leptin concentrations were markedly elevated in participants with obesity and correlated strongly with IR markers. However, this association was attenuated after adjustment for BMI, indicating that leptin primarily reflects adiposity rather than acting as an independent predictor of metabolic dysfunction. These findings are consistent with established evidence of leptin resistance in obesity, where chronic hyperleptinemia fails to induce appropriate satiety and metabolic responses (Al-Amodi et al., 2018; Izquierdo et al., 2019).

Insulin concentrations were also elevated in individuals with obesity, reflecting compensatory hyperinsulinemia secondary to insulin resistance. Among anthropometric measures, waist-to-height ratio (WHtR) showed a strong positive association with insulin levels, supporting its utility as a practical marker of central adiposity-related metabolic risk (Ashwell et al., 2012).

In line with previous literature, fasting ghrelin concentrations were lower in individuals with obesity (Tschöp et al., 2001) and negatively correlated with WHtR (Sadiq & Bhatti, 2015). This reduction is consistent with adaptive suppression of hunger signalling in chronic positive energy balance rather than primary hormonal deficiency.

CCK concentrations were higher in lean individuals and negatively correlated with obesity markers, although this association did not persist after adjustment for BMI. Because fasting CCK poorly reflects functional satiation, this finding should be interpreted cautiously (Pathak et al., 2018).

No significant difference in fasting PYY concentrations was observed between individuals with obesity and lean counterparts. This contrasts with some Western studies reporting lower fasting or postprandial PYY levels in obesity (Batterham et al., 2003; le Roux et al., 2006), but aligns with other reports showing no difference or even higher fasting PYY levels (Brownley et al., 2010; Cahill et al., 2014; Ukkola et al., 2011; Wilbrink et al., 2025). As only fasting measurements were obtained, physiological satiety responses cannot be inferred.

Taken together, the hormonal profile does not indicate isolated endocrine abnormalities but a coordinated metabolic state characterized by insulin resistance and altered satiety hormones in obesity. Rather than single-hormone dysregulation, the pattern reflects an integrated metabolic phenotype in which peptide hormones respond to chronic energy surplus and adiposity.

This interpretation aligns with the broader thesis concept that gut peptides co-vary with metabolic status and microbiota composition.

Gut microbiota composition and adiposity: genus-level patterns and context dependence

Differences in gut microbiota composition were observed between individuals with obesity and lean counterparts, as reflected by variation in β-diversity and differential abundance at the genus level. Specifically, β-diversity analyses indicated differences in microbial community composition between samples across groups, while several genera were associated with adiposity markers. These findings align with previous reports describing compositional variation in obesity, although no consistent microbial signature has been identified across populations (Pinart et al., 2021; Sze & Schloss, 2016). Importantly, the present results reflect compositional associations rather than functional or causal effects. No significant difference in the Firmicutes/Bacteroidetes ratio was detected in the Emirati cohort, supporting growing evidence that phylum-level metrics may have limited utility as universal markers of obesity (Guida & Venema, 2015; Pinart et al., 2021). This observation further reinforces the context-dependent nature of obesity-related microbial patterns rather than supporting a single compositional index.

At the genus level, *Acidaminococcus* was enriched in individuals with obesity and positively correlated with BMI and fat mass. This genus has previously been associated with metabolically adverse microbial profiles (Al-Muhanna et al., 2022; Crovesy et al., 2020) and is known for its amino-acid fermenting metabolic characteristics as well as capacity to produce SCFA (Neis et al., 2015; Vital et al., 2014). However, SCFA production should not be interpreted as universally beneficial, as functional consequences depend on substrate availability, host metabolic state, and microbial ecosystem context. (Blaak et al., 2020; Canfora et al., 2019). Thus, enrichment of Acidaminococcus in this cohort may reflect a context-dependent microbial signature associated with adiposity rather than a uniformly protective or harmful metabolic effect. *Lachnospira* was positively associated with waist-to-height ratio (WHtR), a marker of central adiposity. Although this genus is typically considered metabolically favourable due to its butyrate-producing capacity (Ríos-Covián et al., 2016; Zhang et al., 2015), the present finding illustrates that taxonomic classification alone does not determine metabolic impact. In populations undergoing nutritional transition, differences in dietary substrate availability and host metabolic status may modify the functional relevance of butyrate-producing taxa (De Filippo et al., 2010; Deschasaux et al.,

2018). Accordingly, enrichment of *Lachnospira* should be interpreted within the broader host metabolic context rather than as direct evidence of metabolic protection (Cani, 2012; Turnbaugh et al., 2006).

Genes enriched in lean individuals were inversely associated with adiposity markers. While these compositional differences are informative, they highlight the limitations of genus-level inference and the need for deeper functional characterization to better understand microbe–host interactions. Taxonomic shifts do not necessarily translate into metabolic effects, as demonstrated in human intervention studies altering microbial composition through galacto-oligosaccharides or antibiotics, which resulted in limited or inconsistent metabolic benefits (Canfora et al., 2017; Reijnders et al., 2016).

Bariatric surgery as a system-level metabolic perturbation

Bariatric surgery is one of the most effective clinical treatments for severe obesity, producing substantial and sustained weight loss together with improvements in insulin sensitivity and cardiometabolic risk factors (Angrisani et al., 2018; Haskins, 2022). Beyond mechanical restriction, these procedures induce coordinated physiological changes, including altered gastrointestinal anatomy, nutrient flow, bile acid signalling, and enteroendocrine responses, which occur alongside changes in gut microbiota composition and metabolic regulation (Laferrère & Pattou, 2018; Madsbad et al., 2014).

In this dissertation, surgery was followed by marked reductions in BMI and insulin resistance within three months, accompanied by concurrent changes in gut-derived peptide hormone profiles and gut microbiota composition. These parallel alterations suggest coordinated adaptation across microbial, endocrine, and clinical domains. Following sleeve gastrectomy, gut microbiota composition showed significant restructuring, with increased microbial α-diversity and separation in β-diversity. Increased diversity has been associated with improved metabolic health and ecological resilience of the gut microbiome (Cotillard et al., 2013; Le Chatelier et al., 2013), and similar postoperative increases have been reported in bariatric cohorts (Ilhan et al., 2017; Kong et al., 2013; Palleja et al., 2016).

At the phylum level, relative abundances of Proteobacteria and Saccharibacteria increased postoperatively, whereas the Firmicutes/Bacteroidetes ratio remained unchanged. This finding supports the limited utility of the F/B ratio as a universal marker of obesity or weight loss response (Duncan et al., 2008; Magne et al., 2020; Peters et al., 2018; Schwiertz et al., 2010). Instead, postoperative microbial adaptation appears to involve broader taxonomic restructuring rather than convergence toward a single uniform microbiota configuration.

At the genus level, taxa related to short-chain fatty acid metabolism and energy homeostasis were altered. Decreases in *Roseburia* and increases in *Butyricimonas*, together with enrichment of *Christensenella*, *Ruminococcus*, and *Alistipes*, resemble patterns previously observed in leaner phenotypes (Cao et al., 2022; Ilhan et al., 2017; Palleja et al., 2016). However, these changes should be interpreted cautiously,

as microbial function depends on substrate availability, host metabolism, and community structure (Canfora et al., 2019; Louis & Flint, 2017).

No significant change in *Akkermansia muciniphila* abundance was observed. Although this species has been linked to metabolic health and gut barrier integrity (Dao et al., 2016; Everard et al., 2013), postoperative trajectories are inconsistent across studies. Some cohorts show transient increases after surgery, whereas others show no sustained change (Palleja et al., 2016). The absence of change in this cohort may relate to population-specific microbial patterns, inter-individual variability, or the short follow-up period. Emerging evidence further indicates that its metabolic effects are context-dependent and influenced by host physiology and strain-level variation (Borrego-Ruiz & Borrego, 2025; Depommier et al., 2019; Jian et al., 2023).

Overall, postoperative restructuring did not converge toward a single “healthy microbiome,” but toward a population-specific configuration resembling that observed in lean Emirati individuals.

Postoperative changes in gut-derived peptide hormones occurred in parallel with microbial remodelling and metabolic improvement. Following surgery, fasting GLP-1 and insulin concentrations decreased, PYY increased, and ghrelin showed a modest rise, consistent with early reorganization of enteroendocrine signalling after altered gastrointestinal anatomy and nutrient delivery.

The increase in fasting PYY is compatible with enhanced satiety signalling and aligns with its recognized role in appetite regulation after bariatric surgery (le Roux et al., 2006; Schmidt et al., 2014). In contrast, fasting GLP-1 concentrations decreased in the present cohort. This finding should be interpreted in light of the distinction between fasting and postprandial hormone dynamics. Several studies reporting exaggerated GLP-1 responses after Roux-en-Y gastric bypass have primarily assessed postprandial secretion rather than fasting concentrations (Arakawa et al., 2020).

Therefore, differences between the present findings and previous reports likely reflect variation in surgical technique, timing of hormone measurement, and physiological context rather than contradictory endocrine responses.

Importantly, fasting hormone measurements capture only basal endocrine status. Postprandial secretion dynamics, neural signalling, and receptor sensitivity — major contributors to appetite regulation — were not assessed and may partly contribute to postoperative metabolic improvement.

Together, these observations indicate coordinated endocrine adaptation rather than isolated hormonal effects.

The concurrent remodelling of gut microbiota and systemic gut-derived peptide profiles, therefore, is consistent with integrated metabolic adaptation following bariatric surgery. Although microbial taxa related to SCFA production were increased and short-chain fatty acids can stimulate enteroendocrine L-cells and influence GLP-1 and PYY secretion (Tolhurst et al., 2012), the present findings do not allow determination of directionality. Microbial changes may influence hormonal signalling, hormonal alterations may reshape microbial ecology, or both may arise as parallel responses to altered gastrointestinal physiology and nutrient exposure.

Improvements in insulin sensitivity after surgery likely reflect multiple concurrent mechanisms, including weight loss, reduced gluco- and lipotoxicity, altered incretin signalling, bile acid metabolism, and potentially microbiota-related pathways (Laferrère & Pattou, 2018).

Inter-individual variability in postoperative diet, physical activity, and adherence to clinical recommendations may have contributed to the observed responses but was not systematically assessed. All participants underwent sleeve gastrectomy, limiting extrapolation to other bariatric procedures such as Roux-en-Y gastric bypass (Dang et al., 2022; Murphy et al., 2017; Sánchez-Alcoholado et al., 2019).

Nevertheless, studying an Emirati cohort — an underrepresented population in bariatric microbiome research — provides region-specific insight into early postoperative metabolic adaptation within a distinct dietary and obesity context.

Within three months, surgery was accompanied by substantial weight loss, improved insulin sensitivity, and coordinated hormonal and microbial changes, supporting a system-level adaptation. However, the evidence remains correlational, and causal directionality cannot be inferred.

Population-specific differences in gut microbiota composition: Lebanese and Emirati adults with obesity

Comparative analysis of gut microbiota composition between Emirati and Lebanese adults with obesity revealed clear differences in microbial diversity and taxonomic structure despite geographic proximity. Lebanese participants exhibited higher microbial α-diversity and distinct β-diversity, consistent with the strong influence of ethnicity, habitual diet, and lifestyle on gut microbial ecology (Kim et al., 2019).

At the phylum level, Lebanese participants showed higher relative abundances of Proteobacteria (Pseudomonadota), Mycoplasmatota (Tenericutes), Cyanobacteriota, and Lentisphaerota, whereas Emirati participants exhibited greater abundance of Bacteroidota, particularly *Bacteroides* and *Parabacteroides*. These patterns are compatible with dietary differences between the populations, as *Bacteroides*-dominated profiles are typically associated with diets high in animal fat and protein and lower in dietary fibre, while fibre-rich dietary patterns are linked to greater microbial diversity and enrichment of carbohydrate-fermenting taxa (De Filippo et al., 2010; Mamun et al., 2025).

At the genus level, Lebanese participants showed enrichment of fibre-associated genera, including *Alloprevotella* and *Paraprevotella*, taxa involved in the fermentation of complex carbohydrates and short-chain fatty acid production (Christensen et al., 2019). These microbial features are often interpreted as metabolically favourable; however, obesity remained present in this cohort. This observation suggests that microbial composition alone does not determine metabolic health and must be interpreted within a broader host and environmental context (Anderson & Bisanz, 2023; Leeming et al., 2019; Zmora et al., 2019)

After adjustment for age, several genera—including *Prevotellaceae D_5*, *Clostridiales vadinBB60*, and *Ruminococcaceae UCG-010*—remained enriched in Lebanese participants and have previously been linked to fibre degradation and anti-inflammatory metabolic (Abou-Samra et al., 2025; Xu et al., 2022). Nevertheless, their presence did not correspond to the absence of obesity, emphasizing that taxa often labelled “beneficial” are context-dependent and

influenced by substrate availability, inflammatory state, insulin sensitivity, and microbial community interactions (Zmora et al., 2019).

These microbial differences parallel the population-specific hormonal patterns observed in this thesis. Just as fasting gut peptide profiles differed from Western cohorts, microbiota configurations associated with dietary fibre and diversity did not uniformly predict metabolic health across populations. Together, these findings indicate that both gut microbiota composition and gut-derived peptide signalling function as context-dependent modulators rather than universal biomarkers.

The comparison between Emirati and Lebanese adults, therefore, highlights the importance of regional and ethnic specificity in microbiome research. Applying microbial reference ranges derived from Western populations may lead to misinterpretation in Middle Eastern settings. Although higher fibre intake in Lebanese participants was associated with greater microbial diversity (Rinninella et al., 2023; Zeng et al., 2025), obesity persisted, indicating that dietary quality alone cannot offset broader metabolic determinants, including energy balance, lifestyle, and systemic inflammation.

Overall, these results demonstrate that microbiota–host relationships are population-specific and require integration with hormonal, metabolic, and lifestyle context rather than interpretation based solely on microbial composition.

Methodological considerations, strengths, and limitations

While this thesis provides integrative insights into associations between gut microbiota composition, gut-derived peptide profiles, and metabolic health in Arab populations, its findings must be interpreted within the boundaries of the study designs and measurement approaches applied. Rather than weaknesses, these elements define the type of knowledge generated: population-specific, physiological, and associative rather than mechanistic.

Study design and inference limits

The studies included in this dissertation employed a combination of cross-sectional, prospective, and comparative observational designs. This multi-design approach represents a methodological strength because converging patterns observed across independent cohorts and study designs increase confidence in biological consistency.

However, the observational nature of all studies inherently limits causal inference. Although consistent associations were observed between gut microbiota features, gut-derived peptides, and metabolic markers, the results identify coordinated biological patterns but cannot determine directionality or biological hierarchy.

While bariatric surgery induced parallel changes in microbiota composition, gut peptides, and metabolic outcomes, the present work does not establish whether microbial shifts drive hormonal adaptations, whether endocrine changes shape microbial ecology, or whether both arise concurrently with altered gastrointestinal anatomy, nutrient flow, dietary intake, and weight loss.

Therefore, the thesis characterizes associations rather than causal pathways — an important distinction in human metabolic research where experimental manipulation is limited.

Population-specific focus and external validity

A major strength of this thesis lies in its focus on underrepresented Arab populations, specifically Emirati and Lebanese adults. This shifts microbiome-metabolic research from generalization toward contextualization.

At the same time, this focus limits the direct generalizability of the findings to other ethnic or geographic populations. Microbiota composition, dietary patterns, and metabolic phenotypes differ substantially across regions, and findings derived from Emirati or Lebanese cohorts should not be extrapolated without caution. Accordingly, the results should be interpreted as biologically specific rather than universally representative, underscoring the necessity of population-anchored reference frameworks in microbiome research.

Microbiota profiling methodology

Gut microbiota composition was assessed using 16S ribosomal RNA gene sequencing, enabling taxonomic classification primarily at the genus level. This approach is widely used, cost-effective, and appropriate for large cohort studies, and allows harmonized analysis across all studies within the dissertation.

However, 16S rRNA sequencing does not provide species-level resolution or direct functional characterization. Consequently, functional interpretations—such as short-chain fatty acid production, bile acid metabolism, or signalling capacity—cannot be directly inferred. The findings, therefore, describe ecological structure rather than metabolic function.

This limitation is particularly relevant when interpreting genera traditionally considered “beneficial,” as functional output varies by strain, substrate availability, and host physiology.
Future integration of metagenomics or metabolomics would therefore refine mechanistic interpretation without changing compositional associations observed here.

Hormonal measurements and physiological interpretation

Circulating gut-derived peptides were measured under standardized fasting conditions using validated ELISA assays, ensuring methodological consistency across studies and reliable cross-group comparison.

Nevertheless, fasting concentrations do not capture postprandial dynamics or circadian variation, which are central to the physiological hormone action. Accordingly, the hormonal data reflect regulatory set-points rather than dynamic satiety signalling.

This is particularly relevant when interpreting peptide–microbiota relationships, as microbial metabolites act predominantly after nutrient exposure.

Thus, endocrine–microbial associations observed here represent baseline metabolic state rather than meal-response physiology.

Bariatric surgery cohort considerations

The prospective bariatric surgery study represents a key strength, providing rare longitudinal microbiota data in Middle Eastern populations. The within-subject design minimized inter-individual variability and enabled direct observation of metabolic adaptation following substantial weight loss.

However, the postoperative follow-up was limited to three months, capturing early adaptation rather than long-term stabilization. Additionally, all participants underwent sleeve gastrectomy, limiting extrapolation to procedures with malabsorptive components.

Postoperative diet, physical activity, and behavioural adherence were not systematically quantified. Therefore, postoperative changes should be interpreted as integrated physiological adaptation rather than procedure-isolated biological effects.

Dietary and lifestyle data

Detailed dietary intake and physical activity were not comprehensively measured across studies. Given the central role of diet in shaping microbiota composition and peptide secretion, this constrains the separation of obesity effects from lifestyle effects.

However, observed microbial differences aligned with known regional dietary characteristics. This supports ecological plausibility while preventing quantitative attribution.

Future studies integrating structured dietary and behavioural assessment would allow modelling of microbiota–host interactions with greater precision.

Summary of methodological implications

Taken together, the methodological framework defines the interpretive level of this thesis.

The work identifies reproducible, coordinated biological patterns across populations and interventions, but does not isolate mechanistic pathways.

The strength of the dissertation, therefore, lies in mapping the physiological organization of obesity in humans rather than experimentally dissecting molecular causality.

General Conclusion

Obesity in Arab populations represents a complex metabolic condition that cannot be adequately explained by single biomarkers, isolated biological pathways, or microbiota features considered in isolation.

Across all studies included in this thesis, consistent associations were observed between adiposity, insulin resistance, circulating gut peptides, and microbial community structure. However, these associations did not conform uniformly to patterns reported in predominantly Western cohorts. Instead, both hormonal and microbial patterns exhibited population-specific configurations in Emirati and Lebanese adults, indicating that obesity biology is not universally expressed across ethnic groups.

A central contribution of this work is the demonstration that gut-derived peptide hormones and gut microbiota composition tend to co-vary with metabolic risk. Elevated fasting GLP-1, insulin, and leptin concentrations, alongside suppressed ghrelin and altered CCK patterns, collectively reflected an obesity-associated endocrine milieu linked to insulin resistance and central adiposity.

Similarly, gut microbiota analyses demonstrated that genus-level variation, rather than broad phylum-level ratios such as Firmicutes/Bacteroidetes, provided more informative insight into metabolic associations. Genera such as *Acidaminococcus* and *Lachnospira* were associated with adiposity and central fat distribution in Emirati individuals with obesity, whereas other taxa showed inverse associations with adiposity in lean participants.

The comparative analysis between Emirati and Lebanese adults further strengthened this interpretation. Despite higher microbial diversity and enrichment of fibre-associated genera in Lebanese participants, obesity remained present. These findings suggest that higher diversity and fibre-associated taxa, in isolation, were not associated with the absence of obesity in this cohort. This highlights the need to consider functional and host-related factors alongside taxonomic composition when interpreting microbiota–metabolic relationships (Deschasaux et al., 2018; Zmora et al., 2019).

Bariatric surgery provided a longitudinal perspective on these interactions. Sleeve gastrectomy acted as a system-level metabolic perturbation, accompanied by parallel changes in body weight, insulin sensitivity, gut peptide profiles, and gut microbiota composition. The postoperative state, therefore, is consistent with coordinated physiological changes.

Taken together, the findings of this thesis emphasize that obesity biology in Arab populations is best understood through an integrative framework, in which hormonal regulation, microbial ecology, and metabolic health are interconnected but context-dependent.

From a clinical and translational standpoint, isolated biomarkers appear insufficient for defining metabolic health status. Instead, integrated interpretation of hormonal and microbial patterns may better reflect metabolic phenotype, particularly in Middle Eastern populations where microbiome data remain limited (Asnicar et al., 2021; Myhrstad et al., 2020).

In conclusion, this dissertation advances understanding of obesity in Arab populations by showing that gut microbiota composition and gut-derived peptide profiles are influenced by ethnicity, diet, and clinical intervention. These findings provide leads for future mechanistic and interventional research.

Future Research Directions

The findings of this dissertation identify several unresolved questions regarding microbiota–peptide interactions in obesity, particularly within Arab populations. This work is merely explorative, based on studying group differences and association, but highlights areas requiring mechanistic deepening.

Population heterogeneity

The population-specific patterns observed in Emirati and Lebanese adults indicate distinct phenotypes. Future work should therefore determine how ethnicity, sex, age, and metabolic phenotype influence microbiota–host relationships across populations.

Diet and lifestyle context

The absence of detailed dietary and behavioural measurements limits the interpretation of whether microbial differences reflect adiposity or environmental exposure. Integrating microbiota analysis with quantitative dietary and lifestyle characterization remains necessary to obtain insight into diet/lifestyle-microbiome interactions.

Extension of longitudinal follow-up after bariatric surgery

The early postoperative adaptations observed here leave unresolved whether microbial and hormonal changes represent transient responses or stable metabolic reorganization. Long-term temporal trajectories remain a key unanswered question in human metabolic adaptation to weight loss.

Functional microbiome biology

Because taxonomic composition does not equate to metabolic activity, functional characterization of microbial pathways is required to determine how microbial ecosystems influence host physiology rather than merely correlate with it**.**

Causality and mechanism

The coordinated microbial and endocrine changes identified in this thesis cannot determine biological directionality. Establishing whether microbiota shape hormonal responses, hormones shape microbial ecology, or both arises from shared metabolic regulation remains a central mechanistic challenge.

Translational relevance

Before clinical targeting is considered, future research must determine whether modifying microbial composition meaningfully alters metabolic regulation or merely reflects it.

Precision obesity frameworks

Ultimately, integrating hormonal, microbial, and metabolic profiling may allow classification of obesity phenotypes based on distinct physiological pattern and go beyond body weight alone.

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Summary

Summary

Obesity is a complex chronic disease driven by the interaction of genetic, hormonal, and microbial factors. In the Middle East—particularly the Gulf region—its prevalence has risen rapidly, placing considerable strain on healthcare systems and increasing the burden of cardiometabolic disease. Despite growing global research on gut microbiota and gut-derived peptides as regulators of metabolic health, Arab populations remain underrepresented. Ethnicity, cultural dietary patterns, lifestyle practices, and genetic background may shape gut microbial composition and hormonal responses in ways that differ from Western cohorts. This thesis, therefore, investigated obesity through a multi-dimensional lens, examining gut microbiota, gut-derived peptide hormones, and metabolic health among Emirati and Lebanese adults, while also evaluating how bariatric surgery is associated with changes in host–microbiota interactions. By integrating cross-sectional, prospective, and comparative approaches, this work provides a regionally specific perspective on biological pathways underlying obesity in Arab populations.

Gut-derived peptide hormones in Emirati adults

Emirati adults with obesity demonstrated characteristic hormonal dysregulation, including elevated fasting GLP-1, GLP-2, leptin, insulin, and CCK, along with significantly lower ghrelin. Among these peptides, GLP-1 showed the strongest association with insulin resistance, independent of BMI, indicating potential relevance as a marker of metabolic dysfunction in this population. Leptin correlated with adiposity measures, while lower ghrelin and higher CCK suggested altered appetite and satiety signalling. These findings provide novel hormone–phenotype data for an understudied Arab population and suggest that physiological adaptations to energy balance and metabolic regulation may differ from those observed in Western cohorts.

Gut Microbial Signatures of Obesity in Emirati Adults

Fecal microbiota profiling revealed that the commonly cited Firmicutes/Bacteroidota ratio did not differ between lean and obese participants, supporting the growing body of evidence that this phylum-level marker lacks universality. Instead, genus-level composition proved more informative: *Acidaminococcus* and *Lachnospira* were enriched in individuals with obesity and positively associated with adiposity and central fat accumulation, whereas several

genera enriched in lean individuals correlated inversely with adiposity measures. These results highlight that microbial signatures of obesity are context-dependent and shaped by diet, lifestyle, and population-specific factors, reinforcing the need for high-resolution taxonomic analyses in microbiome research.

Hormonal and Gut Microbiota Adaptations Following Bariatric Surgery

Three months after sleeve gastrectomy, participants exhibited substantial weight loss and improvements in insulin sensitivity. These metabolic gains were accompanied by marked restructuring of the gut microbiota: microbial β-diversity increased, lean-associated genera (e.g., *Christensenella, Ruminococcus, Alistipes*) gained in relative abundance, and phylum-level shifts included increases in Proteobacteria and Saccharibacteria.

Simultaneously, hormonal adaptations occurred: fasting PYY increased, while GLP-1 and insulin decreased; ghrelin showed a modest rise. Collectively, these changes suggest early recalibration of enteroendocrine signalling, occurring alongside microbial restructuring.

While causal relationships cannot be established, this chapter presents the first evidence in an Emirati cohort that bariatric surgery may trigger synchronous microbial and hormonal adaptations associated with metabolic improvement.

Ethnic, Dietary, and Cultural Influences on Gut Microbiota

Comparison between obese Lebanese and Emirati individuals revealed significant inter-population differences. Lebanese participants showed higher microbial α-diversity and greater abundance of fibre-associated genera (*Alloprevotella*, *Paraprevotella*), consistent with higher reported dietary fibre intake. Emiratis, in contrast, were enriched in *Bacteroides* and *Parabacteroides*, taxa typically associated with high-fat, low-fibre diets. These differences persisted after age adjustment, underscoring the strong influence of cultural dietary habits and environmental factors on gut microbial communities.

Notably, the Firmicutes/Bacteroidota ratio remained similar between countries, reinforcing the limited utility of such phylum-based metrics and highlighting the need for context-specific, higher-resolution analyses.

These results demonstrate that even within the Middle East, gut microbiota composition varies significantly between populations, shaped by diet, lifestyle, and ethnic background — with important implications for designing culturally adapted interventions.

Integrated synthesis

Across all chapters, this thesis reveals that obesity in Arab populations is characterized by interconnected alterations in gut-derived peptide hormones, gut microbial composition, and metabolic parameters — shaped by ethnicity, diet, lifestyle, and surgical intervention.

Gut peptides, including GLP-1, GLP-2, insulin, leptin, ghrelin, PYY, and CCK, collectively reflect a hormonal milieu associated with insulin resistance, altered appetite regulation, and metabolic dysregulation.

Microbial genera such as *Acidaminococcus*, *Lachnospira*, *Christensenella*, *Alloprevotella*, and others emerge as population-specific markers associated with adiposity, dietary patterns, and metabolic health.

Bariatric surgery further underscores the dynamic nature of the host–microbiota–hormone axis, acting as a system-level metabolic change that triggers coordinated—but non-causal microbial and hormonal shifts accompanying metabolic improvement. Overall, the thesis indicates that universal microbial or hormonal biomarkers are insufficient; instead, context-specific, culturally grounded, and high-resolution approaches are required to understand and manage obesity in Arab populations.

Overall conclusion and future perspectives

This thesis advances understanding of obesity pathophysiology in underrepresented Arab populations by providing one of the first integrated datasets, combining gut-derived peptides, gut microbiota composition, and metabolic health in Emirati and Lebanese adults. Its findings provide a basis for future investigation of personalized, microbiota-aware, and culturally adapted strategies for obesity prevention and treatment.

Future research should build on these findings by:

- Conducting larger, multi-ethnic, and well-phenotyped cohort studies
- Employing functional microbiome analyses (metagenomics, metabolomics) to assess microbial metabolic capacity
- Integrating detailed dietary, lifestyle, and environmental data
- Evaluating long-term trajectories after interventions such as bariatric surgery or nutritional modulation
- Investigating microbiota or hormone-targeted interventions in randomized controlled trials

By doing so, this body of work lays the foundation for evidence-based, context-sensitive, and equitable obesity management strategies in the Middle East, while contributing to closing gaps in global microbiome and metabolic health research. Importantly, these findings emphasize that effective obesity management in the Middle East requires moving beyond one-size-fits-all models toward culturally and biologically informed approaches.

Impact

Impact

Introduction

Obesity is a major and growing public health issue worldwide and is particularly prevalent in the Middle East, including the United Arab Emirates and Lebanon. Beyond its clinical consequences, obesity exerts substantial pressure on healthcare systems through increased cardiometabolic disease burden and long-term healthcare utilization. Despite increasing recognition of the role of gut microbiota and gut-derived peptide hormones in metabolic regulation, Arab populations remain markedly underrepresented in microbiome and metabolic health research. This lack of representation limits the generalizability of existing evidence and constrains the development of culturally relevant prevention and treatment strategies.

By generating original microbial and hormonal data in Emirati and Lebanese adults, this dissertation addresses this critical knowledge gap and provides population-specific evidence with potential relevance for clinical practice, prevention strategies, and policy development in the Middle East.

The following sections outline the societal, scientific, clinical, and equity-related impacts of this work, as well as its translational and dissemination potential.

Societal Relevance

Obesity as a societal and economic challenge

Rapid urbanization, dietary modernization, and increasingly sedentary lifestyles have contributed to a substantial rise in obesity across the Middle East. In both the United Arab Emirates and Lebanon, obesity is associated with increased cardiometabolic disease prevalence, reduced quality of life, and escalating healthcare costs, placing sustained pressure on national health systems.

Cultural and dietary relevance for Arab populations

Dietary habits and cultural practices are key determinants of gut microbiota composition. Traditional diets in Gulf and Levant populations historically emphasized whole grains, legumes, and fibre-rich foods; however, modernization has led to reduced fibre intake and increased consumption of processed foods.

The findings of this thesis—particularly the lower microbial diversity and reduced abundance of fibre-associated genera in Emirati adults compared with Lebanese adults—reflect these dietary shifts and underscore the importance of cultural context in obesity research.

These results highlight the need for culturally tailored nutrition strategies, including:

- Promoting traditional fibre-rich foods such as lentils, beans, and whole grains
- Integrating microbiota-supporting ingredients into contemporary dietary patterns
- Designing obesity-prevention campaigns that reflect local food cultures in the UAE and Lebanon

Such approaches may strengthen public health initiatives by aligning dietary guidance with cultural norms rather than relying solely on imported Western dietary models.

Public-health relevance of microbial signatures

By demonstrating that genus-level microbial signatures are more informative than phylum-level ratios, this thesis contributes to more accurate metabolic phenotyping in obesity research. These findings also help protect the public from

misleading commercial microbiome tests that overemphasize oversimplified markers with limited reproducibility across populations.

These findings may also help inform public health communication, clinical screening strategies, and the regulation of microbiome-based consumer products.

Scientific Contribution of the Thesis

Advancing knowledge in underrepresented populations

The primary scientific contribution of this thesis lies in generating original datasets from Arab populations that are largely absent from global microbiome research.

This work is among the first to comprehensively examine:

- Gut microbiota profiles in obese and lean Emirati adults
- Gut-derived peptide hormone patterns across BMI categories in Emiratis
- Longitudinal microbial and hormonal changes following bariatric surgery
- Cross-population microbial differences between Emirati and Lebanese adults

These datasets expand the global microbiome evidence base and improve the representation of Arab populations in international scientific discourse.

Challenging oversimplified microbiome concepts

The findings of this thesis challenge the widespread reliance on the Firmicutes/Bacteroidota ratio as a biomarker of obesity. Instead, they demonstrate that specific genera—including *Acidaminococcus* and *Lachnospira*—are more closely associated with adiposity and insulin resistance, while fibre-associated genera are more prevalent in leaner or higher-fibre dietary contexts. This shift toward genus-level interpretation provides a more nuanced and biologically meaningful framework for future microbiome research and future interpretation in diverse populations.

Hormonal–microbial interactions as metabolic regulators

This thesis identifies a strong observational association between fasting GLP-1 levels and insulin resistance, independent of BMI, highlighting GLP-1 as a clinically relevant metabolic marker in Arab populations. By integrating microbial and hormonal profiling, this work reinforces the concept of obesity as a multifactorial condition shaped by interacting metabolic systems and provides a basis for future mechanistic and interventional studies targeting the gut–hormone axis.

Clinical Impact

Implications for bariatric surgery management

The bariatric surgery cohort demonstrated significant postoperative shifts in gut microbial diversity and appetite-regulating hormones, indicating physiological adaptations associated with metabolic improvement.

These insights may contribute to:

- Optimization of postoperative dietary recommendations
- Improved patient monitoring beyond weight loss alone
- Identification of individuals who could potentially benefit from targeted microbiota- or hormone-based interventions

Implications for GLP-1–based therapies

The observed association between fasting GLP-1 and insulin resistance may assist in interpreting variability in response to GLP-1 receptor agonists within Arab populations and suggests a possible role for baseline hormonal profiling in precision obesity treatment.

Advancing non-surgical obesity interventions

The microbial taxa identified as obesity-associated represent candidate features for investigation in:

- Dietary fibre enrichment strategies
- Culturally adapted prebiotic or probiotic interventions
- Microbiota-informed personalized nutrition approaches

These strategies represent avenues for research into non-surgical obesity management.

Equity and Regional Global Health Relevance

Arab and Middle Eastern populations remain substantially underrepresented in global microbiome and genomic research, despite experiencing some of the highest obesity prevalence rates worldwide.

This research:

- Provides foundational microbial and hormonal data from Emirati and Lebanese

adults
- Highlights ethnicity-specific metabolic signatures
- May support the future development of region-specific clinical and nutritional guidelines
- Contributes to building regional microbiome reference datasets

Ensuring inclusion of Arab populations is essential not only for equity but also for the scientific validity and global applicability of microbiome-based diagnostics and interventions currently being developed.

Translation to Clinical Practice and Industry

The findings of this thesis may inform future development of:
- Microbiota-informed nutritional guidelines in the UAE and Lebanon
- Genus-level microbial markers as adjuncts to metabolic screening protocols
- Collaborations between healthcare systems and the food industry to develop culturally relevant, fibre-rich products
- Design of probiotic and prebiotic formulations tailored to Gulf and Levant populations

This work also provides a basis for future precision-nutrition and hormone–microbiome intervention trials in the region.

Dissemination of Research Outcomes

The findings of this dissertation have been disseminated through peer-reviewed journal publications and international scientific conferences. To date, this work has resulted in four peer-reviewed articles addressing gut microbiota composition, gut-derived peptide hormones, and metabolic health in Emirati and Lebanese adults.

In addition, key results have been presented through oral and poster presentations at international conferences, facilitating scientific exchange and knowledge translation within the fields of nutrition, obesity, and microbiome research.

Conclusion

This thesis provides robust observational evidence that microbial and hormonal signatures of obesity are population-specific and shaped by cultural, dietary, and environmental factors. By focusing on underrepresented Arab populations, it

advances global microbiome science, may inform clinical practice, may support the development of culturally adapted interventions, and contributes to public health strategies aimed at addressing the obesity epidemic.

Collectively, this work supports a shift toward precision, population-centered approaches in obesity research and metabolic health management.

Publications

Publications

Peer-reviewed publications

Ali Ahmad, M., Karavetian, M., Moubareck, C. A., Wazz, G., Mahdy, T., & Venema, K. (2022). The association between peptide hormones with obesity and insulin resistance markers in lean and obese individuals in the United Arab Emirates. *Nutrients*, 14(6), 1271. https://doi.org/10.3390/nu14061271

Ahmad, M. A., Karavetian, M., Moubareck, C. A., Wazz, G., Mahdy, T., & Venema, K. (2023). Association of the gut microbiota with clinical variables in obese and lean Emirati subjects. *Frontiers in Microbiology*, 14, 1182460. https://doi.org/10.3389/fmicb.2023.1182460

Ali Ahmad, M., Venema, K., Ayoub Moubareck, C., Wazz, G., Mahdy, T., & Karavetian, M. (2025). Changes in energy homeostasis, gut peptides, and gut microbiota in Emiratis with obesity after bariatric surgery. *PLOS ONE*, 20(2), e0318699. https://doi.org/10.1371/journal.pone.0318699

Ahmad, M. A., Abou-Samra, M., Blaak, E., Karavetian, M., Moubareck, C. A., & Venema, K. (2026). Obesity and the gut microbiota in the Middle East: a cross-cultural study of Lebanese and Emirati adults. *Beneficial Microbes*, 1(aop), 1–22. https://doi.org/10.1163/18762891-bja00111.

Conference presentations

Ahmad, M. A., Venema, K., Ayoub Moubareck, C., Wazz, G., Mahdy, T., & Karavetian, M. (2024). Changes in energy homeostasis, gut peptides, and gut microbiota in Emiratis with obesity after bariatric surgery. Poster presented at the 11th International Yakult Symposium, Amsterdam, The Netherlands.
Awarded Best Poster Presentation.

Ahmad, M. A., et al. (2020). Sleep and lipid profile. Abstract presented at the 12th Virtual Asia Pacific Conference on Clinical Nutrition, Dubai, United Arab Emirates. Awarded Certificate of Appreciation.

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I look forward to applying the knowledge and experiences gained from this journey in the next chapter of my career, and I will always be grateful.

I dedicate this thesis to my father, my mother, my sisters, and my brothers — and to You, my God, my everything.

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Manal

Curriculum Vitae

Curriculum Vitae



Manal Ali Ahmad was born on 25 June 1984 in Lebanon.

She obtained her Bachelor of Science in Biochemistry in 2006 and her Master of Science in Nutrition and Food Service Management in 2008, both from the Lebanese University, Lebanon. In 2009, she completed her dietetic internship at Rafik Hariri University Hospital in Beirut.

Mrs. Ahmad is a licensed nutritionist and dietitian, accredited by the Lebanese Ministry of Public Health since 2009 and by the Dubai Health Authority, United Arab Emirates, since 2015. She has more than 15 years of professional experience in clinical nutrition and food service management across Lebanon, Saudi Arabia, and the United Arab Emirates. Her clinical expertise focuses on medical nutrition therapy in oncology, bariatric care, renal diseases, and critical care.

Following extensive clinical practice, Mrs. Ahmad developed a strong interest in research on obesity and metabolic health. In 2019, she enrolled as a PhD candidate at the School of Nutrition and Translational Research in Metabolism (NUTRIM),

Maastricht University, the Netherlands. Her doctoral research, conducted at Al Qassimi Hospital and Dr. Sulaiman Al Habib Hospital in the United Arab Emirates, investigates gut microbiota composition and gut-derived peptide hormones and their associations with obesity and metabolic health in Emirati and Lebanese populations, including metabolic adaptations following bariatric surgery.

In addition to her clinical and research activities, Mrs. Ahmad is actively involved in continuing medical education programs and public health awareness initiatives. She regularly contributes to scientific dissemination through conference presentations and professional education and has received several awards recognizing excellence in clinical dietetics and research presentations at international scientific meetings.

This thesis explores the interplay between gut microbiota, gut-derived peptide hormones, and metabolic health in obesity.

Using studies in Emirati populations, including before and after bariatric surgery, and comparisons with Lebanese cohorts, it highlights population-specific metabolic and microbial patterns.

The findings support the role of microbiota and peptide hormones in advancing personalized approaches to obesity management.

