UNIVERSIDADE DE SÃO PAULO
FACULDADE DE SAÚDE PÚBLICA

TALITA CESTONARO

Interaction between the gut microbiome and diet in metropolitan Sao Paulo dwellers and rural Amazonian riverine

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ATA DE DEFESA

Ata de defesa de Tese do(a) Senhor(a) Talita Cestonaro no Programa: Nutrição em Saúde Pública, do(a) Faculdade de Saúde Pública da Universidade de São Paulo.

Aos 20 dias do mês de dezembro de 2022, no(a) realizou-se a Defesa da Tese do(a) Senhor(a) Talita Cestonaro, apresentada para a obtenção do título de Doutora intitulada:

"Interação entre microbioma intestinal e dieta em moradores da região urbana de São Paulo e ribeirinhos do interior da Amazônia"

Após declarada aberta a sessão, o(a) Sr(a) Presidente passa a palavra ao candidato para exposição e a seguir aos examinadores para as devidas arguições que se desenvolvem nos termos regimentais. Em seguida, a Comissão Julgadora proclama o resultado:

Nome dos Participantes da Banca	Função	Sigla da CPG	Resultado
Christian Hoffmann	Presidente	FCF - USP	Não Votante
Fabiana Andréa Hoffmann Sardá	Titular	Externo	Aprovada
Sandra Roberta Gouvea Ferreira Vivolo	Titular	FSP - USP	Aprovada
Renata Costa de Miranda	Titular	UFTM - Externo	Aprovada

Resultado Final: Aprovada

Parecer da Comissão Julgadora *

Eu, Maria Aparecida Mendes , lavrei a presente ata, que assino juntamente com os(as) Senhores(as). São Paulo, aos 20 dias do mês de dezembro de 2022.

P/ Fabiana Andréa Hoffmann Sardá

P/ Sandra Roberta Gouvea Ferreira Vivolo

P/ Renata Costa de Miranda

Christian Hoffmann
Presidente da Comissão Julgadora

À minha mãe Terezinha, ao meu pai Leomar (in memoriam) e à minha irmã Taiana pelo amor, cuidado, incentivo e suporte em todas as minhas escolhas.

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“...o pensamento é um trabalho de longa duração, com paradas, voltas, erros, recomeço...”
(CHAUÍ, 2021)

RESUMO

CESTONARO, T. **Interação entre microbioma intestinal e dieta em moradores da região urbana de São Paulo e ribeirinhos do interior da Amazônia**. 2022. Tese (Doutorado) – Faculdade de Saúde Pública, Universidade de São Paulo, São Paulo, 2022.

Nós investigamos a relação entre o microbioma intestinal e a dieta de ribeirinhos da Amazônia (AMZ) (n=49) e comparamos com moradores da região urbana de São Paulo (SP) (n=55). A ingestão alimentar foi mensurada com o recordatório de 24 horas. Foi aplicada a classificação NOVA de alimentos e a ingestão de nutrientes foi ajustada pelo método dos residuais. Usamos análise de clusters para investigar padrões alimentares. A composição do microbioma intestinal foi determinada pelo sequenciamento do rDNA 16S. Alfa e beta diversidade foram calculadas. Os táxons que diferenciam AMZ e SP foram determinados por ANCOM, COREMIC e coeficientes da PERMANOVA. A relação entre dieta e microbioma foi avaliada usando a análise de Procrustes e o coeficiente de correlação de Spearman. A significância foi definida em p ajustado <0,05. AMZ consumiram mais alimentos naturais e minimamente processados (mediana: 86,25 vs 62,18, Mann-Whitney p <0,001) enquanto paulistas consumiram mais alimentos processados e ultraprocessados (mediana: 6,4 vs 0, Mann-Whitney p <0,001 e mediana: 28,96 vs 9,94, Mann-Whitney p <0,001, respectivamente). Os subgrupos NOVA que mais contribuíram para o consumo energético entre AMZ foram peixe, farinha de mandioca, frito de trigo e bolacha salgada, enquanto entre SP foram leite, arroz, carne bovina, pão de panificação e ultraprocessado, e doces. SP apresentaram dieta mais diversa. O consumo de nutrientes foi estatisticamente diferente entre AMZ e SP, exceto para energia, carboidrato, álcool e magnésio. Composições do microbioma intestinal também foi diferente e apresentou relação com a dieta. AMZ apresentaram maior alfa diversidade e a estrutura geral do microbioma intestinal foi diferente entre os grupos (Unifrac, PERMANOVA: Unweighted, p=0.001; weighted, p=0.001). AMZ apresentaram maior abundância de táxons característicos de sociedades tradicionais (ST) como *Prevotela*, *Treponema*, *Succinivibrio* and *Muribaculaceae* enquanto paulistas apresentaram maior abundância de táxons característicos de sociedades industrializadas (SI) como *Alistipes*, *Bacteroides*, *Barnesiela*, *Odoribacter*, *Parasutterella*, *Ruminococcus* and *Parabacteroides.* Os táxons que mais diferenciaram as populações também apresentaram as correlações significativas mais fortes com a dieta. Táxons característicos de ST apresentaram correlação positiva com a dieta dos AMZ, especialmente alimentos in natura e minimamente processados, peixe, farinha de mandioca, frito de trigo e nutrientes relacionados como proteína, gordura poliinsaturada, colesterol, vitamina B12, vitamina B6, vitamina D e selênio. Táxons característicos de SI apresentaram correlação positiva com a dieta ocidentalizada dos SP especialmente alimentos processados e ultraprocessados, leite, pão ultraprocessado, doces, carne bovina e suína, vegetais, molhos industrializados, sobremesas caseiras, queijos, arroz, alimentos pronto para o consumo e nutrientes relacionados como gordura monoinsaturada, saturada e trans, zinco, sódio, ferro, cobre, cálcio, fósforo, tiamina, riboflavina, e vitamina C. AMZ apresentaram dominância de *Prevotella* mesmo com dieta rica em proteína animal e pobre em fibras. Mesmo as diferenças na dieta tendo papel importante em modular o microbioma intestinal, nós acreditamos que a carcaterística principal na determinação desse padrão foi o estilo de vida. Isso porque SP e AMZ são sociedades bastante distintas também no contato com o ambiente natural, saneamento, práticas de higiene e outras práticas socioculturais que potencialmente afetam a dispersão de microrganismos e consequentemente a composição do microbioma intestinal.

Palavras-chave: Microbioma gastrointestinal. Dieta. Amazônia. Ribeirinhos. Comunidades tradicionais.

ABSTRACT

CESTONARO, T. **Interaction between the gut microbiome and diet in metropolitan Sao Paulo dwellers and rural Amazonian riverine**. 2022. Tese (Doutorado) – Faculdade de Saúde Pública, Universidade de São Paulo, São Paulo, 2022.

We investigated the relationship between the gut microbiome composition and diet of rural Amazonian riverines (AMZ) (n=49) and compared them to urban São Paulo dwellers (SP) (n=55). Diet was measured using 24-hour dietary recalls and assessed using an adaptation of NOVA food classification and nutritional composition. Nutrient intake was adjusted using the residual method. Food patterns were investigated using cluster analysis and main sources of nutrients by visual evaluation of bar charts and heatmaps all based on NOVA subgroups. We determined the gut microbiome composition using 16S rDNA sequencing and QIIME 2. Alpha diversity was determined by richness, Pielou's evenness, Shannon diversity and Faith's Phylogenetic diversity. Beta diversity was determined by unweighted and weighted Unifrac distances. Differential taxa were determined by ANCOM, COREMIC and PERMANOVA coefficients. Relation between diet and gut microbiome was done using Procrustes analysis and Spearman's rank correlation. P-values were adjusted using false discovery rate (FDR) and significance was defined at adjusted p-value < 0.05 (q-value). AMZ consumed more natural and minimally processed foods (median: 86,25 vs 62,18, Mann-Whitney p <0,001) while SP consumed more processed and ultra-processed foods (median: 6,4 vs 0, Mann-Whitney p <0,001 and median: 28,96 vs 9,94, Mann-Whitney p <0,001, respectively). NOVA subgroups which most contributed to energy intake among AMZ were fish, cassava products, fried dough and crackers while among SP were milk, beef and pork, rice, industrialized and non-industrialized bread, and goodies. SP had more diverse diet than the AMZ. The consumption of most nutrients was statistically different between the two populations, except for energy, carbohydrate, alcohol, and magnesium. SP and AMZ riverine present different gut microbiome compositions that were related to their different dietary patterns. AMZ showed higher alpha diversity and the overall microbiome structure differed between groups (Unifrac, PERMANOVA: Unweighted, p=0.001; weighted, p=0.001). AMZ showed higher abundance of taxa characteristic of traditional societies like *Prevotela*, *Treponema*, *Succinivibrio* and *Muribaculaceae* while SP showed higher abundance of taxa characteristic of industrialized societies like *Alistipes*, *Bacteroides*, *Barnesiela*, *Odoribacter*, *Parasutterella*, *Ruminococcus* and *Parabacteroides.* Most differential taxa between populations also presented the strongest significant correlation with diet. Traditional societies taxa positively correlated with AMZ diet specially natural and minimally processed foods, fish, cassava flour, fried dough and their related nutrients like protein, polyunsaturated fat, cholesterol, vitamin B12, vitamin B6, vitamin D and selenium. Industrialized societies taxa positively correlated with SP westernized diet specially processed and ultra-processed foods, milk, industrialized bread, goodies, meat, vegetables, industrialized sauce, homemade desserts, cheese, rice, read-to-eat food products and their related nutrients like monounsaturated, saturated and trans fats, zinc, sodium, iron, copper, calcium, phosphorus, thiamine, riboflavin and vitamin C. AMZ presented Prevotella dominance even having a high animal protein and low fiber diet. Even differences in diet play an important role shaping gut microbiome, we believe that the main driver of this pattern is lifestyle because SP and AMZ are very distinguished societies and differ also in environmental contact, sanitation, hygiene, and other sociocultural practices that potentially affect microorganisms' dispersion and consequently their gut microbiome composition.

Keywords: Gastrointestinal microbiome. Diet. Amazon. Riverine. Traditional lifestyle.

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LIST OF ACRONYMS AND ABBREVIATIONS

24HR	24-hour dietary recall
AMZ	Amazonian Riverine
ANCOM	Analysis of Composition of Microbiomes
ASVs	Amplicon sequence variants
BCAA	Branched-chain amino acids
BLAST+	Basic Local Alignment Search Tool
BMI	Body mass index BMI
CAZymes	Carbohydrates active enzymes
CEFAP	Centro de Facilidades para a Pesquisa
CEPSH	Human Research Ethics Committee
CONEP	Comissão Nacional de Ética em Pesquisa
COREMIC	A web-tool to search for a niche associated CORE MICrobiome
DNA	Deoxyribonucleic acid.
FAMS	Total monounsaturated fatty acids
FAPU	Total polyunsaturated fatty acids
FASAT	Total saturated fatty acids
FAT	Total trans fatty acids
FDR	False discovery rate
FSP/USP	School of Public Health, University of São Paulo
IBD	Inflammatory bowel diseases
ICB	Institute of Biological Sciences
IECs	Intestinal epithelial cells
IQR	Interquartile range
NCD	Non-communicable diseases
nMDS	Non-metric multidimensional scaling
NOVA	NOVA food classification
NUPENS	Center for Epidemiological Research in Nutrition and Health
PCA	Principal component analysis
PCoA	Principal Coordinate Analysis
PCR	Polymerase chain reaction
PERMANOVA	Permutational analysis of variance
PROTEST	Procrustes randomization test
QIIME	Quantitative Insights into Microbial Ecology
RDSM	Reserva de Desenvolvimento Sustentável Mamirauá
SCFA	Short-chain fatty acids
SP	São Paulo dwellers
TBCA	"Tabela Brasileira De Composição De Alimentos" or Brazilian food composition table

SUMÁRIO

1 INTRODUCTION

1.1 The human gut microbiome

The human gut microbiome is a set of bacteria, archaea, viruses, fungi, and single-celled eukaryotes which form an ecosystem of host associated microorganisms (VEMURI *et al.*, 2020). The association between the gut microbiome and its human host is a result of an ancient relationship, developed and refined through co-evolution, resulting in co-specialization and a symbiotic relationship (MOELLER *et al.*, 2016). The gut metagenome, the collection of all the microbiome's genomes and genes, is at least 150 times larger than the human host. Today, we understand this genetic potential to be essential a normal human physiology (QIN *et al.*, 2010; VUJKOVIC-CVIJIN *et al.*, 2020). In the absence of pathological processes, forces that shape gut microbiome are related to host physiology-lifestyle, and environmental conditions like host genetics, age, sex, body mass index (BMI), sexual practices, use of antibiotics and other medications, diet, cohousing and geographic location (ASNICAR *et al.*, 2021; DEBELIUS *et al.*, 2016; MAIER *et al.*, 2018; NOGUERA-JULIAN *et al.*, 2016; PALLEJA *et al.*, 2018; SONG *et al.*, 2013; TURNBAUGH *et al.*, 2006; XIE *et al.*, 2016; YATSUNENKO *et al.*, 2012).

Common bacterial phyla in the human microbiome include Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria, Verrucomicrobia, and the Archaea phylum named Euryarchaeota. Less abundant phyla include Fusobacteria, Tenericutes, Spirochaetes, Cyanobacteria, Saccharibacteria (previous TM7), Lentisphaerae and Synergistetes (ARUMUGAM *et al.*, 2011; LOZUPONE *et al.*, 2012; TREMAROLI; BÄCKHED, 2012). Underrepresented phyla such as Saccharibacteria and Elusimicrobia (less typical in human association) are features of a traditional life-style associated gut microbiome, rarely found in industrialized societies (PASOLLI *et al.*, 2019).

1.2 The gut microbiome in health and disease

As part of the human organism and physiology, the gut microbiome is responsible for many functions that are essential for human life and health. Two of the most important functions executed by the gut microbiome involve nutrition and immune functions (DOMINGUEZ-BELLO *et al.*, 2019; LIANG *et al.*, 2018; LYNCH; PEDERSEN, 2016). The gut microbiome is important for the immune system maturation while the latter learns to tolerate commensal microorganisms but still responding to pathogenic ones (SHREINER; KAO; YOUNG, 2015).

The gut microbiota also influences physiology at distant body sites, through microbial-derived biochemical messengers, enteric nervous system signals, and gut-resident immune cells that are trafficked throughout the body (SONNENBURG; SONNENBURG, 2019).

There is ample evidence for the involvement of the gut microbiome with many diseases, but in many of them it is not clear if gut microbiome alteration detected are involved in the causality of disease, or it is a consequence of altered physiology, which in turn impacts the gut microbiome. Either way, the microbiome seems to help perpetuated the pathological conditions, mainly metabolic ones.

Inflammatory bowel diseases (IBD) are related to significant alterations in gut microbiome composition and functionality. IBD are also related to urbanization, and their prevalence has increased in parallel to recent dietary changes promoted by shifts in lifestyle. They are associated with gut microbiome alteration and usually linked with high ingestion of animal products and low fiber intake (ZUO; NG, 2018). Diet has a crucial role in keeping remission periods and managing exacerbation periods of IBD, probably due to gut microbiome immune modulation. Diet has a key role in modulating the gut microbiome and have been linked to that in studies showing relations with dietary patterns, food groups, nutrients, and non-food chemicals (BAILÉN *et al.*, 2020; COTILLARD *et al.*, 2022; JOHNSON *et al.*, 2019; SUEZ *et al.*, 2022).

Cardiovascular diseases, diabetes mellitus and neoplasias are the principal diet- related non-communicable diseases (NCD) that are attributed to unhealthy diets in Brazil, and the main risk factor is high consumption of red mead and sodium, and low intake of whole grains (MACHADO *et al.*, 2022). Red and processed meat are related to increase in risk of colorectal cancer (WORLD CANCER RESEARCH FUND/AMERICAN INSTITUTE FOR CANCER RESEARCH, 2018). Red meat is one of the mainly contributors do energy intake from natural and minimally processed food in Brazil (IBGE, 2020). Obesity is also an important factor impairing health around the world and is strongly related to dietary changes. It is also linked to changes in gut microbiome composition and loss of diversity. Yet, experimental studies show an obesogenic effect of gut microbiome from obese subjects. Together this information shows an important participation of the human gut microbiome in the development and maintenance of NCD that are diet-related, mainly through recent diet alterations, a process leading to a dietary pattern commonly referred to as western diet.

1.3 The gut microbiome around the world

Although the gut microbiome has the same general composition around the world, differences are observed among distinct societies, and a main dichotomy observed is between industrialized versus traditional societies. A very different microbiome is found in societies living an ancestral/ traditional lifestyle, such as hunter-gathers, rural and indigenous populations than those found in urban industrialized societies. The microbiome of these groups has increased bacterial diversity (TETT *et al.*, 2019) and are characterized by higher abundance of genera *Treponema* (Sprirochaete phylum), *Prevotella* (Bacteroidota phylum) and *Succinivibrio* (Proteobacteria phylum) (SHARMA et al.,2020; SCHAAN et al., 2021; SONNENBURG; SONNENBURG, 2019; ROSAS-PLAZA et al., 2022). Higher abundances of *Prevotella* genus and Spirochaetaceae family are also identified in coprolites from ancient human populations, as well as in nonhuman primates, suggesting a long-time relation of these microorganisms with human host (BELKHOU *et al.*, 2021; OBREGON-TITO *et al.*, 2015; SCHAAN *et al.*, 2021; SHARMA *et al.*, 2020; WIBOWO *et al.*, 2021). Usually, when present, *Prevotella* is the dominant genera in gut microbiome (TETT *et al.*, 2019). Mean abundance in industrialized societies is around 30% while in traditional societies this value can be as high as 95% (TETT *et al.*, 2019).

Prevotella species are differentially abundant in traditional and industrialized societies, being highly enriched in the former and of minor expression in the latter, while *Treponema* genus is exclusively found in traditional societies, albeit in small amounts, and rarely found in industrialized populations (PASOLLI *et al.*, 2019). Additionally, *Treponema* genus has also been isolated from other primates, termites, and swine (ANGELAKIS *et al.*, 2018; BELKHOU *et al.*, 2021). The maintenance of such genera in traditional societies may be due to several factors, such as cross-transmission between humans and animals, antibiotic use in industrialized societies (ANGELAKIS *et al.*, 2018), as well as shifts in dietary patterns. Traditional societies present diverse *Treponema* species, mainly *Treponema succinifaciens* (ANGELAKIS *et al.*, 2018; OBREGON-TITO *et al.*, 2015). Species found in traditional societies have also distinct metabolic activity from the only specie found in industrialized societies, the strict opportunistic pathogen *Treponema pallidum* (SCHNORR *et al.*, 2014).

Industrialized societies gut microbiomes are characterized by higher prevalence of genera *Bacteroides*, *Alistipes*, *Parabacteroides* (all from the Bacteroidota Phylum), and *Akkermansia* (Verrucomicrobia phylum) (PASOLLI *et al.*, 2019; ROSAS-PLAZA *et al.*, 2022). *Bifidobacterium* genus (Actinobacteriota phylum) is also a feature of industrialized societies it is not common in most adult traditional societies gut microbiomes (ANGELAKIS *et al.*, 2018; SCHAAN *et al.*, 2021; SCHNORR *et al.*, 2014).

Other distinction between traditional and industrialized societies gut microbiomes is the higher biodiversity of taxa and of carbohydrate-active enzymes (CAZyme) found in the former (ANGELAKIS *et al.*, 2018; MANCABELLI *et al.*, 2017; OBREGON-TITO *et al.*, 2015; ROSAS-PLAZA *et al.*, 2022; SCHAAN *et al.*, 2021; SCHNORR *et al.*, 2014; SONNENBURG; SONNENBURG, 2019; YATSUNENKO *et al.*, 2012). Diversity confers resilience to the ecosystem mainly because there is functional redundance (DOGRA; DORÉ; DAMAK, 2020) (THE HUMAN MICROBIOME PROJECT CONSORTIUM, 2012). Furthermore, traditional societies also carry a greater set of uncatalogued and unnamed species (uncharacterized gut microbiome) (PASOLLI et al., 2019; SCHNORR et al., 2014). Many taxa in traditional gut microbiomes are butyrate-producing, a short chain fatty acid that has been demonstrated to possess an anti-inflammatory activity, induce mucin synthesis, and help keep gut integrity (CONTEVILLE; OLIVEIRA-FERREIRA; VICENTE, 2019).

The differentiation observed between industrialized and traditional societies gut microbiomes are thought to have occurred very recently in human history. They parallel the multiple changes brought by industrial revolution that result in disconnection from the traditional lifestyle prevailing until that moment. At the same time, there was a distancing from traditional sociocultural practices and natural environments, a rise in modern sanitization and medical practices, as well as modern food preservation and manufacturing processes. These changes may act as constant pressures with cumulative effects over generations (SONNENBURG *et al.*, 2016; VANGAY *et al.*, 2018), resulting in permanent gut microbiome changes. These changes are mainly related to the overall loss of diversity, and the ancient taxa lost were well-adapted to their human hosts, and probably may have had a role in shaping human biology (BELKHOU *et al.*, 2021; FRAGIADAKIS *et al.*, 2019; OBREGON-TITO *et al.*, 2015).

1.4 Human diet evolution and nutritional transition

Humans were hunter gathers for most of their evolutionary history and around 12 thousand years ago they started farming and animal husbandry. Archeological studies and research with modern hunter-gatherers suggest that pre-agricultural diets vary in animal and plant sources between societies inhabiting different environments; even plant biomass was more abundant. Diets were also marked by seasonality or availability fluctuations. Even before farming, the use of fire and other techniques for food processing improved the digestibility and consequently the bioavailability of food components, which favored an increase in brain size

and decrease in intestinal size, as there wasn't any longer the need for processing copious amounts of food to get adequate nutritional requirements. After that, farming resulted in the greatest shift in human diet until recent times. Domesticated plants were richer in energy, starch, and fat and poorer in fiber while farmed meat were richer in fat, specially saturated fat, than their wild versions (CRITTENDEN; SCHNORR, 2017; LUCA; PERRY; DI RIENZO, 2010; PONTZER; WOOD, 2021).

Nutrition transition is a much more recent process in human history, referring to large dietary and physical activity changes that reflected in nutritional outcomes, like body composition, and occur in parallel to changes in health status, demography, and socioeconomics (POPKIN, 2006). There was a whole lifestyle change from traditional subsistence-based agrarian communities to industrialized societies, which results in reduced natural environment contact, energy expenditure in working, domestic and leisure activities. Diets changed towards cheaper and more convenient industrial food products with reduced vegetables and grains (coarse) and increased vegetable oils, cheap animal food high in fat and protein, and sweetened food high in simple carbohydrates. Those changes were linked to globalization phenomenon, which boosted urbanization, industrialization, economic growth and liberalization and globalization of food markets (POPKIN, 2006).

This process first occurred in high income countries, and is now occurring at a hastened pace in low- and middle-income countries, overburdening mainly the poorer population (POPKIN, 2002). Nutritional transition leads developing nations to the accumulation of a double burden of malnutrition: undernutrition linked to infectious diseases, and high consumption of unhealth diets linked to obesity and other non-communicable disease (NCD), such as cardiovascular disease and cancer.

To study these recent dietary changes, the Center for Epidemiological Research in Nutrition and Health (NUPENS), at the University of São Paulo (Brazil), developed the NOVA food classification, which groups food according to the extension and purpose of industrial processing (MONTEIRO *et al.*, 2019) (BRASIL, 2014). This food classification system proposes to disaggregate culinary preparations into their ingredients to classify them, as well as other consumed foods and beverages, in four groups. NOVA group 1 includes unprocessed or minimally processed foods like vegetables, fruits, cereals, meat, milk and so on. NOVA group 2 includes culinary ingredients like salt, fat and sugar used in culinary preparations in smaller amounts than main ingredients. NOVA group 3 includes processed foods, which are foods from group 1 mainly added of salt, sugar and fat for conservation or flavor enhancement purposes, such as canned products, cheese, and non-industrialized breads. Finally, NOVA group 4

includes ultra-processed foods made mainly of substances extracted from foods or derived from its constituents (i.e., modified fats and starches) or lab synthesized (food additives), with the use of industrial techniques to prepare ready-to eat foods, industrial breads, soft drinks, sausages, and others. It is not possible to disaggregate industrial preparations in their constituents because ingredients quantity is not known by consumers unlike culinary preparations. Overall, for a food item to be classified as ultra-processed, it should present in their list of ingredients at least one ingredient characteristic of this group: a food substance never or rarely used in kitchens or a cosmetic additive.

High-income countries get as much as 50% of their energy from ultra-processed foods and middle-income countries have seen a recent sharp rise in their energy intake coming from ultra-processed foods (MONTEIRO *et al.*, 2019). In Brazil, approximately 20% of energy intake comes from ultra-processed foods (IBGE, COORDENAÇÃO DETRABALHO E RENDIMENTO, 2020). Increase in ultra-processed foods consumption results in a deterioration of diet's nutritional quality, as they become high in energy obtained from simple sugars, unhealthy fats, and food products high in salt and low in fiber, protein, and micronutrients (MACHADO *et al.*, 2019; MIRANDA *et al.*, 2021; MONTEIRO *et al.*, 2019; RAUBER *et al.*, 2019). An increased consumption of ultra-processed foods is linked with the development of many non-communicable diseases (NCD) like obesity, diabetes, and cancer (FIOLET *et al.*, 2018; HALL *et al.*, 2019; SROUR *et al.*, 2022).

One of the main problems with extensive industrial food processing is the dismantling of the food matrix and higher concentration of some nutrients, which are potentially harmful to health, such as unhealthy fats, salt and sugars. The food matrix refers to the differential properties of food components when they are in a food compared to their isolated forms (AGUILERA, 2019). Food matrix integrity ensures that food components are released in a synergic way along the gastrointestinal tract (CAPUANO; JANSSEN, 2021). An increase in non-communicable diseases (NCD) may be relate to the alteration of the food matrix and loss of synergic interactions between food components (FARDET; ROCK, 2022). This could also have an important role in diet-microbiome interactions, as the release of nutrients from the food matrix by the microbiome is likely to happen at a very different rate than in processed food products, with many consequences to their metabolic activities (PUHLMANN; DE VOS, 2022).

1.5 Human gut microbiome and diet

One of the main activities of gut microbiome is digestion, which benefits both human host and gut bacteria. Human genome encodes only few carbohydrates active enzymes (CAZymes) for glycan (polysaccharide) digestion specifically towards starch, sucrose, and lactose. The gut microbiome encodes 600-fold more CAZymes than the human genome, which allows the digestion of the great diversity of dietary glycans (ZHANG *et al.*, 2014b). As human gut bacteria undergo selection and competition, the ability to utilize dietary and host glycans is essential for their survival. Evolution of CAZymes capable of degrade specific polysaccharides can give a competitive advantage in an environment with finite ecological niches such as the human gut (WARDMAN *et al.*, 2022).

Gut bacteria require substrate to replicate, releasing many metabolic products during this process (ZENG *et al.*, 2022). Nutrients come from host diet, mucus and metabolites (ZENG *et al.*, 2022), as well as from bacterial metabolites (WARDMAN *et al.*, 2022). Dietary fibers are main bacteria substrates, and to a much lesser extent, so are proteins (KORPELA, 2018; OLIPHANT; ALLEN-VERCOE, 2019; ZENG *et al.*, 2022) that scape primary digestion due to excessive ingestion quantities, or structural complexity, and reach the colon (OLIPHANT; ALLEN-VERCOE, 2019). Gut bacterial growth is synchronized with host feeding (ZENG *et al.*, 2022) and the gut microbiome composition depends on the substrate available. Carbohydrate generates the most abundant microbial end-products, the short-chain fatty acids (SCFAs) acetate, propionate, and butyrate (OLIPHANT; ALLEN-VERCOE, 2019). SCFAs generate energy for intestinal epithelial cells (IECs) and other human body requirements (up to 10%). Butyrate improves the integrity of IECs and has an anti-inflammatory activity (OLIPHANT; ALLEN-VERCOE, 2019). Other end-products like carbon dioxide and hydrogen are removed by cross-feeding with other bacteria (OLIPHANT; ALLEN-VERCOE, 2019). On the other hand, protein metabolism by the gut microbiome may release harmful compounds for health (RAIMONDI *et al.*, 2021).

Fibers are carbohydrate polymers that resist digestion and absorption in human small intestine due to a lack of human enzymes to degrade them. The main sources of fiber in the diet are plant cell walls that are composed by cellulose, hemicelluloses, pectin, and the non-carbohydrate compound lignin. Fibers also comprise resistant starch, fructan (i.e. inulin) and other synthetic products (AUGUSTIN *et al.*, 2020; JONES, 2014). Furthermore, fibers intrinsic to the food matrix confer benefits beyond isolate ones, due to the preservation of the plant's cell wall three-dimensional structure (AUGUSTIN *et al.*, 2020). A fiber deprived diet promotes growth of mucus-degrading bacteria, and detrimental mucus erosion, which increases susceptibility to enteral pathogen infections (DESAI *et al.*, 2016). They are also important for

gut microbiome recovery after disturbance (TANES *et al.*, 2021). Such complex substrates generally require a greater number of CAZymes belonging to different microorganisms to be degraded (KAOUTARI *et al.*, 2013; WARDMAN *et al.*, 2022). Small differences in fiber structure induce distinct changes in gut microbiome diversity, composition, and metabolic activity (DEEHAN *et al.*, 2020).

Diet has strong influence in human gut microbiome. In response to long term dietary habits the genome of gut microbiome symbionts can undergo changes like those reported for Asian populations, with the acquisition of CAZymes for algae digestion through horizontal gene transfer from marine bacteria consumed with raw algae (KAOUTARI *et al.*, 2013; WARDMAN *et al.*, 2022).

1.6 The gut microbiome, diet and industrialized societies

Our lifestyle, gut microbiome and diets have never been more distinguished from our ancestors than it is nowadays. Coprolites studies show that modern hunter-gatherer societies have the most similar gut microbiome to our known ancestors and industrialized societies have the least similar. Gut microbiomes of all other societies that fall between those, like agriculturalists and pastoralists, are much more similar to hunter gathers (ROSAS-PLAZA *et al.*, 2022; SMITS *et al.*, 2017) than to industrialized societies gut microbiomes. At the same time, changes from a traditional to an industrialized lifestyle, including changes in diet, parallel the changes observed in the microbiome, such as the genus *Prevotella* being displaced by *Bacteroides,* and the loss in CAZymes related to dietary fiber degradation associated to *Prevotella* in industrialized societies (VANGAY *et al.*, 2018). Loss of *Prevotella* and CAZymes may be related to reduction in nutritionally diverse plant-based foods with different complex and fermentable polysaccharides (FEHLNER-PEACH *et al.*, 2019).

Furthermore, together with *Bacteroides*, two other genera present in higher amount in industrialized gut microbiomes, *Alistipes* and *Bilophila,* have been linked to high-fat and high-animal protein diets characteristics of industrialized societies (DAVID *et al.*, 2014). *Akkermansia,* a mucus degrading bacteria has also been linked to fiber-poor industrialized societies diet (PASOLLI *et al.*, 2019; ROSAS-PLAZA *et al.*, 2022). Additionally, non-food chemicals exclusively present on ultra-processed foods like sweeteners and emulsifiers have been related to alterations in gut microbiome composition and activity resulting in risk of impaired health, such as glucose intolerance and type 2 diabetes (CHASSAING *et al.*, 2022; SUEZ *et al.*, 2014, 2022).

Both changes in diet and in gut microbiome are repeatedly linked to pathological conditions characteristic of industrialized societies named non-communicable diseases (NCD), which are an important cause of health impairment and death in industrialized societies (MACHADO *et al.*, 2022; SROUR *et al.*, 2022) (GBD 2019 DISEASES AND INJURIES COLLABORATORS, 2020). Gut microbiome changes are adaptations that make it possible for human to adapt a variety of environments, lifestyles, and diets (SCHNORR *et al.*, 2014). Contrary to eukaryotic cells, the gut microbiome is much more flexible, and it can be partially changed very rapidly due to environmental and/or sociocultural shifts (DAVID *et al.*, 2014; KNIGHT *et al.*, 2017; VANGAY *et al.*, 2018). The rapid changes undergone by the human gut microbiome and the slower changes undergone by the human host eukaryotic cells due to environmental and lifestyle changes in recent times, including industrialized diets, may result in an incompatibility and inadequate response of the human host do the gut microbiome presence and activity, with and lead to impaired health (SHARMA *et al.*, 2020; SONNENBURG; SONNENBURG, 2019).

2 OBJECTIVE

We investigated the relationship between the gut microbiome composition and diet of a rural Amazonian riverine population and compared them to an urban population living in São Paulo.

3 METHODS

We conducted an observational cross-sectional comparative study with 104 healthy adults between 18 and 58 years old. They were a subsample from two other studies described below.

3.1 Amazonian riverine study

Amazonian rural riverine were recruited for an observational cross-sectional study entitled "Saúde bucal dos ribeirinhos da Reserva de Desenvolvimento Sustentável Mamirauá", where the oral health was the main outcome. The study was approved by the Human Research Ethics Committee (CEPSH) of Institute of Biological Sciences (ICB) of the University of São Paulo (USP) on 08/Dec/2014 (CEPSH/ICB/USP Registry Identifier: 912.361; CONEP Brasil, Registry Identifier: 32845314.1.0000.5464).

Participants were healthy adult couples, between 14 and 49 years old. They were recruited at 26 different communities in the “Reserva de Desenvolvimento Sustentável Mamirauá” (RDSM) located in the Mid-Solimões region in the Brazilian Central Amazon Forest (INSTITUTO DE DESENVOLVIMENTO SUSTENTÁVEL MAMIRAUÁ, 2022) (Figure 1). From 242 participants (DA-GLORIA; PIPERATA, 2019), all provided dietary information and 86 provided fecal samples.

Figure 1 - Approximate location for the “Reserva de Desenvolvimento Sustentável Mamirauá”

Source: Google maps. Red point: Approximated location for the “Reserva de Desenvolvimento Sustentável Mamirauá”.

For making up the sample of the present study, we selected 49 subjects as described in the section “Selection of subjects”. Participants were from 16 different communities (Acari, Batalha de Baixo, Bate Papo, Boa Sorte, Boiador, Curupira, Deus é Pai, Fazendinha São Jorge, Maguari, Nova Jacitara, Pedro Pinho, Porto Alves, Santa Fé, Tacanal, União da Amazônia). Health interviews and fecal sample collection were performed between January/2016 and February/2016. Most dietary and anthropometric data (n=36) were collected during the dry/low-water season (October/2015 - December/2015). The remaining dietary and anthropometric data (n=13) were collected during the rainy/high-water season (May/2015 - July/2015). All data were collected by the same researchers who received standardized training.

Diet interviews were conducted using a 24-hour dietary recall (24HR) for 5 days (most consecutive days including 1 or 2 weekend days). Anthropometric data (weight, height, circumferences, and subcutaneous fat) were measured according to previous published standards (BRASIL, 2011). Participants received a sterile tube, a plastic package for defecation and instructions for feces self-collection. When providing fecal samples, the subjects also reported feces consistency based on the Bristol scale. Feces were delivered at the research base on average 13.15 (SD=11.29) hours after collection and were placed in liquid nitrogen for storage until airplane transportation (kept frozen in dry ice) to the University of São Paulo (USP), where the samples were kept at -80°C until further processing.

RDSM is mostly situated in a floodplain that receives annual flood pulses resulting in two main seasons: the high- and the low-water seasons (MOURA et al., 2015). The reserve extension is approximately 11,240 km² and comprise 200 communities with 1,873 households resulting in 10,867 habitants. The number of households in each community is between 4 and 35 in the floodplain, and 7 and 100 in "terra firme". The former has on average 67 and the latter 127 habitants in each community. The predominant family composition is a couple with children and mean number of residents per household is 6 (range 1 to 22). Average fertility is 9 children per woman and infant mortality rate is 28% (ranging from 18% to 36% in different communities). The distance from Tefé-AM, the main commercial and public services city in the region, is between 1.5 and 20 hours by fluvial transport, depending on the community location and season (MOURA et al., 2015).

Amazonian riverine people live in stilt or floating houses along the rivers and are traditional communities who share culture and use local nature resources according to ancestral knowledge (DE ANDRADE *et al.*, 2021). Stilt houses are built of wood near the rivers and one meter above the ground, while floating houses use a wooden footing base. Both are designed to protect from annual flood pulses. There are on average 3 to 4 rooms. The kitchen is usually separate to facilitate manipulation of the oven and stove (fueled by wood) and the place to make the manioc flour may be also separate from the kitchen. There is usually a garden with small plants and medicinal ones. Usually, there are no toilets and human waste is thrown into the forest or into the river. The lighting service is limited to 4 hours at night (MOURA et al., 2015).

Usually, the water for drinking and cooking is collected from the rain, while the water provided by the river is used for other activities. Some communities have piped water, using solar energy powered systems that capture water from the river, but this system does not make the water potable (MOURA et al., 2015). The water is contaminated by fecal coliforms (53% of samples in low-water season, and 83% in high-water) (MOURA et al., 2015). Approximately half of households (67,6%) use hypochlorite in their drinking water, despite having a high prevalence of intestinal parasites infections (GIATTI; CUTOLO, 2012). They drink little water, probably because of the limitation of potable water (GIATTI; CUTOLO, 2012; PACIFICO *et al.*, 2021).

The characteristic social organization is the peasantry based on family work. That is affected by the seasonality of natural resources, the relation with urban markets and public policies. Families work in multiple productive activities (fishing, agriculture, and extraction of wood and non-wood products). In low-water season fishing is the principal activity and the work concentrated in two months results in 75% of yearly monetary income. In the high-water

season the wood selling rises. Fishing is the predominant economic activity (MOURA et al., 2015).

The largest contributors to the region's domestic economy are government social benefits (44,3%) followed by fishing (20,8%), wages and services (16,4%), and agriculture (12,9%) (PERALTA; LIMA, 2013). Fuel, food, and hygiene items represent 75% of expenses (PERALTA; LIMA, 2013). The average household income was R$ 754 monthly in 2010 and almost 62% of households were below the official poverty line (R$ 140) (PERALTA; LIMA, 2013).

Production for self-consumption is the foundation of biological and social reproduction of the domestic group (PERALTA; LIMA, 2013). The increase of income and market access bettered living standards, and at the same time reduced self-supply (PERALTA; LIMA, 2013), producing changes in dietary patterns with an increase in the consumption of commercial chicken and industrialized food (DE ANDRADE *et al.*, 2021). In 2010, a half of households bought manioc flour in some extension (PERALTA; LIMA, 2013). New food habits coexist with the traditional diet: fish complemented by cassava flour, which represent the main sources of protein and carbohydrate, respectively (DE ANDRADE *et al.*, 2021). Industrialized food also represents an environmental problem in reserves because of the absence of public services for non-organic waste collection (DE ANDRADE *et al.*, 2021).

3.2 São Paulo urban subjects' study

São Paulo urban subjects (n=55) were recruited for an interventional study entitled "Functional Ingredients: Effect in Satiety and Intestinal Health" approved by the Research Ethics Committee of the School of Pharmaceutical Sciences of University of São Paulo (CEP/SFS/USP Registry Identifier: 18 and 194; CONEP Brasil, Registry Identifiers: 0042.0.018.000-11 and 0069.0.018.198-11) on 28/Nov/2011 and 28/Feb/2012. The study is registered at clinicaltrials.gov (NCT02467972). Intervention was a dietary fiber supplementation, and the main outcome was hormonal parameters related to hunger and satiety and intestinal changes (function and gut microbiome). The samples used in this study were the baseline samples, prior to any intervention.

The recruiting site was the University of São Paulo (USP) main campus (Butantan), in an urban region of São Paulo (Brazil). They were healthy adults between 19 and 58 years old, mostly students and staff of the university. Data were collected between September/2012 and

November/2012. We used data from health interviews, dietary recalls, feces sample collection and anthropometric evaluation.

The inclusion criteria were good general health conditions defined as absence of self-reported history of gastrointestinal, cardiovascular, metabolic, endocrine, renal, hepatic diseases (HOFFMANN SARDÁ *et al.*, 2016), detailed at clinical.trial.gov NCT02467972. Exclusion criteria were use of drugs that might affect the digestion and absorption of food, use of antibiotics (both within the last three months prior to study enrollment), women who were pregnant, breastfeeding or using hormonal therapy, and having a BMI of 25kg/m^2 and over.

All dietary data was collected by the same researchers who received standardized training. Diet interviews from baseline were conducted using a 24-hour dietary recall (24HR) in 3 non-consecutive days, including a weekend day, in a range period of 15 days.

Participants were provided with a collection kit for fecal sample self-collection (thermic box and ice for transportation, sterile plastic containers, plastic packages, and gloves). Samples were kept and transported in a container with ice. Time between evacuation and sample delivery at the lab facility was four hours or less. There was no temperature control during transportation. The fecal samples were separated into aliquots within a maximum of eight hours after being received and stored at -80C until further analysis. When providing fecal samples de subjects also reported the stool sample consistency based on the Bristol scale.

3.3 Selection of subjects

We used a convenience sample, and no statistical methods were used to predetermine sample size. The sample of the present study is composed by baseline data (before supplementation) of all subjects of São Paulo study (n=55) and subjects of Amazonian riverine study who matched for sex and age with those (n=49). Except one couple among Amazonian riverine sample, those who were cohabiting were excluded. Three months before stool collection, no São Paulo dwellers took antibiotics or other medication while 24 Amazonian riverine took antibiotics. Six months before stool collection 43 Amazonian riverine took medicines.

3.4 Laboratory methods

Samples were processed at School of Pharmaceutical Sciences and sequenced at “Centro de Facilidades para a Pesquisa (CEFAP)” of University of São Paulo (USP). Fecal

samples from São Paulo urban subjects had their DNA extracted following the collection samples in May-September/ 2013 and DNA were kept at -20°C. Amazonian riverine fecal samples were kept at -80°C from 2016 until March-July/2017 when the DNA was extracted and kept at -20°C. Samples underwent the same extraction protocol and were sequenced in the same run in October/2017.

3.5 DNA extraction and sequencing

Total fecal DNA was extracted and processed as described in (HANSEN et al., 2019) using the PSP Spin Stool DNA Plus Kit (Stratec Molecular, Germany - Ref 1038100399) following manufacturer's instructions, with a modified bead-beating method with Lysing Matrix E (MP Biomedicals - Ref 6914100) prior to sample extraction. DNA was eluted in a 100 uL PSP Spin Stool DNA Plus Kit buffer and quantified using NanoDrop 2000 (Thermo Scientific, MA, EUA) before being stored at -20°C.

Polymerase Chain Reactions (PCR) reactions were performed in quadruplicate for DNA amplification using the AccuPrime Taq DNA Polymerase System (Invitrogen, Thermo Fisher Scientific Inc, USA) and primers targeting 16S rRNA V1-V2 region (BSF8 e BSR357) (MINOT *et al.*, 2013; WU *et al.*, 2011) composed of barcode and Illumina sequencing platform adapter, following technique described previously (CAPORASO *et al.*, 2011, 2012). PCR products were bead-purified with Agencourt AMPure XP beads (Beckman-Coulter) and DNA concentration was determined with Quant-iT PicoGreen dsDNA (Invitrogen, Thermo Fisher Scientific Inc, USA). Blank DNA extractions (only reagents, without sample) and PCR blank reactions were performed as negative controls (HOFFMANN *et al.*, 2013). Samples were pooled in equal amounts and sent to the sequencing facility (CEFAP/USP), where the pool was quantified using Qubit High Sensitivity dsDNA Assay Kit (Invitrogen, Thermo Fisher Scientific Inc, USA), prior to sequencing. Paired-end sequencing for microbiome profiling was performed in the Illumina MiSeq platform using MiSeq v2 Reagent 500 cycle kit (2 × 250 bp cycles).

3.6 Dietary data processing

The Amazonian riverine dietary information was first digitized in the Nutritionist Pro™ software. We received the dietary information extracted from Nutritionist Pro™ software in Excel spreadsheets format. The spreadsheets contained the foods and preparations consumed

and the respective amounts in grams for each subject's recalls. During data insertion in the Nutritionist Pro™ software the food names were altered according to those of the reference food composition databases of the software, which did not include the Brazilian food composition table (TABELA BRASILEIRA DE COMPOSIÇÃO DE ALIMENTOS - TBCA, 2020). That, together with the perception of outliers' values in quantity of foods and preparations consumed were the reasons we checked all Amazonian riverine recalls against the original data registered on paper. We recovered the original food and preparation names, and portions of consumption in household measures as related by the participants.

After that, we converted the food consumption from household measures to grams using a reference table constructed by researchers for use during fieldwork and a popular reference table in Brazil, named Tabela para Avaliação de Consumo Alimentar em Medidas Caseiras (Table for the Assessment of Household Measures) (PINHEIRO et al., 2000). Both tables present portions of food in household measures and their corresponding weight in grams. The researchers' reference table were constructed through direct weighing of food portions (during field work) and culinary experiments conducted in the laboratory of dietetic technique at School of Public Health, University of São Paulo (FSP/USP) for this purpose. If the consumed food or preparation was not found on those tables, we reproduced the food or preparation and weighted them using a domestic scale (due to the pandemic period). The final dataset used in our analysis was composed of original food and preparation names (reported by the participants during the interviews) and consumption in grams done by the method described above, except for fish, and some vegetables and fruits, which weight was kept as digitized in the Nutritionist Pro™ software (with no further rechecking).

We had 157 recalls from São Paulo dwellers and 234 recalls from Amazonian riverine. Nutrient and energy consumption were evaluated using the Brazilian food composition table (TABELA BRASILEIRA DE COMPOSIÇÃO DE ALIMENTOS - TBCA, 2020). Calculation of each individual energy and nutrient intake was made thought arithmetic mean of their recalls. Means of individual nutrient intake were adjusted by energy intake through residual method (WILLETT; HOWE; KUSHI, 1997) and those values were used in all downstream analysis. Mann-Whitney U test was used for comparing nutrient intake between São Paulo dwellers and Riverine.

When we did not find the exact food or preparation in TBCA we used the most similar for matching nutritional content. The following preparations were missing from the TBCA, and had their nutritional content calculated based on the recipes obtained from the study volunteers: sweetened juices, reconstituted and sweetened dairy compound, sweetened tea, shredded

arapaima, fried dough, preparations with river turtle (*Podocnemis unifilis*), porridge, smoothies, corn cake, avocado-based preparation, manioc cake.

Food consumption was evaluated using an adaptation of NOVA food classification (LOUZADA *et al.*, 2015) where foods are classified into three major groups and their related subgroups. This was done as information about ingredients for culinary preparations were unavailable for São Paulo dwellers, which prevented us from disaggregating culinary preparations into their ingredients for food classification, as original proposed by the NOVA food classification (MONTEIRO *et al.*, 2019). This adaptation collapse NOVA group 1 and NOVA group 2 from original classification into a unique group called NOVA group 1. NOVA group 1, namely natural or minimally processed foods, included unprocessed or minimally processed foods, culinary ingredients (fat, salt, sugar) and culinary preparations based on these foods. As a result of non-disaggregating, these culinary preparations may contain ingredients of NOVA groups 2 and 3, but ingredients were predominantly from NOVA group 1. NOVA group 2, namely processed foods, included processed foods and culinary preparations based on them like sandwiches with non-industrial bread, cheese, and other ingredients. NOVA group 3, namely ultra-processed foods, in general were industrial preparations with at least one ingredient characteristic of ultra-processed foods like a food substance never or rarely used in kitchens or a cosmetic additive.

We performed classification of foods and preparations by two experienced researchers in the fields of food and nutrition, and if disagreements were present, they were discussed with a third researcher for consensus. Uncertainties about the classification of food items were checked with Center for Epidemiological Research in Nutrition and Health (NUPENS), the NOVA food classification developers. For better characterization of food consumption, each NOVA group was divided in their related subgroups based in the similarity of foods and preparations in terms of traditional food groups (e.g., cereal, vegetables, fruits, meats, milk and so on). We computed the percent of energy contribution of each NOVA group and each NOVA subgroup for individual´s daily total energy intake. All analysis using NOVA groups and subgroups were done with these percentage values.

Amazonian riverine data were detail rich (preparation items, labels, pictures and local of consumption) and generated almost no uncertainties about classification. São Paulo dwellers consumed many foods that could be a homemade preparation or an industrial one. Since São Paulo dwellers subjects were students and staff of university of São Paulo (USP) campus Butantan, for better NOVA classification we collected information about the campus food

availability at the time of research fieldwork (university restaurants, cafeteria, and other food sellers) and staff food habits.

Dietary data was analyzed in JAMOVI (THE JAMOVI PROJECT, 2021) and Excel software. Mann-Whitney test was performed for comparing São Paulo dwellers and Amazonian riverine by nutrient and NOVA groups and subgroups intake. Statistical differences were considered for tests with a p-value <0.05.

We created bar charts of NOVA subgroups contribution to each nutrient intake and did a visual evaluation for identifying the NOVA subgroups which shows the highest contribution to each nutrient intake (Appendix A). Then, we check in the x axis the corresponding value, which we considered the cut-off points to establish the main nutrient sources (Table 1) present in the subsection “Nutrient Sources”.

Table 1 - Cut-off points for selection of NOVA subgroups which most contributed to nutrient intake

Nutrient (unit)	**Cut-off point**	**Nutrient (unit)**	**Cut-off point**
Energy (kcal)	>40	Manganese (mg)	>0.1
Water (g)	>30	Zinc (mg)	>0.2
Carbohydrate (total and available) (g)	>5	Copper (mg)	>0.02
Protein (g)	>2	Selenium (mcg)	>5
Lipids (g)	>2	Vitamin A (RE) (mcg)	>10
Alcohol (g)		Vitamin A (ERA) (mcg)	>10
Fiber (g)	>0.4	Vitamin D (mcg)	0.1
Cholesterol (mg)	>10.5	Vitamin E (mg)	>0.1
FASAT (g)	>1	Thiamine (mg)	>0.02
FAMS(g)	>0.5	Riboflavin (mg)	>0.025
FAPU (g)	>0.4	Niacin (mg)	>0.5
FAT (g)	>0.05	Vitamin B6 (mg)	>0.025
Calcium (mg)	>50	Vitamin B12 (mcg)	>0.5
Iron (mg)	>0.2	Vitamin C (mg)	>2.5
Sodium (mg)	>40	Folate equivalent (mcg)	>6
Magnesium (mg)	>10	Add salt (g)	>0.05
Phosphor (mg)	>50	Add sugar (g)	>0.5
Potassium (mg)	>50		

Source: Author.

We also created heatmaps of NOVA subgroups contribution to each nutrient intake and highlighted contribution values higher than percentile 90 (Appendix B, Appendix C). After that,

we performed a visual evaluation for identifying the NOVA subgroups which showed the highest contribution to each nutrient intake, as performed for the bar charts.

The Shannon diversity index was used to evaluate the diversity of NOVA subgroups contribution to energy, macronutrient, and fiber intake. We used the following equation: $H' = -\sum_{i=1}^{S} pi \ln pi$ where i refers to each NOVA subgroup, S is the total of NOVA subgroups contributing to the category (energy, macronutrient or fiber), and pi is the proportion of each NOVA subgroup contribution to energy, macronutrient, or fiber intake.

We carried a cluster analysis with k-means and a principal component analysis (PCA), both with consumption of NOVA subgroups by São Paulo dwellers and Amazonian riverine. For cluster analysis, the optimal number of clusters was determined by Elbow method as 3 clusters, the number of random starting partitions determined was 100 and the maximum number of iterations allowed was 10.

3.7 Bioinformatic and Statistical Methods

Microbiome sequence data was processed with Quantitative Insights into Microbial Ecology 2.0 (QIIME2 version 2022.2) (BOLYEN *et al.*, 2019) and R (R CORE TEAM, 2022). Microbiome sequencing resulted in a total of 2797447 reads (minimum:11415; maximum: 52200; mean: 26898,53; median: 26328). Data were imported into QIIME2 and demultiplexed with "demux" plugin. Denoising, dereplication e sequence quality control was done using "q2-dada2-denoise paired" plugin (CALLAHAN *et al.,* 2016) with minimum read length of 230 bases for forward reads and 225 bases for reverse reads, and minimum overlap length of 20 bases. That resulted in 1884706 joined reads and 6892 unique amplicon sequence variants (ASVs) for 104 samples with mean length and standard deviation of 315.88 and 11.51 respectively (minimum length of 276 and maximum length of 425).

A phylogenetic tree was done using "q2-phylogeny" plugin with its "align-to-tree-mafft-fasttree" pipeline. Taxonomic assignment using "q2- feature-classifier" (BOKULICH *et al.*, 2018) plugin with Basic Local Alignment Search Tool (BLAST+) consensus classifier as the method (CAMACHO *et al.*, 2009) and SILVA v138 as reference database (at 99% similarity) (GLÖCKNER *et al.*, 2017; QUAST *et al.*, 2013; YILMAZ *et al.*, 2014). Alpha and beta diversity were calculated using "q2-diversity" plugin with "core-metrics-phylogenetic: Core diversity metrics (phylogenetic and non-phylogenetic)" pipeline using sampling depth of 7771.

Diversity within samples were calculated using the following alpha diversity indexes: Richness (observed species), Pielou´s evenness, Shannon diversity index and Faith's Phylogenic Diversity (Faith's PD). Between samples diversity (beta diversity) were evaluated unweighted and weighted Unifrac distances (LOZUPONE *et al.*, 2011). Permutational analysis of variance (PERMANOVA) test was used for hypothesis testing (ANDERSON, 2017) (R function: ADONIS3 from GUniFrac package). Beta diversity relations were visualized using Principal Coordinate Analysis (PCoA).

The COREMIC tool was used with "q2-coremicrobiome" plugin in QIIME, with a maximum adjusted Benjamini-Hotchberg p-value = 0.05 (RODRIGUES *et al.*, 2018). The final ASV selection for each group represents the core microbiome e.g., the common ASVs which most distinguish the groups. This technique is based in presence/absence data. Differential abundance between São Paulo dwellers and Amazonian riverine was tested using Analysis of Composition of Microbiomes (ANCOM), which were implemented using "q2-composition" plugin in QIIME, and visualized as heatmaps and log-fold change charts (MANDAL *et al.*, 2015).

We used PERMANOVA model coefficients absolute values for verifying de 10 ASVs which most differentiate São Paulo dwellers and Riverine. For that, we used Bray-Curtis and Jaccard beta diversity measures. The former use abundance while the second use presence/absence data, which emphasize the more abundant ASVs by the Bray Curtis and in rare ASVs by Jaccard.

Non-metric multidimensional scaling (nMDS) plot using unweighted and weighted Unifrac was used to visualized genera which drive the pattern towards São Paulo dwellers and Amazonian riverine samples.

Overall agreement between microbiome and diet was verified using Procrustes analysis and the related hypothesis testing PROTEST (JACKSON, 1995; PERES-NETO; JACKSON, 2001). Procrustes analysis evaluates the congruency between two data sets by the superimposition of their shapes until de minimum sum of squared differences is obtained. Then, Procrustes randomization test (PROTEST) performs symmetric Procrustes analysis repeatedly (999 permutations) to estimate the significance of the Procrustes statistic (if the degree of concordance is greater than expected by random association). We performed Procrustes and Protest on ordination results of PCoA (vectors) of dietary (Bray-Curtis's distance matrices) and microbiome (weighted and unweighted Unifrac distance matrices) data using vegan R package (OKSANEN et al., 2012). Dietary data matrices were percentage of energy contribution to total

energy intake of NOVA groups (sum 100% or 1) and NOVA subgroups (sum 100% or 1). Non-phylogenetic microbiome matrices were done with relative abundance of genera.

For checking the correlations between microbiome and diet variables we performed a Spearman's rank correlation test using taxa (genus) and NOVA groups and subgroups, and nutrients. P-values were adjusted using false discovery rate (FDR) and significance was defined at adjusted p-value < 0.05 (q-value).

4 RESULTS

4.1 Population

There was no difference in age (Table 2) and sex between São Paulo dwellers (F=40/M=15) and Amazonian riverine (F=36/M=13) (sex Chi-square test=0.00725, P value=0.932). Amazonian riverine BMI was higher than São Paulo dwellers and the former had eight obese participants (8/47, 16.67%) while the latter had three obese participants (3/55, 5.45%). Amazonian riverine also shows higher prevalence of intestinal infections (6/48, 12.5%) within the days preceding fecal sample collection, and antibiotic use in the last 3 months (at least once) (24/48, 50%) preceding sample collection. São Paulo dwellers have no cases of intestinal infection or antibiotic use in the same period. Bristol scale classification between 3 and 5 were present by 64.70% of São Paulo dwellers (33/51) and 39.58% Amazonian riverine (18/48) (Chi-square test=7.33, P=0.007).

Table 2 - Age and BMI São Paulo dwellers and Amazonian riverine

		Min	Max	IQR	25th	Median (50th)	75th	Statistics*	P value
Age	AMZ (n=49)	18	42	10.00	22.00	28.00	32.00	1217	0.395
	SP (n=55)	19	58	8.00	24.00	28.00	32.00		
BMI	AMZ (n=47)	19.2	36.3	5.70	23.25	26.10	28.95	823	0.002
	SP (n=51)	17.6	37.6	4.80	21.50	23.60	26.30		

Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine. * Mann-Whitney U test. Min: minimum. Max: maximum. IQR: interquartile range. 25th, 50th, 75th: percentiles.

4.2 Nutrients Intake

There was no difference between energy, carbohydrate, alcohol, magnesium, added salt and added sugar intake between Amazonian riverine and São Paulo dwellers (Table 3). All other assessed nutrients were significantly different between the two populations. Protein, cholesterol, polyunsaturated fatty acids (FAPU), selenium, vitamin D, niacin, vitamin B6, vitamin B12 intakes were higher among Amazonian riverine, while total lipids, fiber, alcohol, saturated fatty acids (FASAT), monounsaturated fatty acids (FAMS), trans fatty acids (FAT), calcium, iron, sodium, magnesium, phosphor, potassium, manganese, zinc, copper, vitamin A,

vitamin E, thiamine, riboflavin, vitamin C and folate equivalent intakes were higher in São Paulo dwellers (table 3)

Table 3 - Consumption of energy and nutrients by São Paulo dwellers and Amazonian riverine

Dietary Variables		Min	Max	IQR	25th	Median (50th)	75th	Statistic*	P value
Energy (kcal)	AMZ	659.73	4762.80	1205.13	1630.59	2205.66	2835.72	1304	0.779
	SP	988.49	8075.47	1081.37	1797.19	2171.99	2878.57		
Water (g)	AMZ	562.28	3103.13	390.92	776.46	956.44	1167.38	997	0.023
	SP	-108.12	2317.04	388.60	976.73	1135.40	1365.33		
Carbohydrate (total) (g)	AMZ	210.45	515.13	54.21	271.35	292.01	325.56	1342	0.974
	SP	142.96	419.74	40.41	275.45	298.97	315.86		
Carbohydrate (available) (g)	AMZ	191.73	488.90	51.37	256.80	280.95	308.17	1299	0.755
	SP	135.43	385.62	38.97	257.72	276.59	296.69		
Protein (g)	AMZ	71.06	224.53	36.69	109.00	126.17	145.69	523	< .001
	SP	72.51	157.38	19.53	93.36	100.57	112.89		
Lipids (g)	AMZ	14.76	123.81	19.58	73.75	84.83	93.33	899	0.004
	SP	46.98	124.99	17.97	84.00	92.47	101.97		
Fiber (g)	AMZ	9.12	31.49	4.46	13.96	16.09	18.42	949	0.01
	SP	3.86	47.33	6.49	15.86	18.40	22.35		
Alcohol (g)	AMZ	-1.18	6.64	0.60	-0.20	0.11	0.40	1089	0.093
	SP	-2.84	17.33	0.62	-0.07	0.28	0.54		
Cholesterol (mg)	AMZ	220.17	1134.33	180.73	383.50	453.69	564.23	533	< .001
	SP	99.26	567.62	82.75	299.06	336.02	381.81		
FASAT (g)	AMZ	-9.51	38.41	11.03	17.52	23.31	28.55	266	< .001
	SP	15.19	83.76	11.94	32.87	37.73	44.81		
FAMS (g)	AMZ	5.70	33.29	6.54	19.32	23.15	25.86	679	< .001
	SP	15.39	46.63	6.02	24.24	27.66	30.26		
FAPU (g)	AMZ	6.25	61.92	12.88	15.59	21.61	28.48	534	< .001
	SP	-12.09	41.27	4.75	11.14	13.80	15.89		
FAT (g)	AMZ	-0.64	3.16	1.06	0.81	1.29	1.87	443	< .001
	SP	0.76	6.84	1.12	1.84	2.42	2.96		
Calcium (mg)	AMZ	-705.00	1799.88	677.16	571.74	884.21	1248.90	502	< .001
	SP	443.44	4375.36	539.50	1191.03	1405.24	1730.53		
Iron (mg)	AMZ	3.61	35.60	2.39	8.45	9.95	10.85	654	< .001
	SP	6.00	18.63	3.09	10.99	12.18	14.07		
Sodium (mg)	AMZ	-553.01	6496.94	841.45	1072.55	1411.15	1913.99	167	< .001
	SP	2162.88	4751.60	808.87	2578.83	2918.21	3387.70		
Magnesium (mg)	AMZ	179.54	438.69	82.44	267.23	310.92	349.67	1113	0.128
	SP	241.03	488.10	53.52	295.03	328.34	348.56		
Phosphor (mg)	AMZ	-283.35	2774.15	932.61	1180.81	1698.85	2113.42	690	< .001
	SP	840.38	6173.16	673.43	1875.18	2085.75	2548.61		
Potassium (mg)	AMZ	1228.90	4361.84	973.93	2579.82	3189.74	3553.75	1004	0.026
	SP	1826.84	5234.09	793.43	2949.60	3370.49	3743.03		
Manganese (mg)	AMZ	1.02	20.98	1.06	2.21	2.53	3.27	839	< .001
	SP	1.31	10.54	1.45	2.69	3.35	4.13		
Zinc (mg)	AMZ	3.66	16.62	2.12	6.92	7.83	9.04	218	< .001
	SP	8.14	66.50	3.96	11.00	12.73	14.96		

Dietary Variables		Min	Max	IQR	25th	Median (50th)	75th	Statistic*	P value
Copper (mg)	AMZ	0.16	3.43	0.37	0.61	0.76	0.98	312	< .001
	SP	0.75	6.48	0.34	1.05	1.16	1.40		
Selenium (mcg)	AMZ	42.69	480.24	76.83	117.50	137.46	194.33	344	< .001
	SP	-16.52	452.83	37.41	40.43	58.43	77.84		
Vitamin A (RE) (mcg)	AMZ	-722.36	9568.35	655.89	223.70	532.01	879.59	873	0.002
	SP	18.79	2018.92	371.92	642.81	807.32	1014.73		
Vitamin A (RAE) (mcg)	AMZ	-770.18	9400.04	542.13	133.83	373.57	675.96	736	< .001
	SP	-27.02	1203.23	326.51	543.65	714.74	870.15		
Vitamin D (mcg)	AMZ	-7.76	271.05	6.56	4.45	8.63	11.01	662	< .001
	SP	-27.02	1203.23	326.51	543.65	714.74	870.15		
Vitamin E (mg)	AMZ	2.17	21.52	1.88	4.56	5.59	6.44	877	0.002
	SP	-1.87	24.37	2.46	5.55	6.49	8.02		
Thiamine (mg)	AMZ	-0.52	1.90	0.39	0.38	0.62	0.77	333	< .001
	SP	0.71	3.51	0.54	1.01	1.21	1.55		
Riboflavin (mg)	AMZ	-1.34	2.05	1.27	0.03	0.68	1.30	188	< .001
	SP	0.89	6.30	0.84	1.70	2.04	2.54		
Niacin (mg)	AMZ	11.38	37.79	8.09	14.87	19.08	22.96	1014	0.03
	SP	-12.78	47.66	10.97	10.52	16.45	21.48		
Vitamin B6 (mg)	AMZ	0.66	4.26	0.53	1.35	1.56	1.88	287	< .001
	SP	0.05	4.40	0.38	0.69	0.88	1.08		
Vitamin B12 (mcg)	AMZ	6.51	42.02	7.68	12.73	15.61	20.41	86	< .001
	SP	-1.91	13.34	3.30	5.02	6.67	8.32		
Vitamin C (mg)	AMZ	-19.36	118.69	36.51	21.15	37.59	57.66	345	< .001
	SP	-4.05	544.59	107.44	67.73	119.11	175.17		
Folate equivalent (mcg)	AMZ	53.24	1140.49	138.55	262.26	345.71	400.80	884	0.003
	SP	211.66	715.00	96.30	342.99	401.57	439.30		
	SP	-4.81	63.98	20.60	9.15	19.76	29.75		

Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine. Statistic: Mann-Whitney U test. Min: minimum. Max: maximum. IQR: interquartile range. 25th, 50th, 75th: percentiles. FAPU: polyunsaturated fatty acids. FASAT: saturated fatty acids. FAMS: monounsaturated fatty acids. FAT: trans fatty acids.

4.3 NOVA food classification

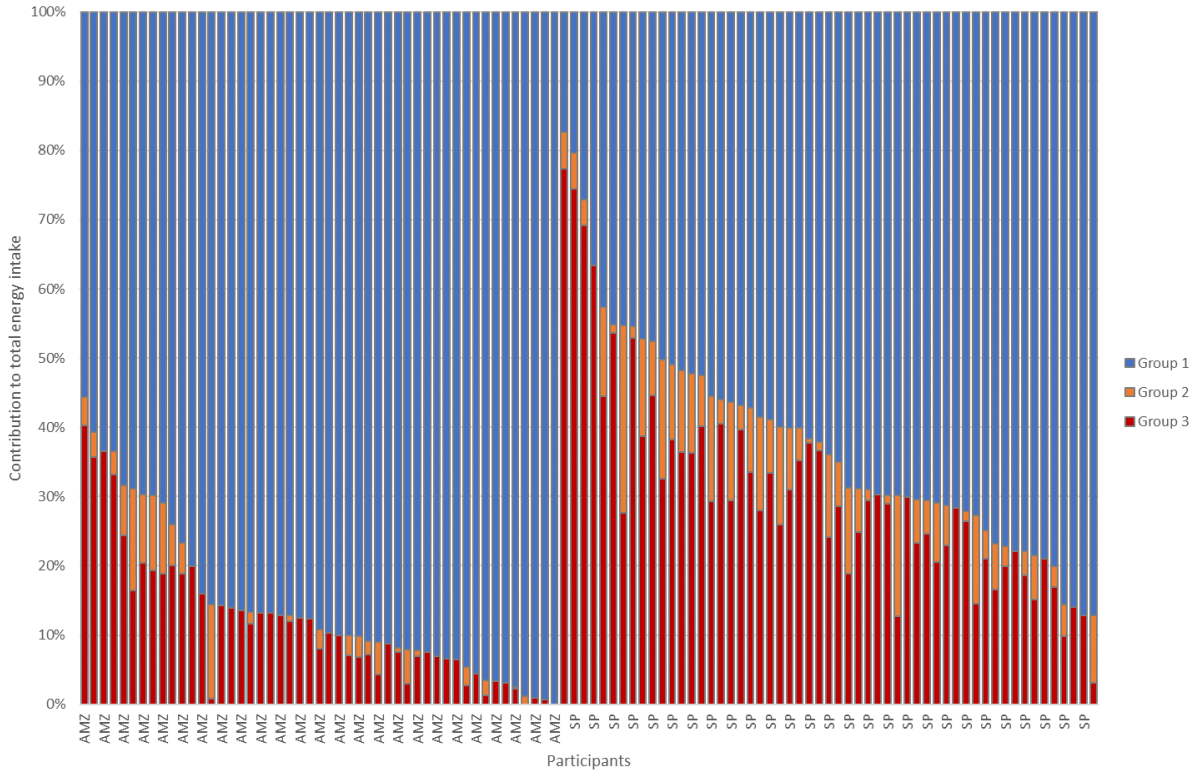
The NOVA group 1, natural or minimally processed foods, showed the greatest contribution to energy intake in both populations followed by NOVA group 3, ultra-processed, and 2, processed, respectively (Table 4, Figure 2). The contribution of NOVA group 1 to total energy intake was bigger in Amazonian riverine than in São Paulo dwellers, while NOVA groups 2 and 3 had bigger contributions to São Paulo dwellers than Riverine.

Table 4 - Contribution of NOVA groups to total energy intake among São Paulo dwellers and Amazonian riverine

NOVA		Min	Max	IQR	25th	Median (50th)	75th	Statistic*	P value
Group 1 Natural or minimally processed foods	AMZ	55.67	100	7.52	85.55	89.25	93.07	180	< .001
	SP	17.33	87.2	18.07	52.43	62.18	70.5		
Group 2 Processed foods	AMZ	0	13.6	2.14	0	0	2.14	333	< .001
	SP	0	27.1	8.07	3.53	6.4	11.6		
Group 3 Ultra-processed foods	AMZ	0	40.2	9.92	4.37	9.94	14.29	309	< .001
	SP	3.03	77.3	16.67	20.52	28.96	37.19		

Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine. * Mann-Whitney U test. Min: minimum. Max: maximum. IQR: interquartile range. 25th, 50th, 75th: percentile.

Figure 2 - Contribution of NOVA groups to individual total energy intake among São Paulo dwellers and Amazonian riverine



Source: Author. Y axis: percentual contribution to total energy intake. X axis: subjects. AMZ: Amazonian Riverine (n=49). SP: São Paulo dwellers (n=55).

NOVA groups were constituted by different food groups (NOVA subgroups) (Appendix D), which shows different contribution to total energy intake between São Paulo dwellers and Amazonian riverine (Table 5). There were 20, 4 and 13 subgroups in natural/ minimally processed, processed, and ultra-processed NOVA groups, respectively. Among Amazonian riverine, natural or minimally processed food subgroups were mainly composed by fish, cassava products (cassava flour) and fried dough, while among São Paulo dwellers the principal foods were milk, rice-based preparations, and red meat (beef and pork) (Figure 3). Processed food subgroups were mainly composed by non-industrialized bread, cheese, and few foods high in salt, sugar, or fat among São Paulo dwellers while among Amazonian riverine the consumption of food from NOVA 2 subgroups were almost inexistent and based in non-industrialized bread (Figure 3). Ultra-processed food subgroups were mainly composed by crackers and chips, and spreads (margarine) in Amazonian riverine and by goodies and industrialized bread in São Paulo dwellers (Figure 3).

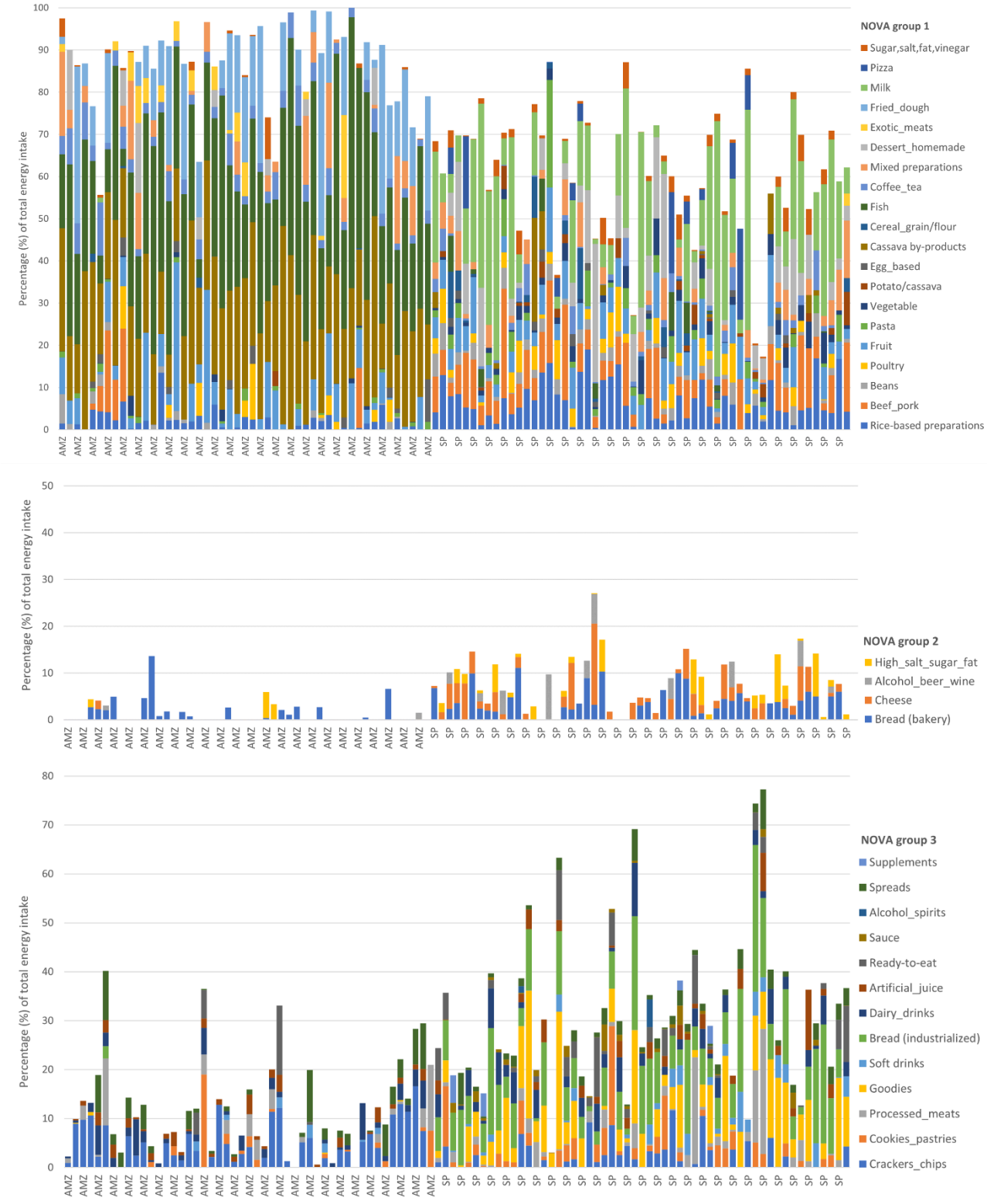
Table 5 - Contribution of NOVA subgroups to total energy intake among São Paulo dwellers and Amazonian riverine

NOVA groups	NOVA subgroups		Min	Max	IQR	25th	Median (50th)	75th	Statistic*	P value
1	Rice-based preparations	AMZ	0.00	13.49	2.68	0.00	1.43	2.68	470	< .001
		SP	0.00	19.05	5.33	3.07	5.29	8.40		
1	Beef and pork	AMZ	0.00	19.36	0.00	0.00	0.00	0.00	449	< .001
		SP	0.00	26.03	7.05	2.38	5.47	9.43		
1	Beans	AMZ	0.00	6.95	0.73	0.00	0.00	0.73	590.5	< .001
		SP	0.00	6.36	2.49	0.58	1.39	3.07		
1	Poultry	AMZ	0.00	13.14	0.00	0.00	0.00	0.00	817.5	< .001
		SP	0.00	10.49	3.99	0.00	1.91	3.99		
1	Fruit	AMZ	0.00	35.24	8.74	0.00	3.28	8.74	1103	0.111
		SP	0.00	16.85	5.35	3.01	4.96	8.37		
1	Pasta	AMZ	0.00	2.88	0.78	0.00	0.00	0.78	944	0.004
		SP	0.00	25.50	2.97	0.00	0.82	2.97		
1	Vegetable	AMZ	0.00	4.79	0.10	0.00	0.00	0.10	343	< .001
		SP	0.00	8.66	2.55	0.44	1.29	2.99		
1	Potato/cassava	AMZ	0.00	3.53	0.00	0.00	0.00	0.00	900	< .001
		SP	0.00	7.90	1.16	0.00	0.00	1.16		
1	Egg-based preparations	AMZ	0.00	10.14	0.00	0.00	0.00	0.00	1300	0.691
		SP	0.00	2.86	0.33	0.00	0.00	0.33		
1	Cassava products	AMZ	7.69	46.99	10.74	17.20	21.02	27.94	32	< .001
		SP	0.00	24.54	0.00	0.00	0.00	0.00		
1	Cereal and /grain/flour	AMZ	0.00	2.41	0.00	0.00	0.00	0.00	1041.5	0.007
		SP	0.00	12.06	0.44	0.00	0.00	0.44		
1	Fish	AMZ	4.15	64.25	15.08	21.43	27.49	36.51	12	< .001
		SP	0.00	9.08	0.00	0.00	0.00	0.00		
1	Coffee and tea	AMZ	0.00	12.55	2.53	2.12	3.01	4.64	471.5	< .001
		SP	0.00	9.43	1.59	0.17	0.69	1.76		
1	Mixed preparations	AMZ	0.00	20.74	5.01	0.00	0.00	5.01	1276	0.623
		SP	0.00	13.63	4.68	0.00	1.30	4.68		
1	Homemade dessert	AMZ	0.00	16.56	0.00	0.00	0.00	0.00	755	< .001
		SP	0.00	32.77	7.91	0.00	3.53	7.91		
1	Exotic meats	AMZ	0.00	19.72	1.81	0.00	0.00	1.81	957	< .001
		SP	0.00	2.96	0.00	0.00	0.00	0.00		
1	Fried dough	AMZ	0.00	43.30	18.33	0.00	8.57	18.33	467.5	< .001
		SP	0.00	0.00	0.00	0.00	0.00	0.00		
1	Milk	AMZ	0.00	1.10	0.00	0.00	0.00	0.00	200	< .001
		SP	0.00	60.59	23.29	3.13	13.00	26.43		
1	Pizza	AMZ	0.00	0.00	0.00	0.00	0.00	0.00	1078	0.001
		SP	0.00	21.55	0.00	0.00	0.00	0.00		
1	Ingredients (sugar, salt, fat, vinegar)	AMZ	0.00	9.92	0.28	0.00	0.00	0.28	586.5	< .001
		SP	0.00	6.31	2.14	0.10	0.73	2.25		
2	Non-industrialized bread	AMZ	0.00	13.64	1.68	0.00	0.00	1.68	799	< .001
		SP	0.00	11.09	4.66	0.00	2.47	4.66		
2	Cheese	AMZ	0.00	1.84	0.00	0.00	0.00	0.00	441	< .001

NOVA groups	NOVA subgroups		Min	Max	IQR	25th	Median (50th)	75th	Statistic*	P value
		SP	0.00	17.34	3.60	0.00	1.59	3.60		
2	**Beer and wine (alcohol)**	AMZ	0.00	1.55	0.00	0.00	0.00	0.00	1125	0.012
		SP	0.00	9.77	0.00	0.00	0.00	0.00		
2	**Food high in salt, sugar and fat**	AMZ	0.00	5.56	0.00	0.00	0.00	0.00	869.5	< .001
		SP	0.00	10.16	1.33	0.00	0.00	1.33		
3	**Crackers and chips**	AMZ	0.00	16.65	5.93	0.95	3.41	6.88	865	0.001
		SP	0.00	11.68	3.44	0.00	0.74	3.44		
3	**Cookies and pastries**	AMZ	0.00	19.00	0.55	0.00	0.00	0.55	806.5	< .001
		SP	0.00	20.23	3.06	0.00	1.06	3.06		
3	**Processed meats**	AMZ	0.00	13.66	0.94	0.00	0.00	0.94	929	0.004
		SP	0.00	25.55	1.94	0.00	0.65	1.94		
3	**Goodies**	AMZ	0.00	0.70	0.00	0.00	0.00	0.00	214	< .001
		SP	0.00	28.11	9.22	1.46	4.72	10.68		
3	**Soft drinks**	AMZ	0.00	2.67	0.00	0.00	0.00	0.00	835	< .001
		SP	0.00	8.23	2.49	0.00	0.03	2.49		
3	**Industrialized bread**	AMZ	0.00	2.52	0.00	0.00	0.00	0.00	154	< .001
		SP	0.00	29.99	7.87	4.07	6.86	11.94		
3	**Dairy drinks**	AMZ	0.00	7.49	1.84	0.00	0.81	1.84	1156	0.203
		SP	0.00	10.91	3.79	0.00	1.43	3.79		
3	**Artificial juices**	AMZ	0.00	4.00	1.39	0.00	0.59	1.39	1287	0.687
		SP	0.00	12.34	2.22	0.00	0.11	2.22		
3	**Ready-to-eat**	AMZ	0.00	14.16	0.00	0.00	0.00	0.00	856	< .001
		SP	0.00	12.17	2.44	0.00	0.00	2.44		
3	**Industrialized sauce**	AMZ	0.00	0.00	0.00	0.00	0.00	0.00	514.5	< .001
		SP	0.00	5.37	0.66	0.00	0.09	0.66		
3	**Spirits (alcohol)**	AMZ	0.00	0.00	0.00	0.00	0.00	0.00	1298.5	0.184
		SP	0.00	5.62	0.00	0.00	0.00	0.00		
3	**Spreads**	AMZ	0.00	10.59	2.38	0.00	0.34	2.38	1173.5	0.247
		SP	0.00	8.10	2.27	0.00	1.10	2.27		
3	**Supplements**	AMZ	0.00	0.00	0.00	0.00	0.00	0.00	1249.5	0.057
		SP	0.00	5.65	0.00	0.00	0.00	0.00		

Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine. Statistic: Mann-Whitney U test. Min: minimum. Max: maximum. IQR: interquartile range. 25^{th}, 50^{th}, 75^{th}: percentiles

. Figure 3 - Contribution of NOVA subgroups to individual total energy intake among São Paulo dwellers and Amazonian riverine



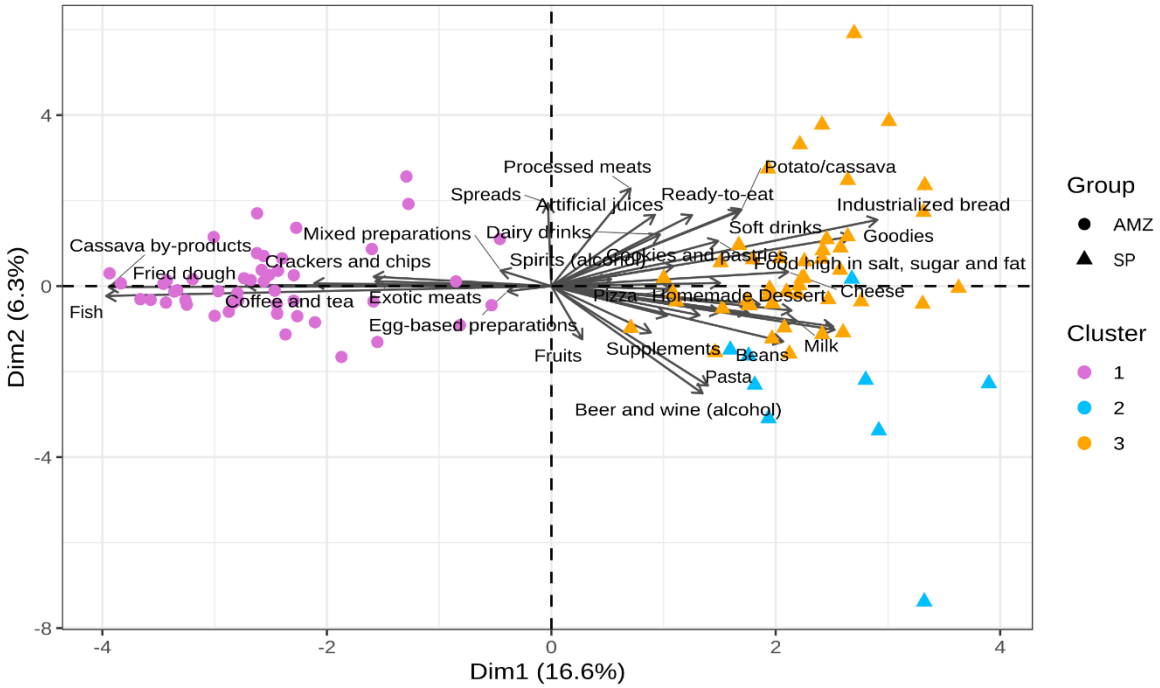
Source: Author. Y axis: percentage of total energy intake. X axis: subjects. SP: São Paulo dwellers. AMZ: Amazonian riverine. Top chart: NOVA subgroups belonging to NOVA group 1. Middle chart: NOVA subgroups belonging to NOVA group 2. Bottom chart: NOVA subgroups belonging to NOVA group 3.

The consumption of almost all NOVA subgroups was significantly different between São Paulo dwellers and Amazonian riverine, except for fruits, egg-based preparations, mixed preparations, dairy drinks, artificial juices, spirits (alcohol), spreads and supplements (Table 5). São Paulo dwellers consumed significantly more of the following natural and minimally processed food subgroups: rice-based preparations, beef and pork, beans, poultry, pasta, vegetables, potato/cassava, cereal and grain/flour, homemade dessert, milk, pizza, ingredients (sugar, salt, fat, vinegar) while Amazonian riverine consumed significantly more cassava products, fish, coffee and tea, exotic meats, and fried dough. São Paulo dwellers consumed significantly more of all processed food subgroups: non-industrialized bread, cheese, beer and wine (alcohol), food high in salt/sugar/fat. Ultra-processed food subgroups more consumed by São Paulo dwellers were processed meats, goodies, soft drinks, industrialized bread, ready-to-eat, cookies and pastries and industrialized sauce. Crackers and chips were the only ultra-processed food subgroups with greater consumption by the Riverine.

4.4 Food Pattern

Cluster analysis of NOVA subgroups consumption showed separation between one Amazonian riverine cluster and two São Paulo dwellers clusters (Figure 4). Amazonian riverine cluster (1) were well defined and marked by consumption of fish, cassava products, fried dough, coffee and tea, crackers and chips, and exotic meats while São Paulo dwellers clusters (2 and 3) were very dispersed and extensively overlapped, and markedly by importance of industrialized bread, goodies and milk. The principal component analysis (PCA) of the NOVA subgroups intake annotated with the 3 clusters detected is shown on figure 3.

Figure 4 - Cluster analysis and Principal Component Analysis (PCA) based on consumption of NOVA subgroups

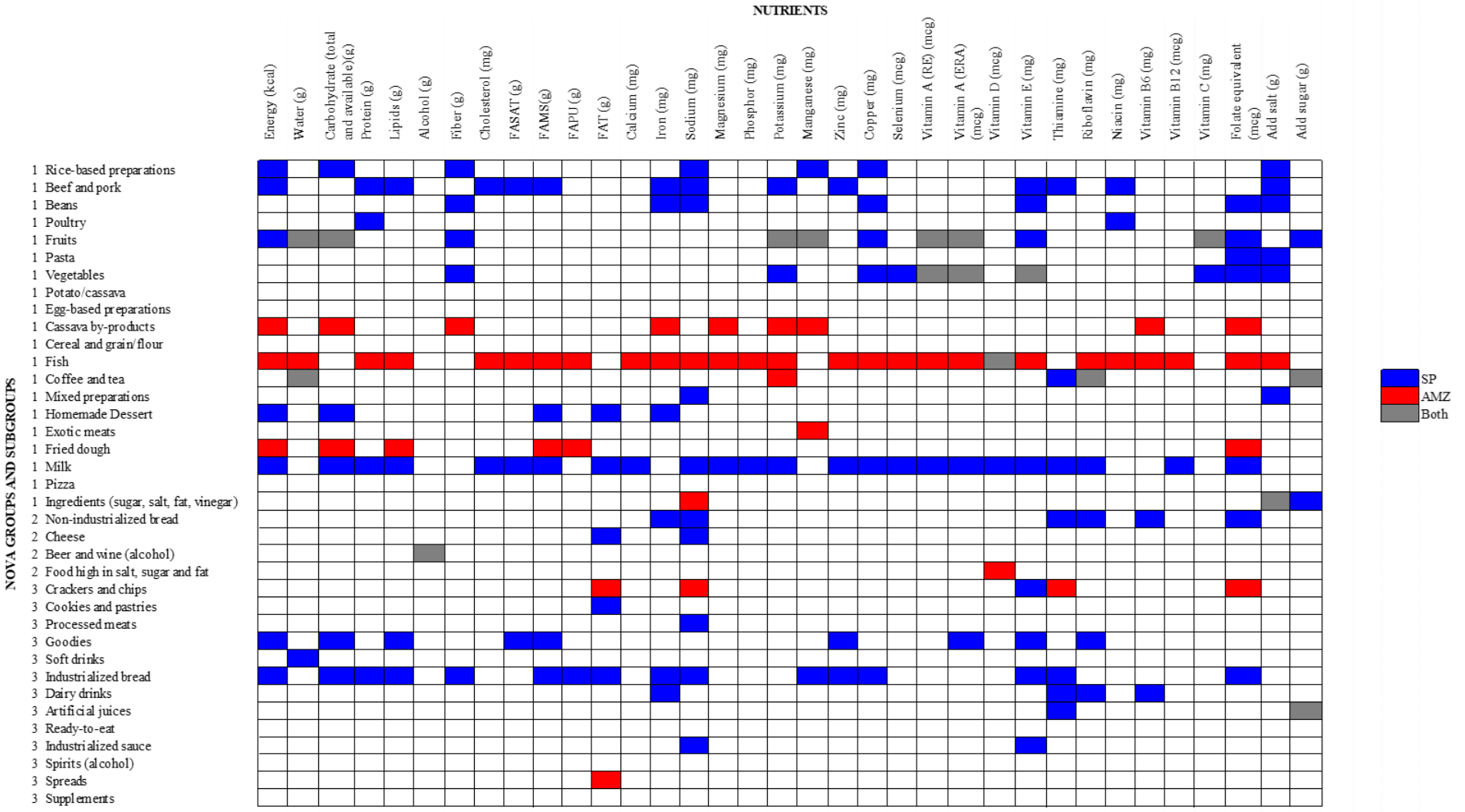


Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine.

4.5 Nutrient sources

Inside each NOVA subgroup there is a greater variety of foods among São Paulo dwellers than among Amazonian riverine (data not shown). NOVA subgroups which most contributed to nutrient intake among São Paulo dwellers were milk, industrialized bread, beef and pork, fruits, rice-based preparations, and goodies while among Amazonian riverine were fish, cassava products, fruits and fried dough (Figure 5). Fish alone is the main source of various nutrients (protein, cholesterol, saturated fatty acids, calcium, zinc, copper, selenium, phosphor, niacin, and vitamin B12) among Riverine. Milk alone was the main source of calcium, magnesium, phosphorus, riboflavin, and vitamin B12 among São Paulo dwellers (Figure 5).

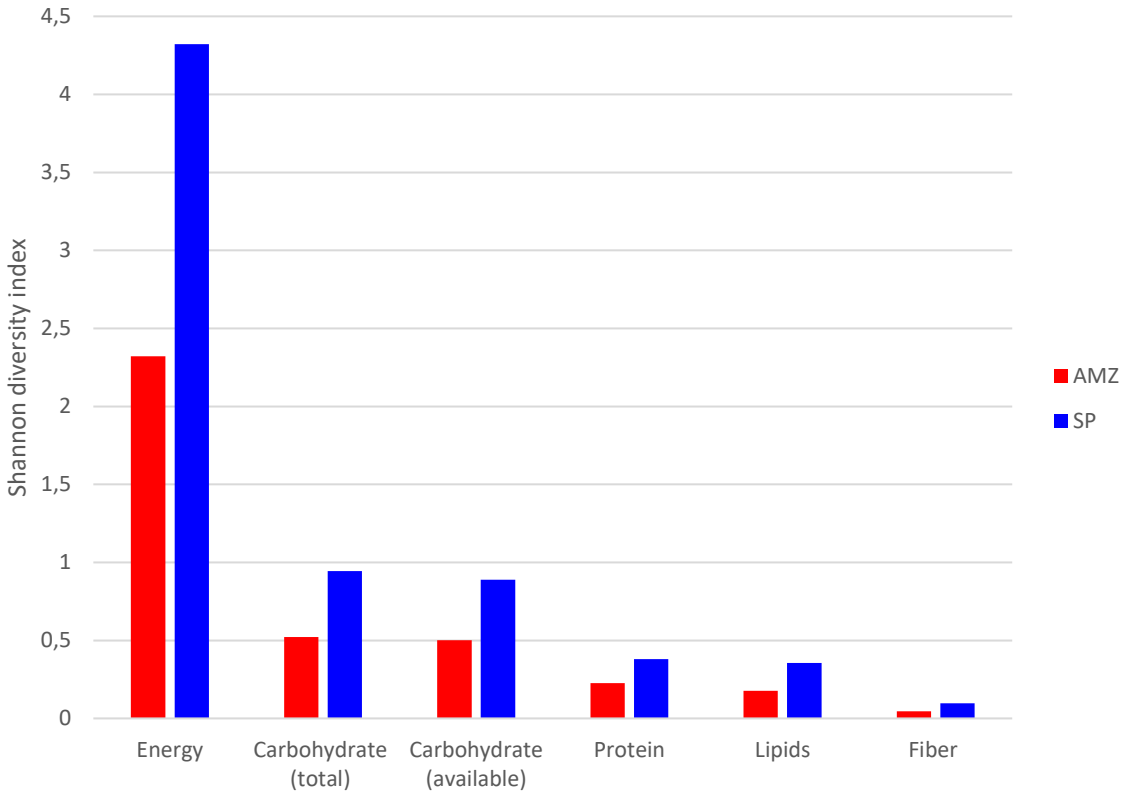
Figure 5 - Contribution of NOVA subgroups to nutrient intake among São Paulo dwellers and Amazonian riverine



Source: Author. A cell labelled in blue indicates that the corresponding food item (rows) contributed greatly to that nutrient intake (columns) in the Sao Paulo dwellers, while red labels indicated the same for Amazonian riverine. SP: São Paulo dwellers. AMZ: Amazonian riverine.

In general, the food sources of each nutrient were more diverse among São Paulo dwellers than among Amazonian riverine as shown by Shannon diversity index (Figure 6).

Figure 6 - Diversity of NOVA subgroups contribution to energy and nutrient intake

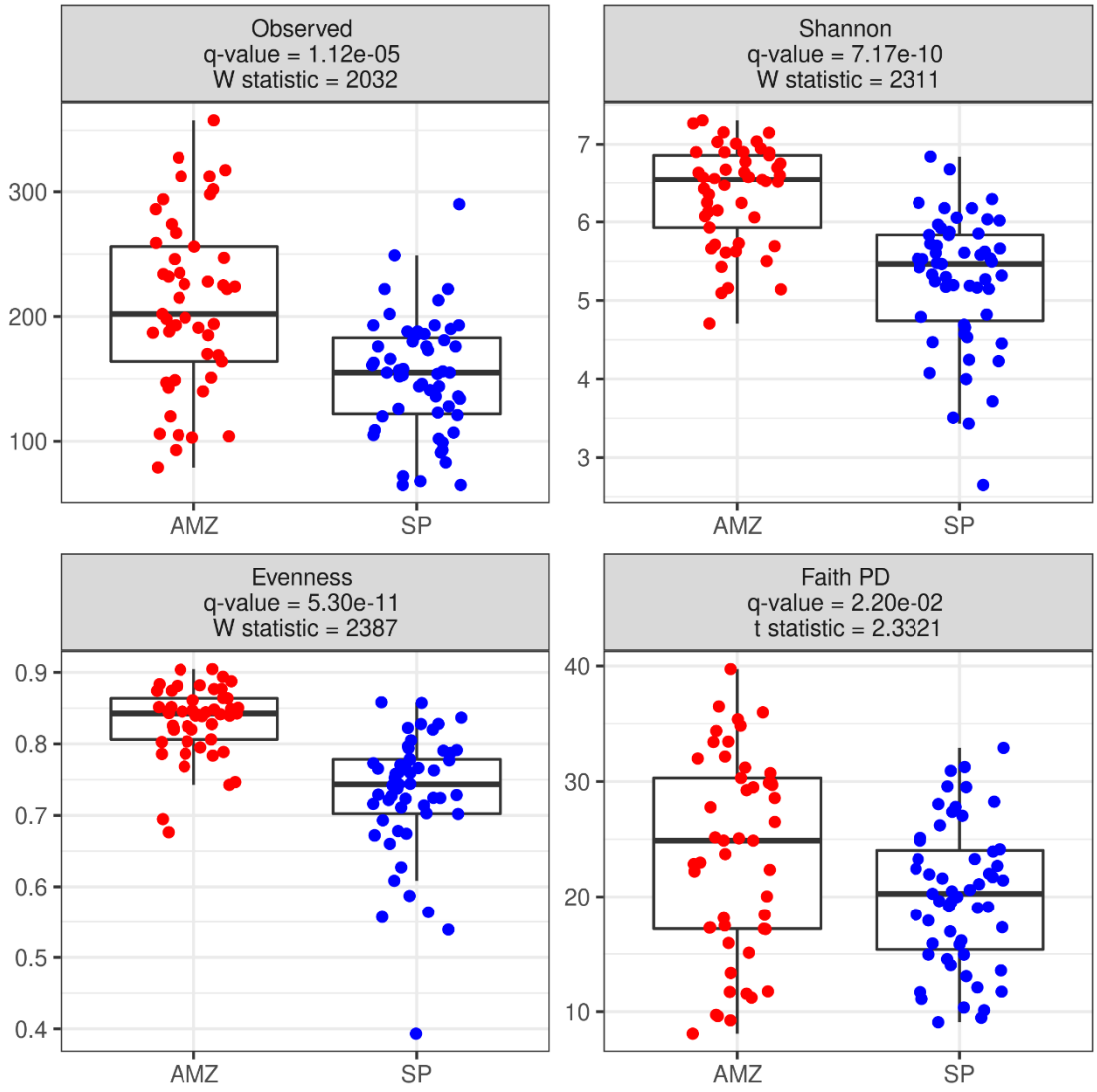


Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine.

4.6 Gut microbiome alpha diversity

Alpha diversity was significantly higher among Amazonian riverine according to different alpha diversity metrics used: richness, Pielou's evenness, Shannon diversity and Faith's Phylogenetic diversity (Figure 7).

Figure 7 - Differences in alpha diversity between São Paulo dwellers and Amazonian riverine

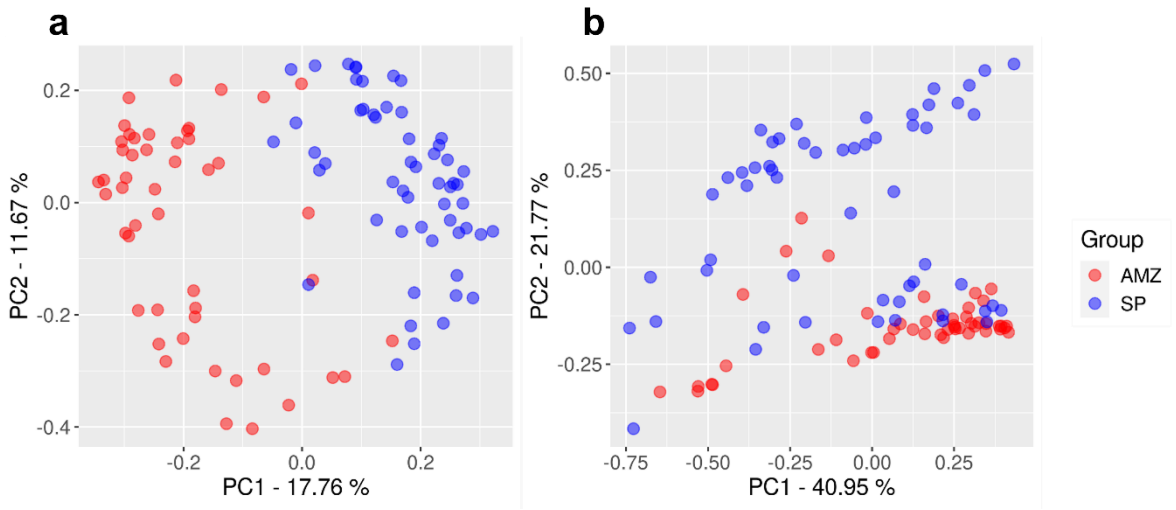


Source: Author.

4.7 Beta diversity analysis

There was a significant difference in the overall gut microbiome structure between São Paulo dwellers and Amazonian riverine according to beta diversity measures, unweighted Unifrac (PERMANOVA F=16.75365124; R^2= 0.141079041; p=0.001) and weighted Unifrac (PERMANOVA F=16.65899399; R^2= 0.140393858; p=0.001) (Figure 8)

Figure 8 - PCoA of unweigthed (A) and weighted (B) Unifrac beta diversity measures among São Paulo dwellers and Amazonian riverine

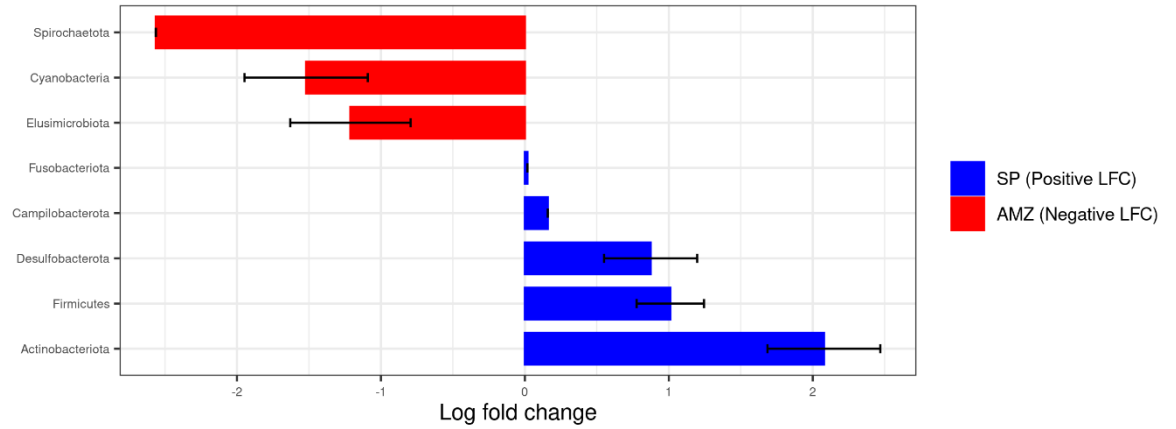


Source: Author.

4.8 Differential taxa abundance between populations

We detected a total of 15 phyla across all samples, and eight of which were differentially abundant between the two populations: Actinobacteriota, Firmicutes, Desulfobacterota, Campilobacterota and Fusobacteriota are more abundante in Paulista samples while Spirochaetota, Cyanobacteria and Elusimicrobiota phyla are more abundante in Amazonian riverine (Figure 9).

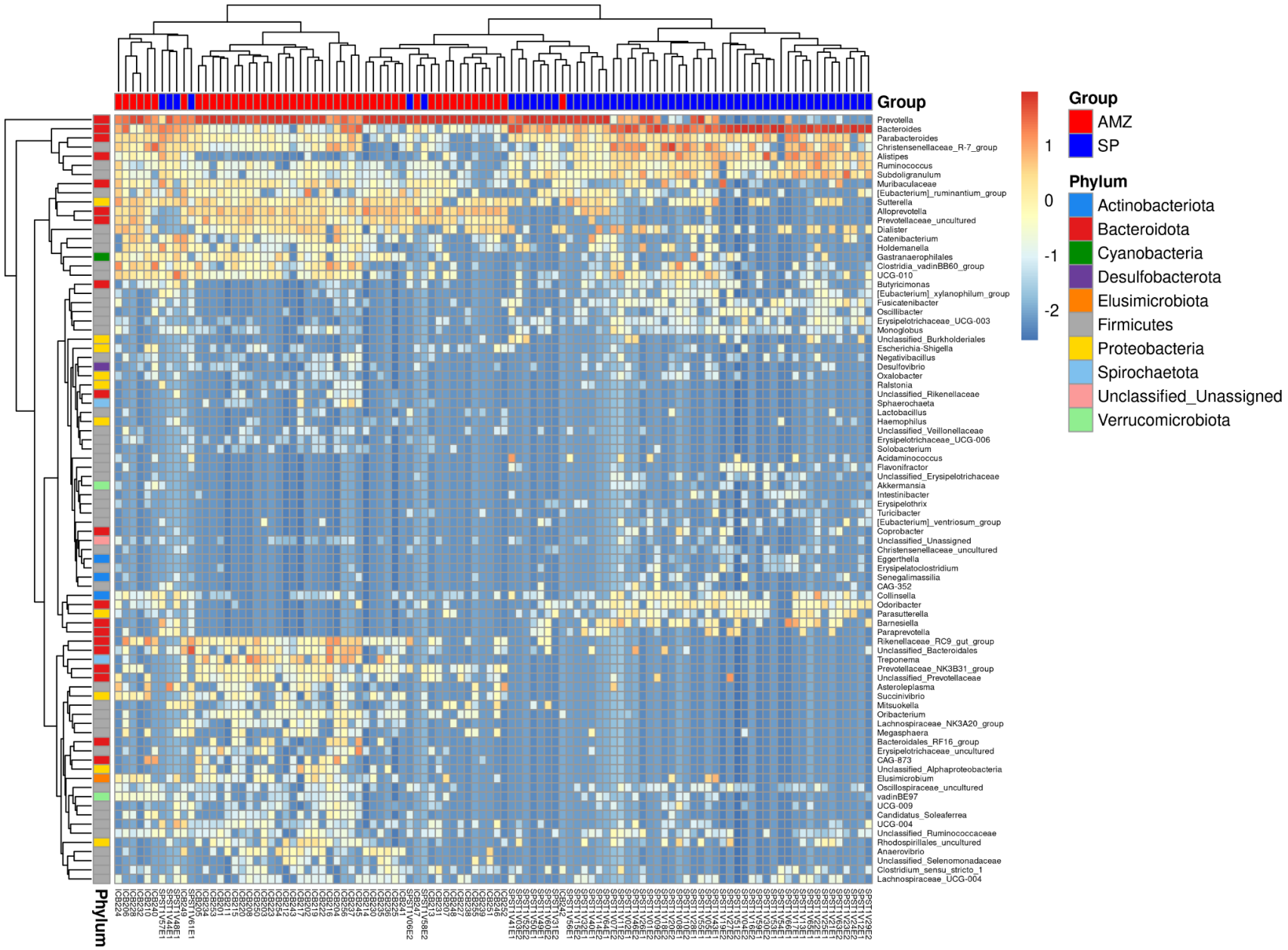
Figure 9 - Log fold change of phyla differential abundance between São Paulo dwellers and Amazonian riverine



Source: Author.

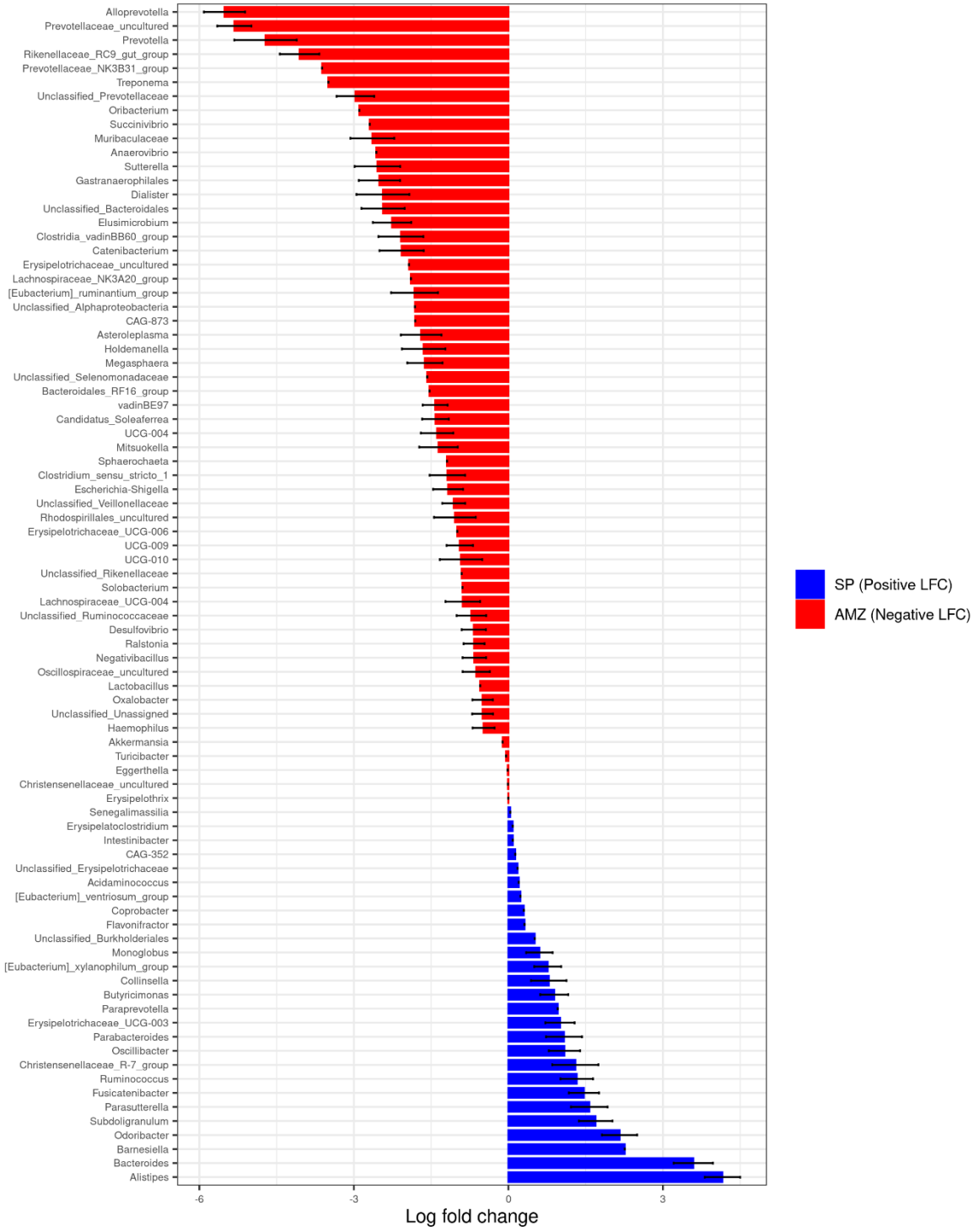
The most abundant genus among Amazonian riverine was *Prevotela* and among São Paulo dwellers as *Bacteroides* (Figure 10) Using ANCON test, we found 57 different abundant genera between São Paulo dwellers and Amazonian riverine. *Alistipes* and *Bacteroides* had higher abundances among São Paulo dwellers, while *Alloprevotella*, *uncultured Prevotellaceae*, *Prevotella*, *Rikenellaceae RC9 gut group*, *Prevotellaceae NK3831 group* and *Treponema* genera had higher abundances among Amazonian riverine using a cutoff point of at least 3 times (Figure 11).

Figure 10 - Heatmap of genera abundance among São Paulo dwellers and Amazonian riverine



Source: Author.

Figure 11 - Log fold change of genera differential abundance between São Paulo dwellers and Amazonian riverine



Source: Author. AMZ: Amazonian riverine. SP: São Paulo dwellers.

4.9 Core microbiome

We use COREMIC tool for checking the frequency of common genera which most distinguish the groups (Table 6). São Paulo dwellers were characterized by higher frequency of *Alistipes* (two different ASVs), *Bacteroides* (three different ASVs), *Parabacteroides* and *Ruminococcus* genera. Two *Bacteroides* genera were present in all São Paulo dwellers samples and only in 69% of Amazonian riverine samples. Amazonian riverine were characterized by higher frequency of *Prevotella*, *Alloprevotella*, *Muribaculaceae*, *Sutterella* and one uncultured Bacteroidota (Prevotellaceae family) genera.

Table 6 - Core microbiome differential genera frequency between São Paulo dwellers and Amazonian riverine

Reference group: São Paulo dwellers	**p-value**	**Corrected p-value**	**SP Presence**	**AMZ Presence**
p__Bacteroidota;**g__Alistipes**;s__unc. bac.	2.5142E-16	9.4281E-14	0.92727	0.16327
p__Bacteroidota;**g__Alistipes**;__	5.0018E-15	9.3783E-13	0.94546	0.22449
p__Bacteroidota; **g__Bacteroides**;s__unc._organism	2.4772E-14	3.0964E-12	0.94546	0.2449
p__Bacteroidota;**g__Parabacteroides**;__	9.2506E-13	8.6724E-11	0.92727	0.26531
p__Bacteroidota;**g__Bacteroides**;__	3.3025E-06	0.0001032	1	0.69388
p__Bacteroidota;**g__Bacteroides**;s__unc._bac.	3.3025E-06	0.0001032	1	0.69388
p__Firmicutes;**g__Ruminococcus**;s__unc._bac.	0.00211456	0.02531399	0.92727	0.69388
Reference group: Amazonian riverine	**p-value**	**Corrected p-value**	**SP Presence**	**AMZ Presence**
p__Bacteroidota;**g__uncultured**;s__unc._bac.	4.1524E-20	1.5572E-17	0.09091	0.93878
p__Bacteroidota;**g__Alloprevotella**;s__unc._bac.	3.1831E-19	5.9684E-17	0.16364	0.97959
p__Proteobacteria;**g__Sutterella**;__	2.2195E-14	1.6646E-12	0.2	0.91837
p__Bacteroidota;**g__Muribaculaceae**;s__unc._bac.	5.8712E-09	1.8347E-07	0.45455	0.95918
p__Bacteroidota;**g__Prevotella**;s__unc._bac.	9.3358E-07	1.945E-05	0.65455	1

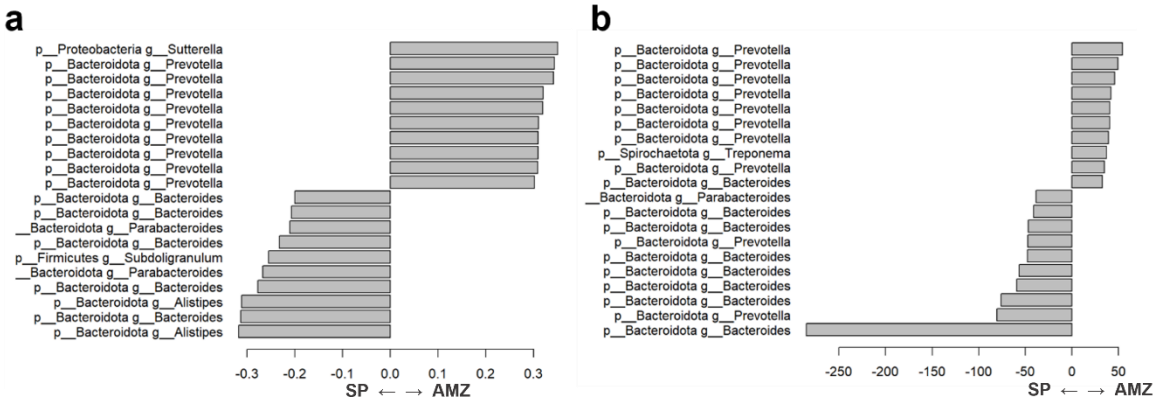
Source: Author. SP: São Paulo dwellers. AMZ: Amazonian riverine. p: phylum. g: genus. s: specie. unc: uncultured. Bac: bacterium.

4.10 Top 10 differential taxa

Top ten most differential ASVs between São Paulo dwellers and Amazonian riverine based on PERMANOVA coefficients absolute values for Jaccard (presence/absence) (**a**) and Bray-Curtis (abundance) (**b**) distances showed the enrichment of many ASVs of *Bacteroides* among São Paulo dwellers while among Amazonian riverine there was the enrichment of a distinguished *Bacteroides* ASVs. Amazonian riverine had enrichment of many *Prevotella* ASVs while São Paulo dwellers had the enrichment de two distinguished *Prevotella* AVSs. São Paulo dwellers also had enrichment of *Parabacteroides* (2 distinguished ASVs),

Subdoligranulum and *Alistipes* (2 distinguished ASVs) and Amazonian riverine had also enrichment of *Sutterella* and *Treponema* (Figure 12).

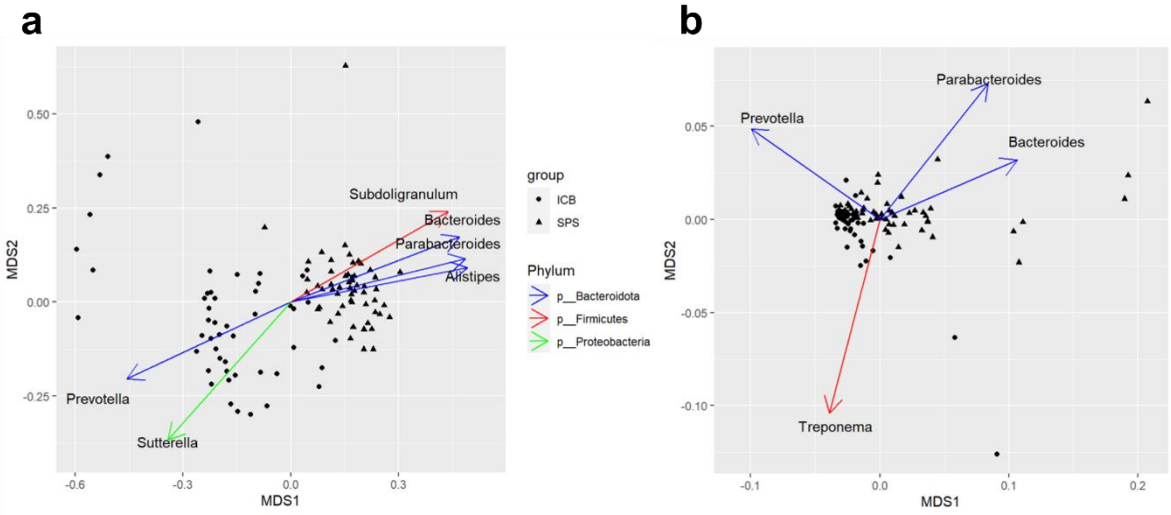
Figure 12 - Top 10 most differential taxa between São Paulo dwellers and Amazonian riverine



Source: Author. PERMANOVA coefficients absolute values for Jaccard (a) and Bray-Curtis (b) distances. AMZ: Amazonian Riverine. SP: São Paulo Dwellers.

Non-metric multidimensional scaling (nMDS) plot using unweighted and weighted Unifrac shows *Alistipes*, *Parabacteroides*, *Bacteroides* and *Subdoligranulum* driven the pattern towards São Paulo dwellers samples while *Prevotella*, *Sutterella* and *Treponema* driven the pattern towards Amazonian riverine samples (Figure 13).

Figure 13 - Non-metric multidimensional scaling (nMDS) plot of unweighted and weighted Unifrac



Source: Author. a) Unweighted unifrac distance. b) Weighted unifrac distance.

4.11 Global gut microbiome and diet relationships

Procrustes analysis shows there is a significant agreement between gut microbiome and NOVA food classification (groups and subgroups) data (Table 7).

Table 7 - Overall agreement between gut microbiome and diet according to Procrustes analysis

	Procrustes Analysis		
	M_2 Statistics	Correlation (r)	p-value
Gut microbiome (Weighted Unifrac) / Diet - NOVA groups (Bray-Curtis)	0.8657	0.3665	0.001
Gut microbiome (Unweighted Unifrac) / Diet - NOVA groups (Bray-Curtis)	0.8517	0.3851	0.001
Gut microbiome (Weighted Unifrac) / Diet - NOVA subgroups (Bray-Curtis)	0.7281	0.5214	0.001
Gut microbiome (Unweighted Unifrac) / Diet - NOVA subgroups (Bray-Curtis)	0.5999	0.6326	0.001

Source: Author.

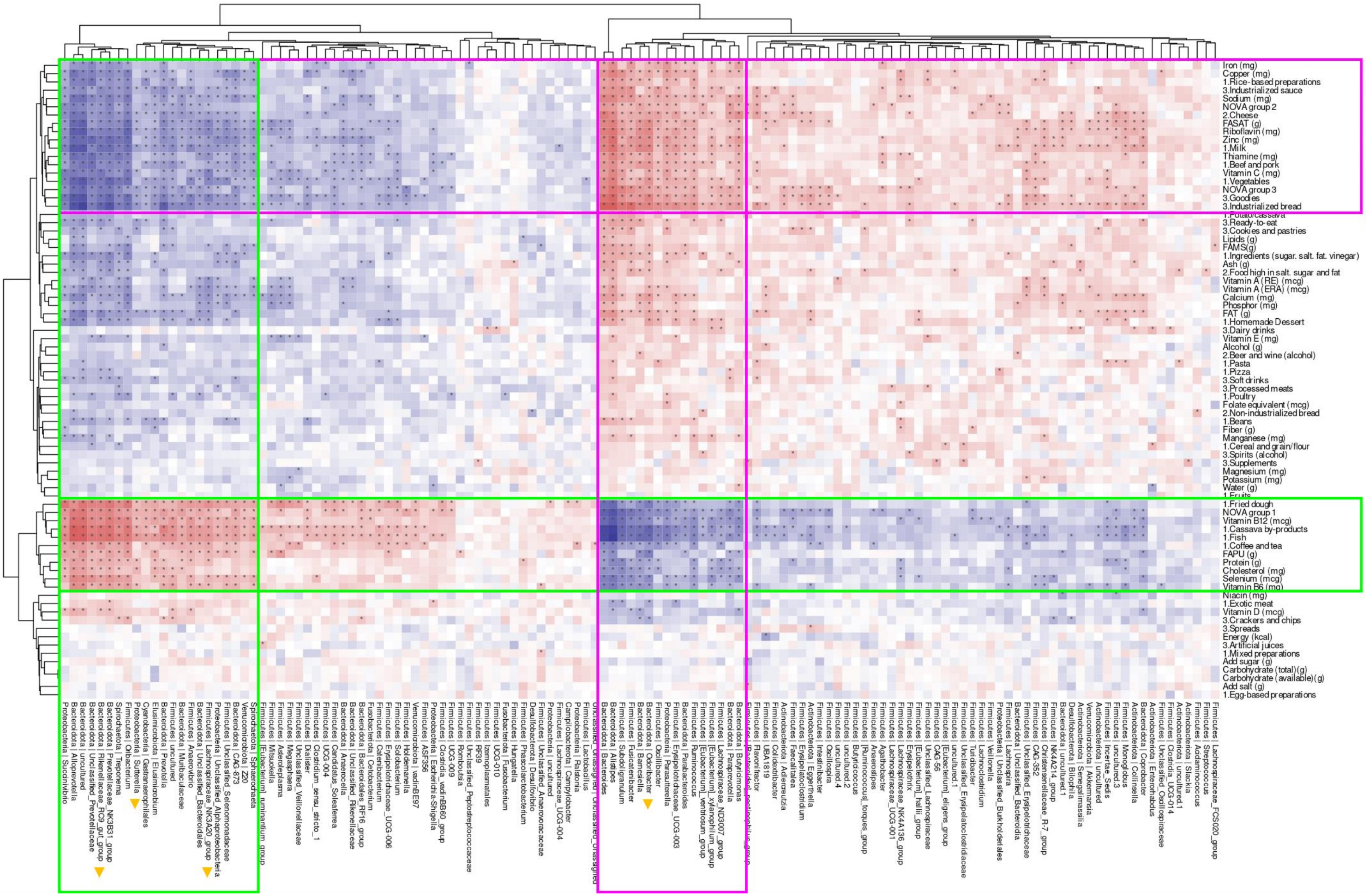
4.12 Correlations between nutrient intake and bacterial genera

Genera that showed positive correlation with Amazonian riverine food pattern (bottom left cluster) also showed negative correlation with São Paulo dwellers food pattern (top left cluster) (Figure 14). The strongest taxa correlation was with *Alloprevotella*, uncultured Bacteroidota, unclassified *Prevotellaceae*, *Rikenellaceae* RC9 gut group, *Prevotellaceae* NK3B31 group, *Treponema* and *Oribacterium*. The strongest dietary variables correlations were with fish, cassava products, vitamin B12, NOVA group 1 and fried dough.

Genera that showed positive correlation with São Paulo dwellers food pattern (top - middle) also showed negative correlation with Amazonian riverine food pattern like (bottom-middle). The strongest taxa correlations were with *Bacteroides*, *Alistipes*, *Subdoligranulum*, *Fusicatenibacter*, *Barnesiela* and *Odoribacter*. The strongest dietary variables correlations were with industrialized bread, goodies, NOVA group 3, milk, zinc, riboflavin and saturated fatty acids.

Genera with strong significative positive correlation with dietary features (Figure 14) were also those that most differentiated both populations across different analyses (Figure 10, Table 6, Figure 11) and are summarized in Table 8.

Figure 14 - Spearman correlation between genus and dietary features



Source: Author. Horizontal axis: phylum|genus. Vertical axis: dietary features (NOVA group and subgroup, nutrients). *Correlations with FDR < 0,05. Green boxes: taxa positively correlated with Amazonian riverine food pattern (and negatively correlated with São Paulo dwellers food pattern). Magenta boxes: taxa positively correlated with São Paulo dwellers food pattern (and negatively correlated with Amazonian riverine food pattern).

Table 8 - Summary of differential taxa with significantly strong diet correlations

	Phylum	Family	Diet correlation	ANCOM	COREMIC	PERMANOVA coefficient (Bray-Curtis)	PERMANOVA coefficient (Jaccard)
Amazonian Riverine	Bacteroidota	Prevotellaceae	Alloprevotela	Alloprevotela	Alloprevotela	x	x
	Bacteroidota	Prevotellaceae	Prevotellaceae (unclassified) (family)[1,4]	Prevotellaceae (unclassified) (family)[1,4]	Prevotellaceae (uncultured) (family)[1,4]	x	x
	Bacteroidota	Prevotellaceae	Prevotella[2,5,6]	Prevotella[2,5,6]	Prevotella[2,5,6]	Prevotella[2,5,6] (8 ASVs)	Prevotella[2,5,6] (9 ASVs)
	Bacteroidota	Rikenellaceae	Rikenellaceae RC9 gut group	Rikenellaceae_RC9_gut_group	x	x	x
	Bacteroidota	Prevotellaceae	Prevotellaceae NK3B31 group	Prevotellaceae NK3B31 group	x	x	x
	Spirochaetes	Treponemataceae	Treponema[2,3,4,5,6]	Treponema[2,3,4,5,6]	x	Treponema[2,3,4,5,6]	x
	Bacteroidota	Prevotellaceae	x	Prevotellaceae (unclassified) (family) [1,4]	x	x	x
	Firmicutes	Lachnospiraceae	Oribacterium	Oribacterium	x	x	x
	Protobacteria	Succinivibrionaceae	Succinivibrio[2,4,5]	Succinivibrio[2,4,5]	x	x	x
	Bacteroidota	Muribaculaceae	Muribaculaceae[2]	Muribaculaceae (family)[2]	Muribaculaceae (family)[2]	x	x
	Firmicutes	Selenomonadaceae	Anaerovibrio	Anaerovibrio	x	x	x
	Protobacteria	Sutterellaceae	Sutterella[4]	Sutterella[4]	Sutterella[4]	x	Sutterella[4]
	Candidatus Melainabacteria	x	Gastranaerophilales (order)	Gastranaerophilales (order)	x	x	x
	Firmicutes	Veillonellaceae	Dialister	Dialister	x	x	x
	Bacteroidota	x	Bacteroidales (unclassified) (order)	Bacteroidales (unclassified) (order)	x	x	x
	Bacteroidota	Bacteroidaceae	x	x	x	Bacteroides	x
	Bacteroidota	x	Bacteroidota (uncultured) (phylum)	x	x	x	x
	Firmicutes	x	Firmicutes (uncultured) (phylum)	x	x	x	x
	Elusimicrobia	Elusimicrobiaceae	Elusimicrobium	Elusimicrobium	x	x	x
	Bacteroidota	Prevotellaceae	Prevotella sp. CAG-873 (specie)	Prevotella sp. CAG-873 (specie)	x	x	x
	Firmicutes	Lachnospiraceae	Lachnospiraceae NK3A20group (specie)[2,4,5]	Lachnospiraceae NK3A20group (specie)[2,4,5]	x	x	x
	Protobacteria	x	Alphaproteobacteria (unclassified) (class)	Alphaproteobacteria (unclassified) (class)	x	x	x
	Firmicutes	Selenomonadaceae	Selenomonadaceae (unclassified) (family)	Selenomonadaceae (unclassified) (family)	x	x	x
São Paulo dwellers	Bacteroidota	Rikenellaceae	Alistipes[3, 4]	Alistipes[3, 4]	Alistipes[3, 4]	x	Alistipes[3, 4] (2ASVs)
	Bacteroidota	Bacteroidaceae	Bacteroides[2,5]	Bacteroides[2,5]	Bacteroides[2,5]	Bacteroides[2,5] (7 ASVs)	Bacteroides[2,5] (5 ASVs)
	Bacteroidota	Barnesiellaceae	Barnesiella[3, 4]	Barnesiella[3, 4]	x	x	x
	Bacteroidota	Odoribacteraceae	Odoribacter[4]	Odoribacter[4]	x	x	x
	Firmicutes	Oscillospiraceae*	Subdoligranulum	Subdoligranulum	x	x	Subdoligranulum
	Protobacteria	Sutterellaceae	Parasutterella[4]	Parasutterella[4]	x	x	x
	Firmicutes	Lachnospiraceae	Fusicatenibacter	Fusicatenibacter	x	x	x
	Firmicutes	Oscillospiraceae*	Ruminoccocus[5]	Ruminoccocus[5]	Ruminoccocus[5]	x	x
	Firmicutes	Christensenellaceae	x	Christensenellaceae R-7 group	x	x	x
	Firmicutes	Oscillospiraceae*	Oscillibacter[5]	Oscillibacter[5]	x	x	x
	Bacteroidota	Tannerellaceae	Parabacteroides[2]	Parabacteroides[2]	Parabacteroides[2]	Parabacteroides[2]	Parabacteroides[2] (2 ASVs)
	Firmicutes	Erysipelotrichaceae	Erysipelotrichaceae UCG 003	Erysipelotrichaceae UCG 003	x	x	x
	Bacteroidota	Prevotellaceae	Paraprevotella	Paraprevotella	x	x	x
	Bacteroidota	Odoribacteraceae	Butyricimonas	Butyricimonas	x	x	x
	Actinobacteria	Coriobacteriaceae	x	Collinsella*	x	x	x
	Bacteroidota	Prevotellaceae	x	x	x	Prevotella (2 ASVs)	x
	Firmicutes	Oscillospiraceae*	Flavonifractor*	Flavonifractor*	x	x	x

Source: Author. Taxa with statistically significant result for each statistical test (columns). Analyses used genus level for NOVA and nutrient correlation, ANCON and COREMIC, and ASVs level for PERMANOVA coefficients based on Bray-Curtis and Jaccard distances. **Yellow: typical taxa of traditional societies**. **Blue: typical taxa of industrialized societies**. Reference studies: 1. (ROSAS-PLAZA *et al.*, 2022); 2. MCDONALD et al. (2018); 3. (MANCABELLI *et al.*, 2017); 4. (DE FILIPPO *et al.*, 2017); 5. (SCHNORR *et al.*, 2014); 6. (DE FILIPPO *et al.*, 2010). Appendix E: summary of reference studies. *Collinsella and Flavonifractor: there was significative correlation, but it was not strong neither with various dietary variables. *Previously Ruminococcaceae.

5 DISCUSSION

Traditional societies that are not fully integrated into industrialized lifestyles present a distinct gut microbiome that is related to their lifestyle, in which diet is extensively based on natural or minimally processed food from their own production and/or gathering and hunting. Although generally plant biomass largely outweigh animal biomass and is of easier access, those societies are diverse and present various dietary patterns with different contributions of plant and animal food sources (CRITTENDEN; SCHNORR, 2017; PONTZER; WOOD, 2021).

Here, we showed that São Paulo dwellers and Amazonian riverine present different gut microbiome compositions that are related to their different dietary patterns. Amazonian riverine showed higher alpha diversity and mostly taxa characteristic of traditional societies but also some features of industrialized societies. Generally, São Paulo dwellers showed mostly taxa typical of industrialized societies. They have markedly distinct diets, with Amazonian riverine keeping a more traditional diet, with much larger contribution of natural and minimally processed foods, while São Paulo dwellers have a more westernized diet with significant contribution of processed and ultra-processed foods. Nevertheless, Amazonian riverine eat less fiber and more protein than São Paulo dwellers who eat more fat than the former.

5.1 Diet

Traditional Amazonian riverine food is based on fresh fried/cooked fish and cassava flour, frequently eaten for lunch and dinner. On breakfast and snack times, the most common food is fried dough dumpling (wheat flour, water, and sugar) or ultra-processed crackers, and sweetened coffee. These foods together with some game meat (exotic meats) strongly characterize the Amazonian riverine food pattern while the São Paulo dwellers have more diversified pattern with greater variety of foods and emphasis on milk, industrialized bread, meat, rice, goodies, and homemade desserts.

Amazonian riverine remote geographic location and limited market integration may enforce their traditional lifestyle including their traditional diet. But economic transition driven by increased access to cash is altering household subsistence strategies and Amazonian riverine lifestyle, which consequently has been changing their diet (PIPERATA *et al.*, 2011a, 2011b). Various Amazonian riverine populations show a shift from local staple food like cassava flour and fish to purchased food like crackers, vegetable oil, beef and poultry, sugar, beans, rice,

ultra-processed meats (NARDOTO *et al.*, 2011; PIPERATA *et al.*, 2011a). Most purchased foods in the study region are coffee and sugar followed by oil, pasta, beans, rice, dairy, sweets, drinks (mainly soda), canned foods, frozen chicken, wheat, powdered chocolate (SILVA *et al.*, 2017).

Access to some food items like pasta, powdered milk, butter, and sugar, is not a recent phenomenon around Solimões river (SILVA *et al.*, 2017). Market integration and wetland residence favor consumption of purchased foods because of money increase and easier access to urban centers by river (SILVA *et al.*, 2017). Increasing urbanization along Solimões river result in escalation of dependence on market food like sugar and meat (beef and chicken) and decreasing reliance on locally produced food like cassava flour and fish (NARDOTO *et al.*, 2011).

The purchase of cassava flour, locally or from outside sources, is of particular importance in the region. In 2010, 32% of the householders purchased their cassava flour and 20% bought locally produced cassava flour as a complement to their supply in the studied region (PERALTA; LIMA, 2013). This is a result of decreasing in manioc cultivation, with a related shift from more subsistence-based economy to a market economy, largely driven by financial benefits from government, city contact and self-work perception (PIPERATA *et al.*, 2011a). Government benefits increase contact with cities and a desire for "city stuff", including food, and a more modern lifestyle, which depends on money and makes subjects value more wage labor than work for subsistence. Subsistence based work is linked to social reproduction and their decay, such as reduction and abandon of cassava cultivation, results in the dismantling of the traditional lifestyle, including the traditional diet. This process is characteristic of nutrition transition and has been shown to be linked with health consequences around the world (POPKIN, 2006).

All ultra-processed foods are purchased and depend on money access. The most consumed ultra-processed food among studied Amazonian riverine are crackers, but artificial juice, powdered dairy compound, processed meats and spreads are also frequent. Interestingly, Amazonian riverine have almost no consumption of processed foods pointing a direct transition from natural and minimally processed to ultra-processed food consumption. Local reasons for their ultra-processed consumption include desire, food preferences, meal variation and preservation in a very humid environment.

As expected, differences in food consumption are reflected in nutrient intake, which are almost all different between the two populations. They do not differ in energy and carbohydrate consumption but Amazonian riverine eat more protein while São Paulo dwellers eat more

dietary fiber and fat. São Paulo dwellers dietary fats and proteins comes mainly from natural and minimally processed milk and beef. Ultra-processed breads and goodies are also expressive sources of fats and proteins in their diet. On the other hand, Amazonian riverine have their fats and proteins from fresh fish (fried or cooked). Fried dough dumpling made with minimally processed ingredients is also an important source of fat among Amazonian riverine. Dietary fiber and carbohydrate have common food sources. Minimally processed cassava flour is largely the mainly source of dietary fiber among Amazonian riverine while São Paulo dwellers have diverse sources specifically natural and minimally processed beans, fruits, vegetables, and rice-based preparations, and ultra-processed bread. Differences between Amazonian riverine and São Paulo dwellers are beyond nutrients consumption and go through food processing. Important food sources of energy, carbohydrates, fats, fibers and micronutrients among São Paulo dwellers include ultra-processed foods while Amazonian riverine largely rely on natural and minimally processed food for those nutrients.

Although protein sources for the two populations are both unprocessed (natural), São Paulo dwellers eat farmed milk and meat while Amazonian riverine eat wild/free living fresh fish. Food domestication changed their composition and farmed meat became richer in fat, specially saturated fatty acids (PONTZER; WOOD, 2021). This agrees with the higher saturated fatty acids consumption among São Paulo dwellers while Amazonian riverine have a higher polyunsaturated fatty acids and cholesterol consumption from fish. Domestication also altered plants composition increasing starch and energy and decreasing fiber (PONTZER; WOOD, 2021). In addition to this, consumption of meat in industrialized societies are linked to detrimental health effects on contrary of hunter-gatherers wild meat-based diets, which do not present detrimental health effects (CORDAIN *et al.*, 2002).

São Paulo dwellers have a more varied diet considering their consumption of natural and minimally processed foods as well as the consumption of processed and ultra-processed foods. Four natural and minimally processed food groups contributed the most for all nutrient intake among Amazonian riverine (fish, cassava flour, fried dough, fruits) alongside one ultra-processed group (crackers), while six natural and minimally processed food groups contributed the most among São Paulo dwellers (milk, fruits, meat, homemade desserts, rice-based preparations, and vegetables), alongside two ultra-processed groups (industrialized breads and goodies). The dietary diversity accessed using the Shannon diversity index shows almost 2 times more diversity in energy and macronutrient food sources among São Paulo dwellers than Amazonian riverine. Increasing diet diversity is also pointed by current literature as a feature

of transition from traditional to industrialized lifestyle (DE FILIPPO *et al.*, 2017; MANCABELLI *et al.*, 2017).

It is also noteworthy that the São Paulo dwellers diet has industrialized bread as its second most important energy source. Even though they have a more varied diet, including also more natural and minimally processed food, they still get a higher amount of energy from ultra-processed and processed foods than the Amazonian riverine. On the other hand, the Amazonian riverine low dietary diversity reinforces the importance of their local staple food, fish and cassava flour, for their nutrient acquisition and food security.

5.2 Gut microbiome, diet, and lifestyle

Amazonian riverine still harbor a gut microbiome more similar to traditional societies with *Prevotela*, *Treponema*, *Succinivibrio* and *Muribaculaceae* while São Paulo dwellers harbor a gut microbiome more similar to industrialized societies with *Alistipes*, *Bacteroides*, *Barnesiela*, *Odoribacter*, *Parasutterella*, *Ruminococcus* and *Parabacteroides* (AYENI *et al.*, 2018; DE FILIPPO *et al.*, 2017; GOMEZ *et al.*, 2016; MARTÍNEZ *et al.*, 2015; ZHANG *et al.*, 2014a). Most differential taxa between populations also showed the strongest significant correlation with diet. There was a positive correlation between taxa characteristic of traditional societies and Amazonian riverine traditional dietary features, such as fish, cassava flour, fried dough and coffee, as well as nutrients related to those food, such as protein, polyunsaturated fat, cholesterol, vitamin B12, vitamin B6, and selenium. Traditional societies taxa were also positively correlated with natural and minimally processed foods. Meanwhile, taxa characteristic of industrialized societies were positively correlated with São Paulo dwellers westernized dietary features such as milk, industrialized bread, goodies, meat, vegetables, industrialized sauce, homemade desserts, cheese, rice, read-to-eat food products, as well as their related nutrients like monounsaturated, saturated and trans fats, zinc, sodium, iron, copper, calcium, phosphorus, thiamine, riboflavin and vitamin C. Industrialized societies taxa were also positively correlated with processed and ultra-processed food.

The most abundant differential genus among Amazonian riverine gut microbiome was *Prevotella* while among São Paulo dwellers was *Bacteroides*, like others traditional and industrialized societies, respectively (AYENI *et al.*, 2018; DE FILIPPO *et al.*, 2017; GOMEZ *et al.*, 2016; MARTÍNEZ *et al.*, 2015; ZHANG *et al.*, 2014a). Amazonian riverine harbor a much higher number of *Prevotella* taxa while São Paulo dwellers harbor higher number of Bacteroides taxa (also shown in other studies).

Many studies have linked *Prevotella* dominance to plant-based and fiber-rich traditional diets, and *Bacteroides* dominance to greater consumption of less complex carbohydrate and higher amounts of animal protein and industrialized food (VANGAY *et al.*, 2018; YATSUNENKO *et al.*, 2012).

Both *Prevotella* and *Bacteroides* are from Bacteroidota phylum and have carbohydrate as their main energy source (KORPELA, 2018). *Bacteroides* are known by their substrate flexibility and present a large repertoire of carbohydrate-active enzymes (CAZymes) with emphasis in animal glycans, including those produced by the host like mucins, and oligo- and disaccharides (AAKKO *et al.*, 2020; KAOUTARI *et al.*, 2013) which allow Bacteroides species to thrive on low-fiber diets. Bacteroides along other industrialized genera like *Alistipes* and *Parabacteroides* are the primarily proteolytic taxa in the gut (KORPELA, 2018). *Prevotella* has a carbohydrate-active enzymes (CAZymes) repertoire even larger than *Bacteroides* resulting in greater potential for degradation of complex polysaccharides derived from plants (AAKKO *et al.*, 2020). Although many *Prevotella* may use other substrates (AAKKO *et al.*, 2020), *Prevotella copri*, the main species in the human gut, uses only plant polysaccharides (FEHLNER-PEACH *et al.*, 2019).

As we showed, Amazonian riverine present a *Prevotella* dominant gut microbiome, even though they have a diet rich in animal protein and low in fiber. A possible explanation could be diet induced microbiome modulation resulting in species with higher potential for carbohydrate degradation in fiber-rich diets, and an increase in proteases and vitamin B, folate and branched-chain amino acids (BCAA) biosynthesis repertoire in protein-rich diets (FILIPPIS *et al.*, 2019). However, these results are exclusively from industrialized societies and when the comparison is broadened to include a variety of populations from around the world, the difference in *Prevotella* strains follows a separation between traditional and industrialized societies (FILIPPIS *et al.*, 2019). Traditional and industrialized societies have different *Prevotella* consortiums, with different gene repertoires, being the former enriched in complex carbohydrate degradation genes and in the amount and diversity of strains (FILIPPIS *et al.*, 2019; TETT *et al.*, 2019). *Prevotella* diversity decreases with westernization (HANSEN *et al.*, 2019; TETT *et al.*, 2019) and a western plant-based diet is still not effective in establishing a *Prevotella* strains consortium typical of traditional societies (FILIPPIS *et al.*, 2019).

Immigration from Thailand to United States reduce *Prevotella* dominance and CAZymes dominant in the gut microbiome, although, there was no significant associations between fiber content and the microbiome structure between populations (VANGAY *et al.*, 2018). Even keeping a distinct dietary pattern, second generation immigrants also present a gut

microbiome similar to that normally observed in the United States. Another study also shows that high expression of *Prevotella* enzymes did not correlate with fiber intake, which were indeed low (AAKKO *et al.*, 2020).

Other traditional population, the rural Mongolians from Khentii, which consumed low fiber and high animal-protein (meat and fermented dairy) also presents a gut microbiome with traditional features, such as *Prevotella* dominance and, *Treponema* and *Succinivibrio* presence (ZHANG *et al.*, 2014a), as that observed in other traditional populations that have a plant-based diet (YATSUNENKO *et al.*, 2012), or even those altering the bases of their diet seasonally (SMITS *et al.*, 2017). Likewise, in industrialized societies, different dietary patterns lead to similar gut microbiome composition (ROSAS-PLAZA *et al.*, 2022; VANGAY *et al.*, 2018). Considering that different diets in the same lifestyle pattern (traditional or industrialized) result in similar gut microbiome, it is plausible that lifestyle as a whole could be the main driver of gut microbiome composition.

There is a gradient of urbanization-industrialization, which begins in hunter-gatherer pre-agriculture societies, pass through farming and pastoralism, and end up in fully industrialized societies. Hunter-gatherers gut microbiome is the most similar to the ancestral gut microbiome and overlaps in some extent with agriculturists and pastoralists who still harbor a traditional gut microbiome (coherent with their more traditional lifestyle) (HANSEN *et al.*, 2019; OBREGON-TITO *et al.*, 2015; ROSAS-PLAZA *et al.*, 2022) (MCDONALD et al., 2018). The largest shift currently associated with changes in the human gut microbiome was driven by industrialization, which has changed the gut microbiome composition away from what was present in our ancestors, and currently still seem in traditional societies gut microbiomes. Thus, lifestyle may be understood as de context where the set of variables that influence the gut microbiome composition and metabolism are embedded and potentially interacting, a hard set of variables to disentangle.

Our studied populations do not differ only in their diets, but in their entire lifestyles, which limits our power to credit their differences in gut microbiome composition only to diet. São Paulo dwellers have a western-like lifestyle with limited natural environment contact, sanitation system and frequent use of sanitizing products, but also with a less communal life and more processed and ultra-processed food. Amazonian riverine remote location and limited market integration determine their intense contact with the natural environment. Their houses are very close or over the rivers to facilitate access to water for hygiene, cooking and sometimes drinking (otherwise collected from rain). From the river water they extract fish, and cassava is cultivated nearby. Rivers also allow their transportation by boats. Limited piped water and

sanitizing products for individual hygiene and cleaning of physical space along with no sanitation system and more communal life may favor the ecological process of microbial dispersal (spatial movement of microorganisms), which has an important role in shaping the traditional societies' gut microbiome (COSTELLO *et al.*, 2012; MARTÍNEZ *et al.*, 2015). Conversely, industrialized societies are experiencing dispersal limitation through modern hygiene practices and distinct selective environments through less communal life with emphasis in housing and individualized diets that may be reducing rates of successful colonization and together with antibiotics (and other medications) and insufficient dietary substrate leading to bacterial extinction (COSTELLO *et al.*, 2012; MARTÍNEZ *et al.*, 2015; SONNENBURG *et al.*, 2016).

Modern hygiene practices are important for limiting transmission of pathogens, but they also limit dispersal of gut symbionts (MARTÍNEZ *et al.*, 2015). Amazonian riverine lack of sanitation impact amount and quality of water for hygiene, cooking and drinking, which may be related to high intestinal infection prevalence caused by dispersal of pathogens indicating that dispersal of symbionts may also occur in high rates.

Close environmental contact in Amazonian riverine may also determine the presence of certain genera within their microbiome, such as *Cetobacterium* (Fusobacteria phylum). This taxon is present in some fish´s gut and it was also found in Bassa rural community (Nigeria, Africa), which may be related with their regular fish consumption, or environmental exposure, and use of Usuma river waters (AYENI *et al.*, 2018). Among Amazonian Riverine, *Cetobacterium* was correlated to consumption of fish, vitamin B12 and natural and minimally processed foods.

Analysis of Hadza hunter gathers shows that in a natural environment without barriers to limit microbial dispersion, the main differential taxa more abundant in traditional societies are present in hands of community members and in many environmental samples (game meat, honey, water) suggesting role of microbial dispersal and environmental contact in keeping traditional taxa among the metacommunity (FRAGIADAKIS *et al.*, 2019).

Hunter gathers gut microbiome present a seasonality related to dietary fluctuations (SMITS *et al.*, 2017). *Succinivibrionaceae*, *Paraprevotellaceae*, *Spirochaetaceae*, and *Prevotellaceae* are some of the taxa that fluctuate seasonally. Those are specifically the taxa that differentiate industrialized societies from traditional societies and may indicate strong relation of taxa with diet.

5.3 Intermediated features

Local dynamics (industrialization gradients) may integrate features into the two main distinct gut microbiome clusters, traditional and industrialized, resulting in gut microbiomes with transitioning or intermediated profile. Using of the term "transitioning" recognizes an ongoing process of lifestyle change while the term "intermediated" valorized the local dynamics that may not fully reach the industrialized typical pattern (SCHAAN *et al.*, 2021; TAMBURINI *et al.*, 2022). Intermediated features in our study may be due more recent placement of social phenomenon of industrialization or due local characteristics as significant preservation of traditional traits like diets rich in natural and minimally processed foods (IBGE, 2020). Also important is the change in life of inhabitants of more remote rural environment that get access to electricity, tap water and communications and transport systems. Particularly, Amazonian riverine get more access to boat motors and fuel that increase access to urban environments and cash through market integration.

The most striking intermediated feature is retaining *Prevotella* dominance in 1/5 of São Paulo dwellers. Significant *Prevotella* dominance is also seen in Belém (Pará, Brazil) (SCHAAN *et al.*, 2021) and in sewage of Salvador city (Bahia, Brazil) (KOSKEY *et al.*, 2014). *Prevotella* is more representative of Brazilian sewage than *Bacteroides* (as observed in industrialized nations) (KOSKEY *et al.*, 2014), indicating that Brazilians may retain some *Prevotella* dominance overall. São Paulo dwellers also harbor *Paraprevotella genus* (similar to *Prevotella*) that is a characteristic of traditional societies while Amazonian riverine harbor a *Rikenelaceae* family member and *Suterella* (genus), both of which are normally more commonly found among industrialized societies.

Akkermansia genus (Verrucomicrobia phylum) is a mucus degrader (SONNENBURG *et al.*, 2016; TANES *et al.*, 2021) that is a feature of industrialized societies specially linked to their low fiber diet (HANSEN *et al.*, 2019; SMITS *et al.*, 2017). It did not show strong correlation with diet, but it was a differential taxon more abundant in Amazonian riverine, which could be linked to their low fiber diet and indicate a transitioning feature.

5.4 Role in health and disease

Since new sequencing methods allowed deeper studies of the gut microbiome, it became clear its relationship with health and disease. Most of the studies present only associations and do not allow for inferring causality. Assign gut symbionts role in health and disease is not an

easy task, as they are part of normal functioning of human gut ecosystem and as taxon changes may occur that maintain the gut microbiome's functionality (LOZUPONE *et al.*, 2012). Moreover, different microbial strains can present distinct metabolic activities (DE FILIPPIS *et al.*, 2016) and even when microorganisms have been identified, metabolic activity of many taxa have not yet been studied, as many still have not been cultivated (FEHLNER-PEACH *et al.*, 2019). Also, it is likely that pathophysiological influences of symbionts are exerted by groups of microorganisms and not by individual microorganisms. As a rule, our study reached genus or higher-level taxonomy identifications, and found microorganisms already known as gut symbionts, and some of them already have been linked to health and disease, although with little consensus in the current literature.

5.5 Other variables influencing gut microbiome composition

Amazonian riverine and São Paulo dwellers do not differ statistically in age and sex, but they were different in relation to obesity (BMI), intestinal infections, feces consistency (Bristol scale) and antibiotic use. All those variables may be related to gut microbiome composition but is likely that their influence is smaller than that of diet and lifestyle in these populations (FILIPPIS *et al.*, 2019). Besides that, studies considering those variables are strictly conducted in industrialized or traditional societies making it hard to talk about their influence in different lifestyles.

Curiously, Amazonian riverine had much higher antibiotic use close to the date of feces collection, which may be a bias because its recent use was not a excluding criteria for them, but it was for São Paulo dwellers. It also highlights that Amazonian riverine do have constant access to medical services (and the use of other medications that may alter gut microbiome composition). The greatest known consequence of antibiotic use is the perturbation in early microbiome assembly (REYMAN *et al.*, 2022) and selection of antibiotic resistant genes (ANTHONY *et al.*, 2022), both with possible future health consequences. Use in adulthood may be followed by long time for recovering pre-antibiotic composition but has not been evaluated in traditional societies. Rural Papua New Guineans are a traditional society with high antibiotic use that harbor a gut microbiome markedly different from US dwellers, including *Prevotella* rich status and higher alpha diversity (MARTÍNEZ *et al.*, 2015), although they lack some traditional features, such as *Treponema* and S*uccinivibrio* in differential analysis. At the same time higher intestinal infection and no-normal feces consistency (Bristol scale out of 3 to 5 classification) may be related to absence of sanitation system. A study that includes rural and

urban dwellers shows geographic location was more important for sample clustering than BMI (ODUARAN *et al.*, 2020) indicating that BMI influence on gut microbiome is smaller than lifestyle.

CONCLUSIONS

Our study is the first to consider a very detailed diet investigation, while comparing the gut microbiome of traditional and industrialized societies. We used a quantitative approach, with data obtained from 5 and 3 dietary recall questionnaires for Amazonian riverine and São Paulo Dwellers respectively, and a complete characterization of traditional food items, while most studies do a qualitative evaluation observing traditional societies dynamics and using only a food frequency questionnaire among industrialized societies. Such detailed dietary data gives us a more complete picture of food consumption and allowed us to contribute to the deconstruction of the stereotype of higher consumption of vegetables and fiber across all traditional populations that has not yet completely gone through the nutritional transition.

We show that São Paulo dwellers and Amazonian riverine present different gut microbiome compositions, with clear relationships to their different dietary patterns. São Paulo dwellers shows lower alpha diversity and taxa typical of industrialized societies that is related to their more westernized diet with significant contribution of processed and ultra-processed foods. On the other hand, Amazonian riverine shows higher alpha diversity and taxa typical of traditional societies that is related to their traditional diet based on local fresh fish and cassava flour. Like other traditional societies, Amazonian riverine diet is based on natural and minimally processed food. Exceptionally, they have high animal protein intake and low fiber intake which is uncommon for tropical climate traditional societies. Similar dietary pattern has been present by other contemporary traditional society where it is also coherent with traditional gut microbiome. However, São Paulo dwellers and Amazonian riverine are completely different societies and differ in a variety of variables related to their very distinct lifestyles, like environmental contact, sanitation, hygiene and other sociocultural practices that potentially affect microorganisms' dispersion and their gut microbiome composition. Considering that, we conclude that diet may play an important role in shaping these populations´ gut microbiome, but the entire set of all distinct variables that characterize these societies, e.g., their lifestyle, is likely the major driver.

LIMITATIONS

Important limitations of our study are related to sampling, available data and employed methods. Our convenience sample did not allow us to draw definitive conclusions. We did not conduct a systematic evaluation of diet and gut microbiome variation across seasons, as we used a non-systematic approach using a small sample.

We did not decompose the food preparations to their ingredients for using NOVA food classification because the data was not collected with the detail needed for such analysis, and that may have affected the final estimation of NOVA groups and subgroups consumption. At the same time, it prevented us to evaluate consumption of some ingredients important for our analysis like added sugar. We used the food composition table that is current the most complete and recommended for research use in Brazil (TBCA), but there was a limitation of food items and preparations in relation to that found in our study, which may have influenced the nutritional composition data.

Gut microbiome was assessed mostly in relation to its genus taxonomy, so we are not able to distinguish different lower-level taxa that may differentiate the two populations. Also, differences in taxa resolution level among different studies limit accurate comparisons with our study. Finally, we did not investigate non-bacterial members that could affect gut microbiome composition as bacteriophages (BARR, 2019).

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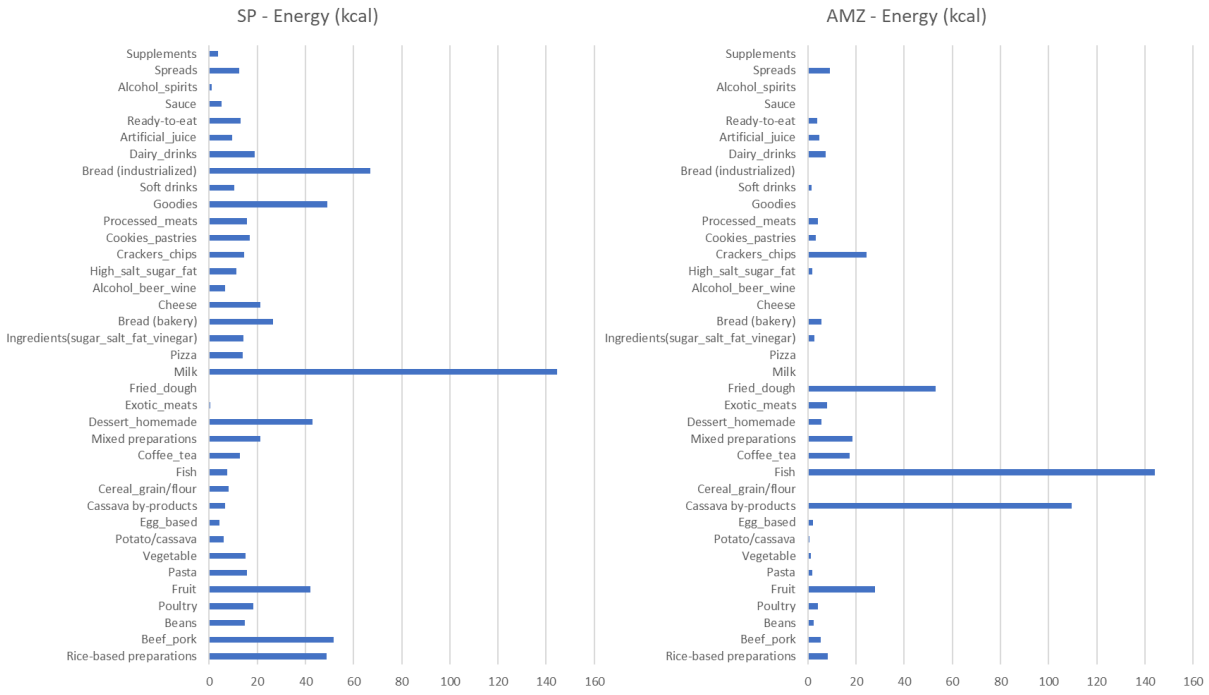
APPENDIX A

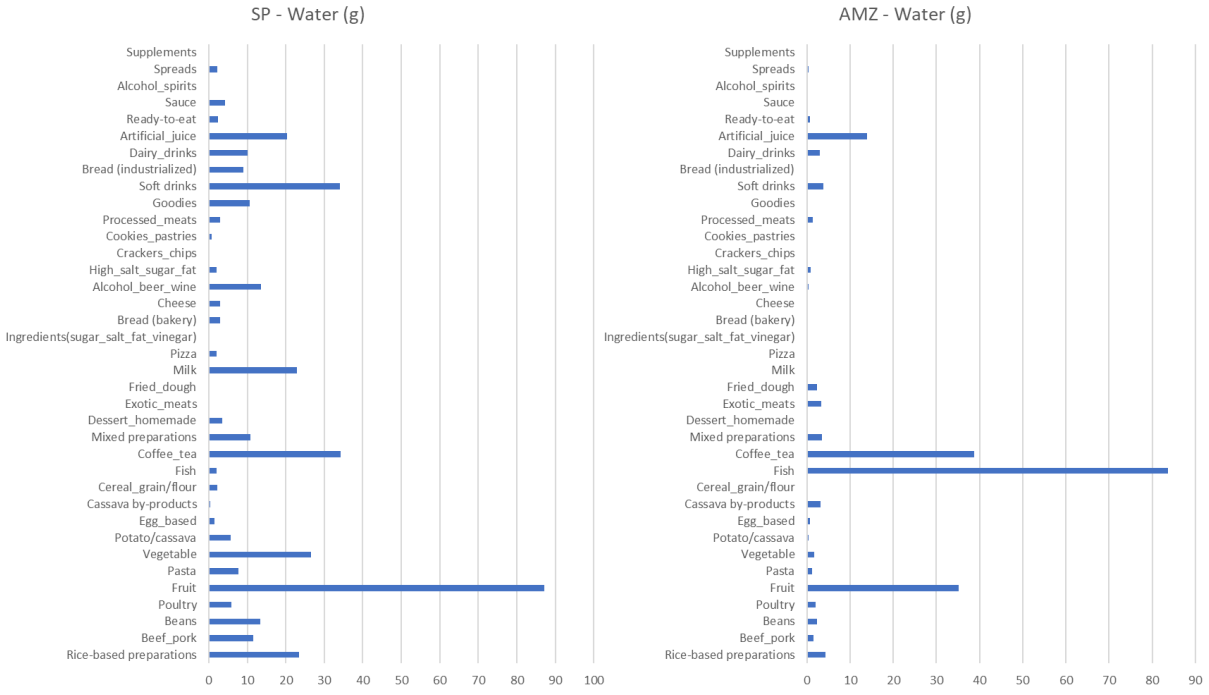
Contribution of NOVA subgroups for energy and nutrient intake (horizontal axis: nutrient quantity according to unit display in the title; vertical axis: NOVA subgroups)

Energy



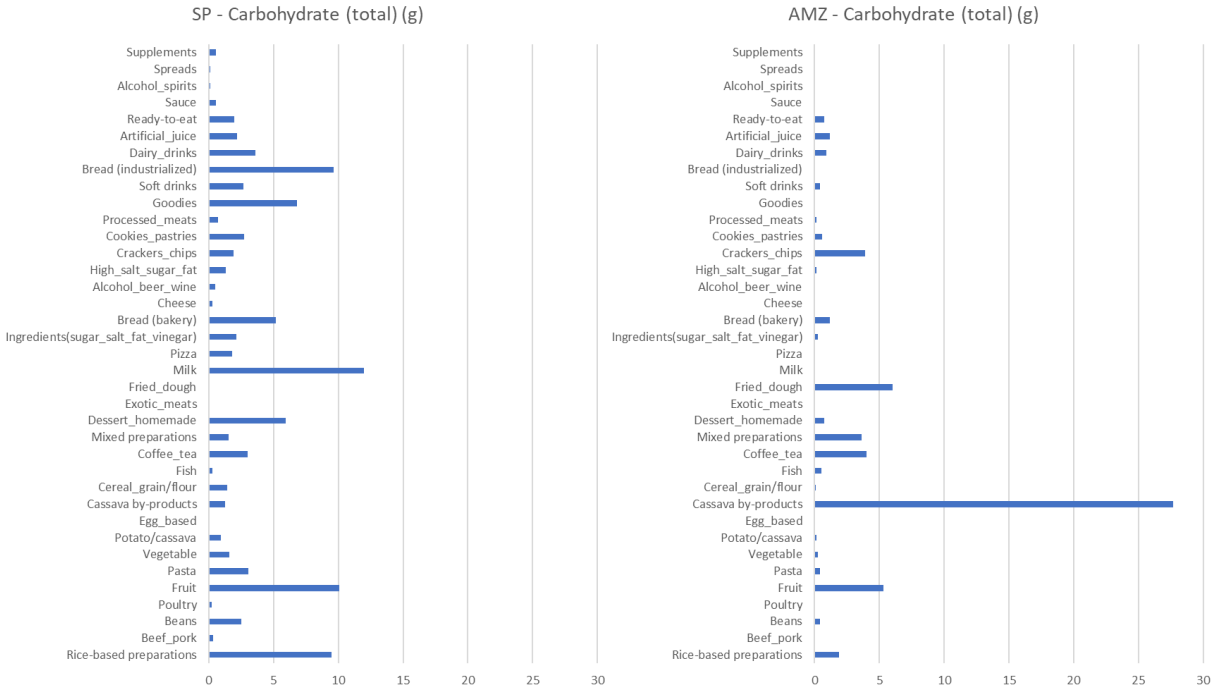
Source: Author.

Water



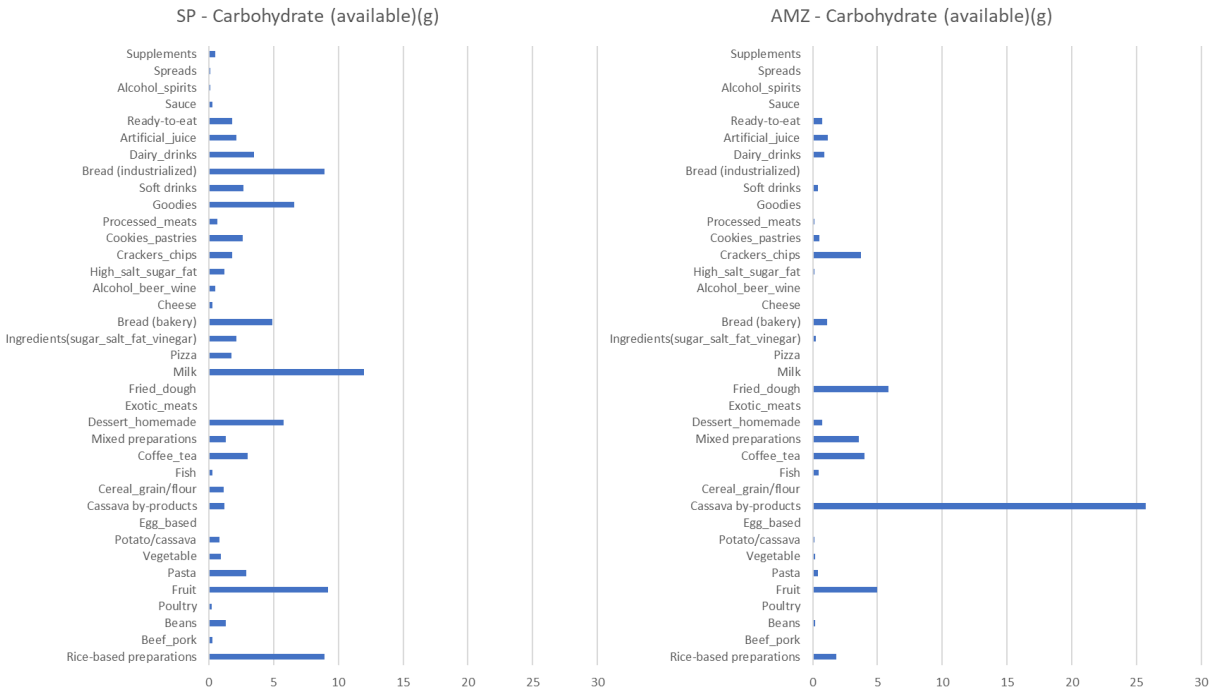
Source: Author.

Total carbohydrate



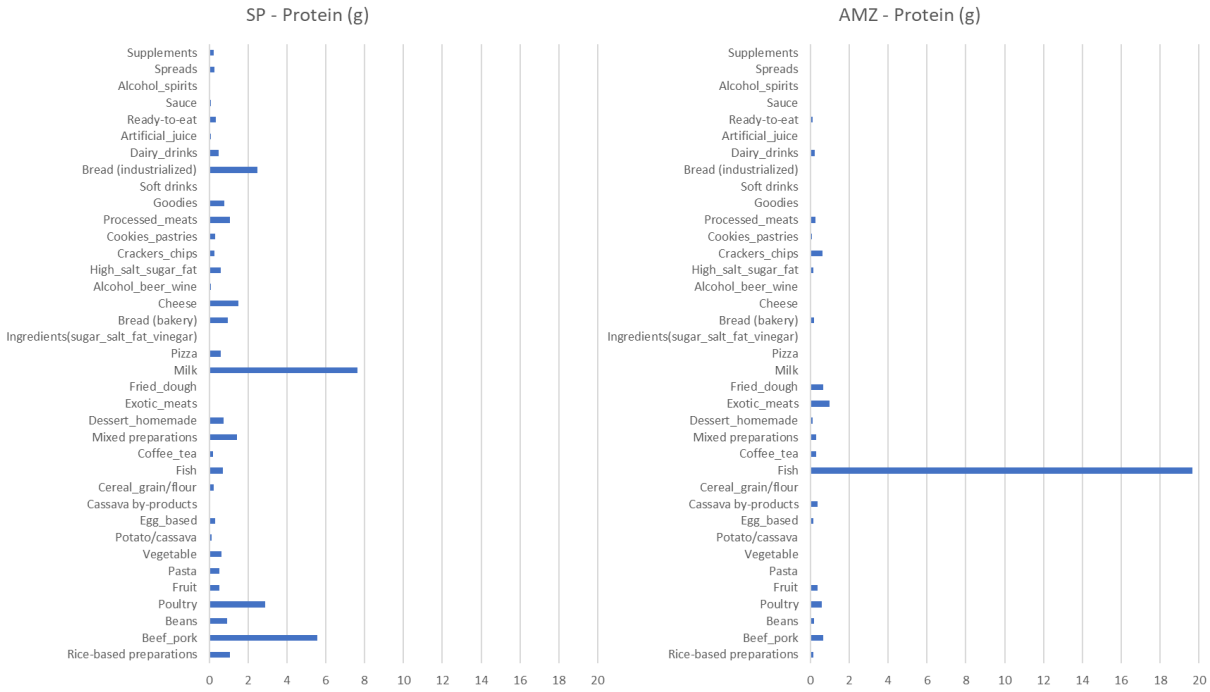
Source: Author.

Available carbohydrate



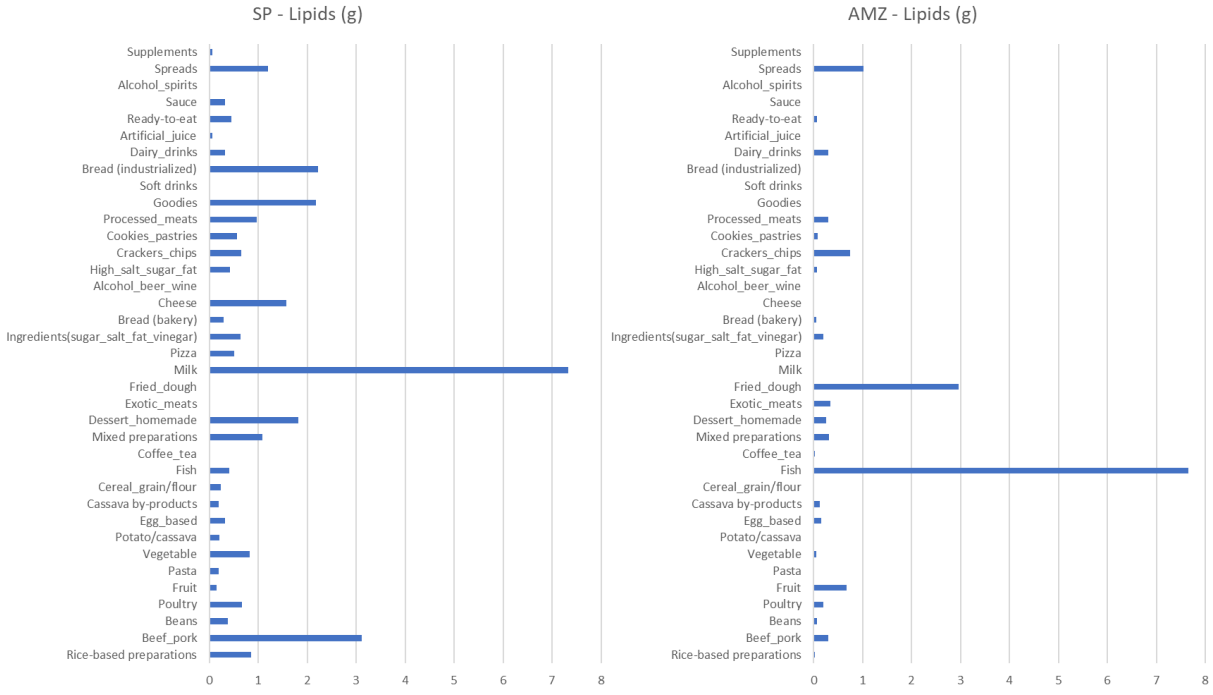
Source: Author.

Protein



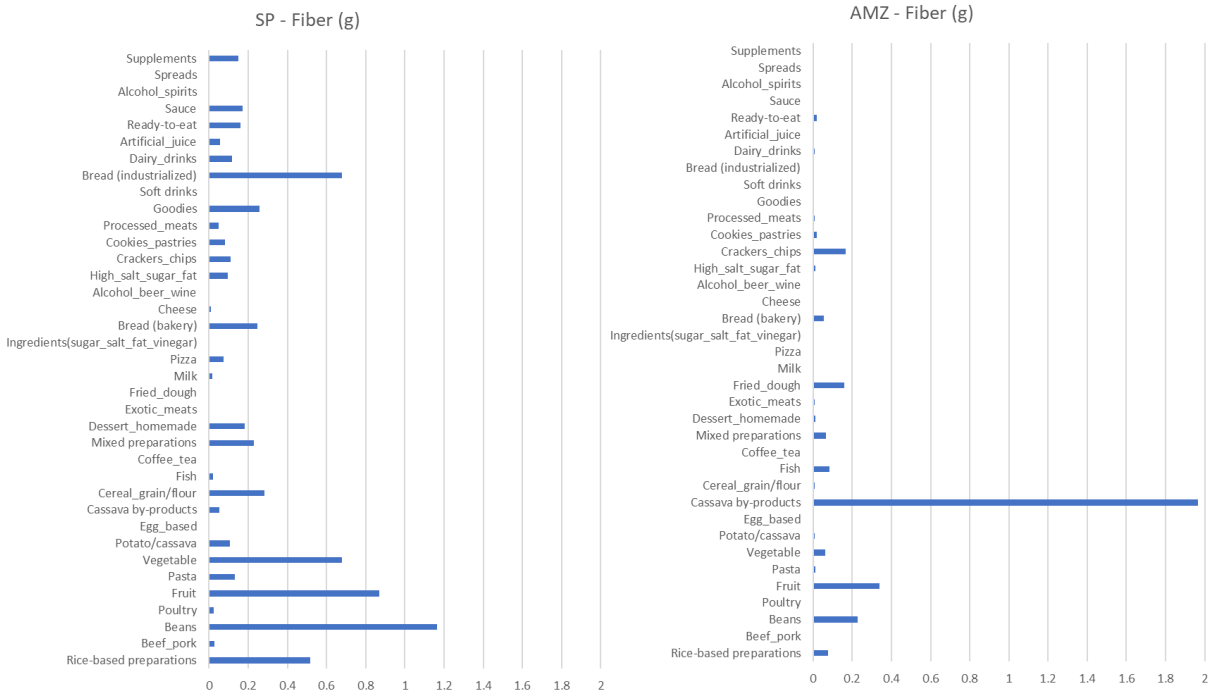
Source: Author.

Lipids



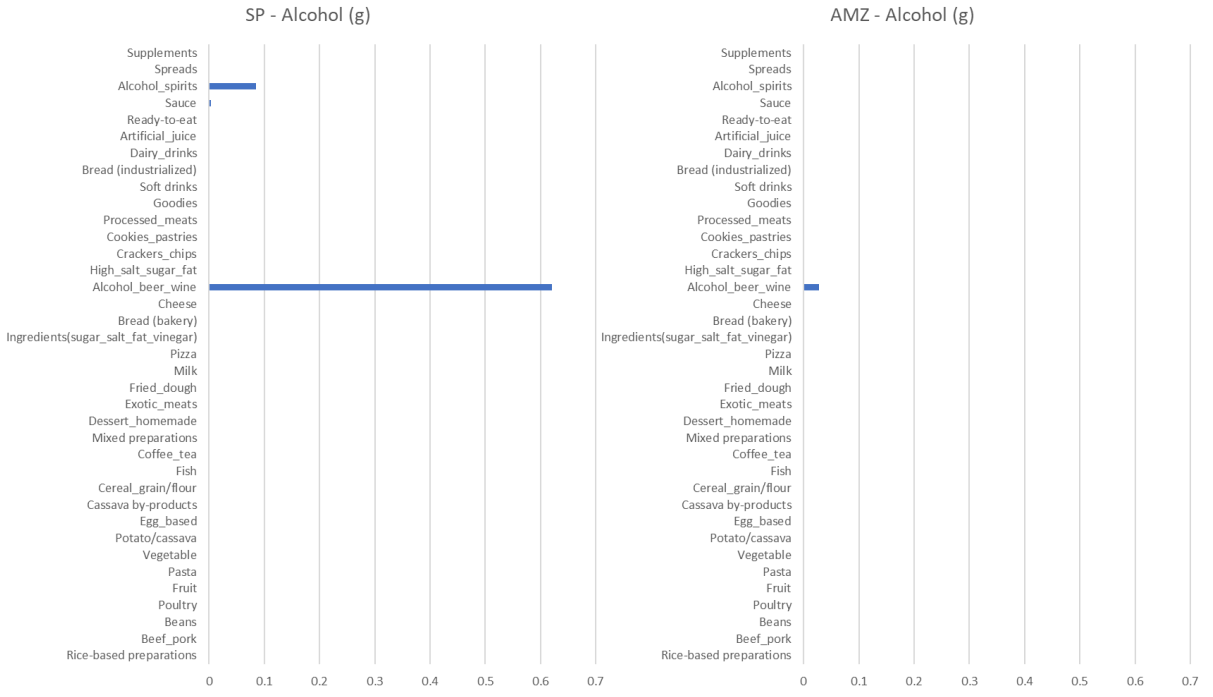
Source: Author.

Fiber



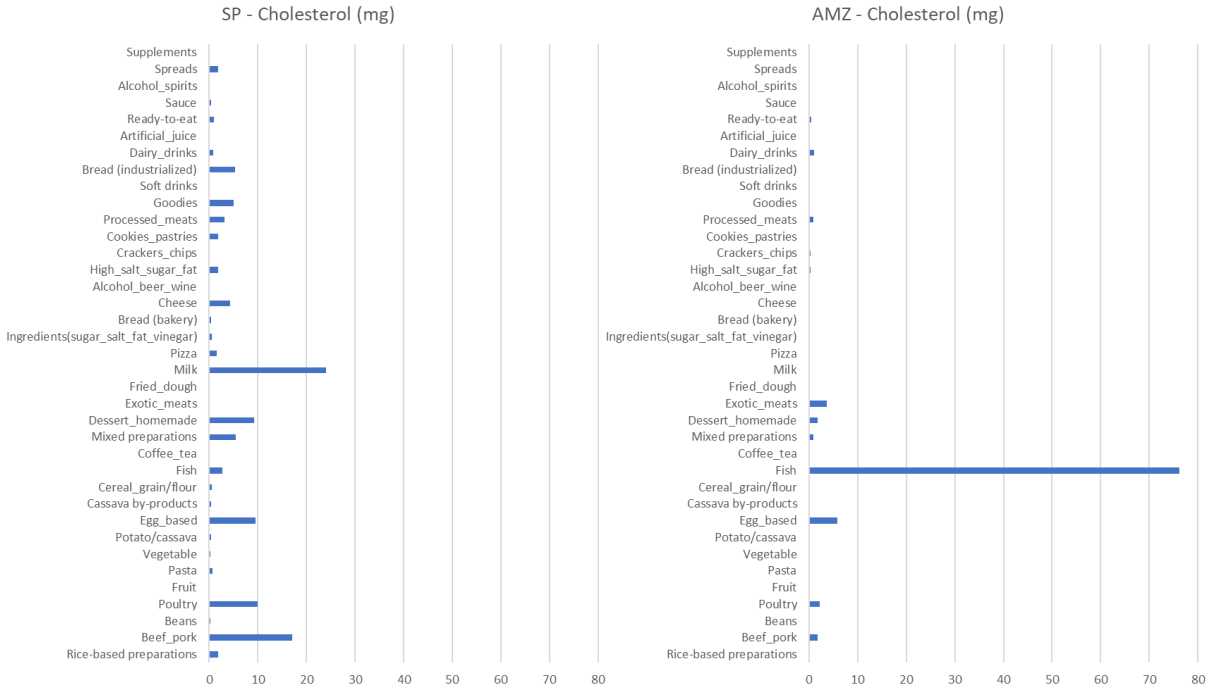
Source: Author.

Alcohol



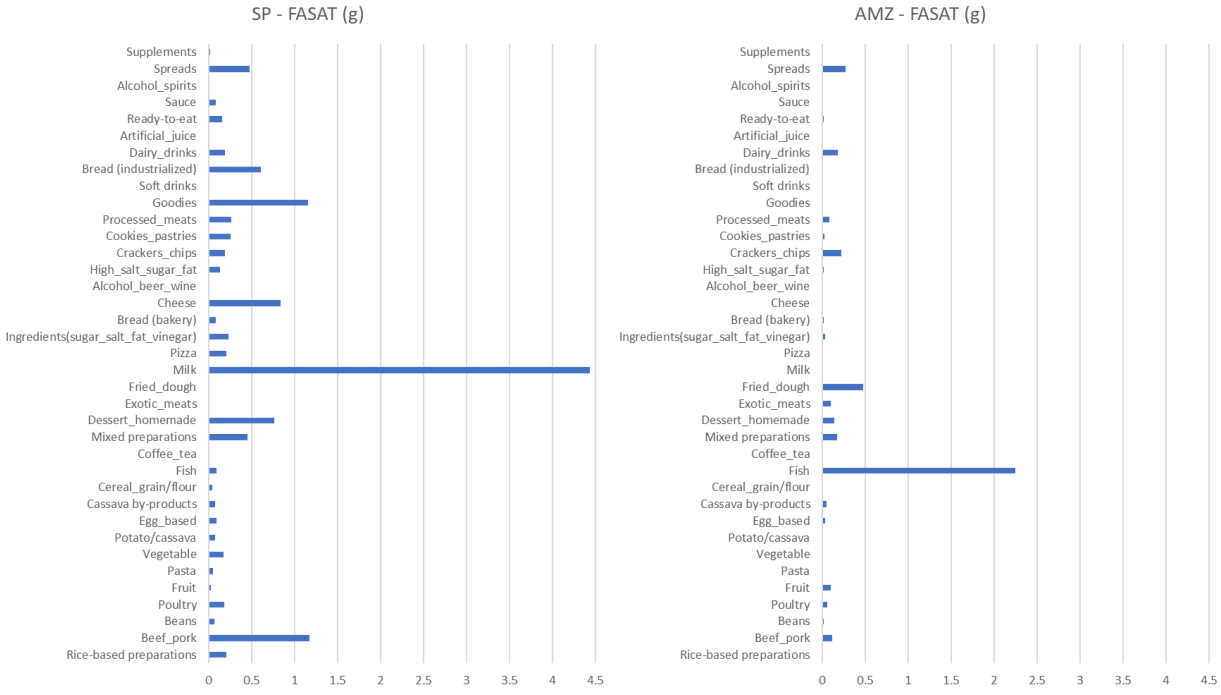
Source: Author.

Cholesterol



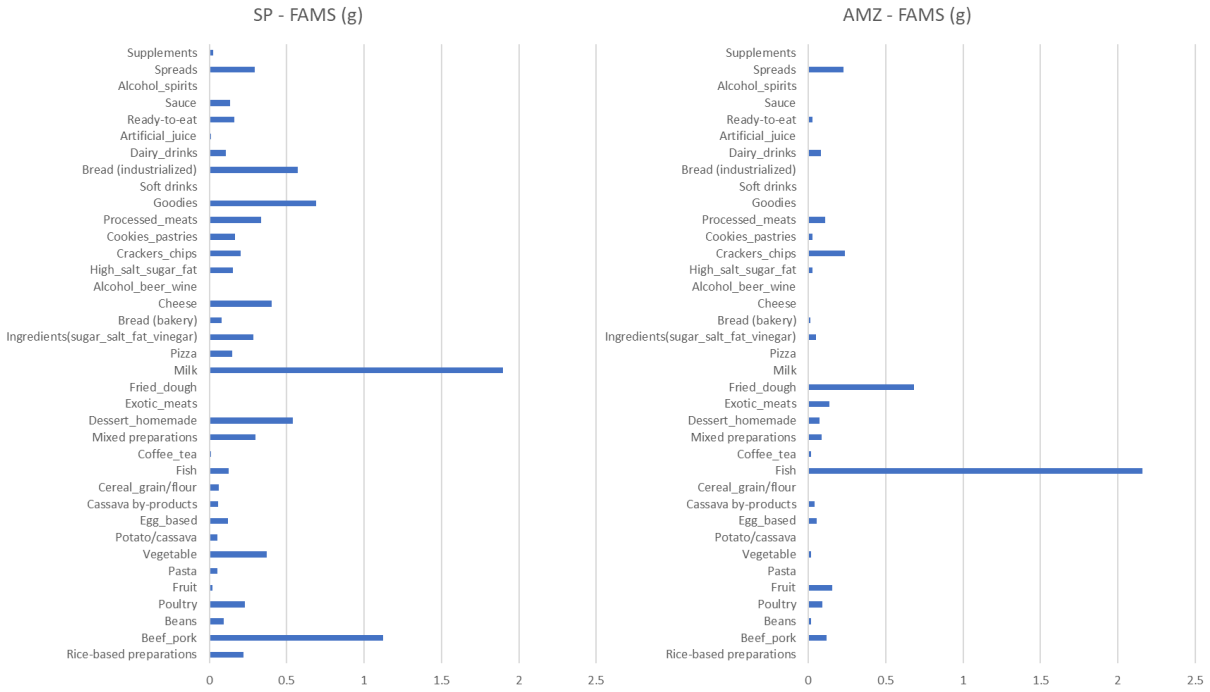
Source: Author.

Saturated fat



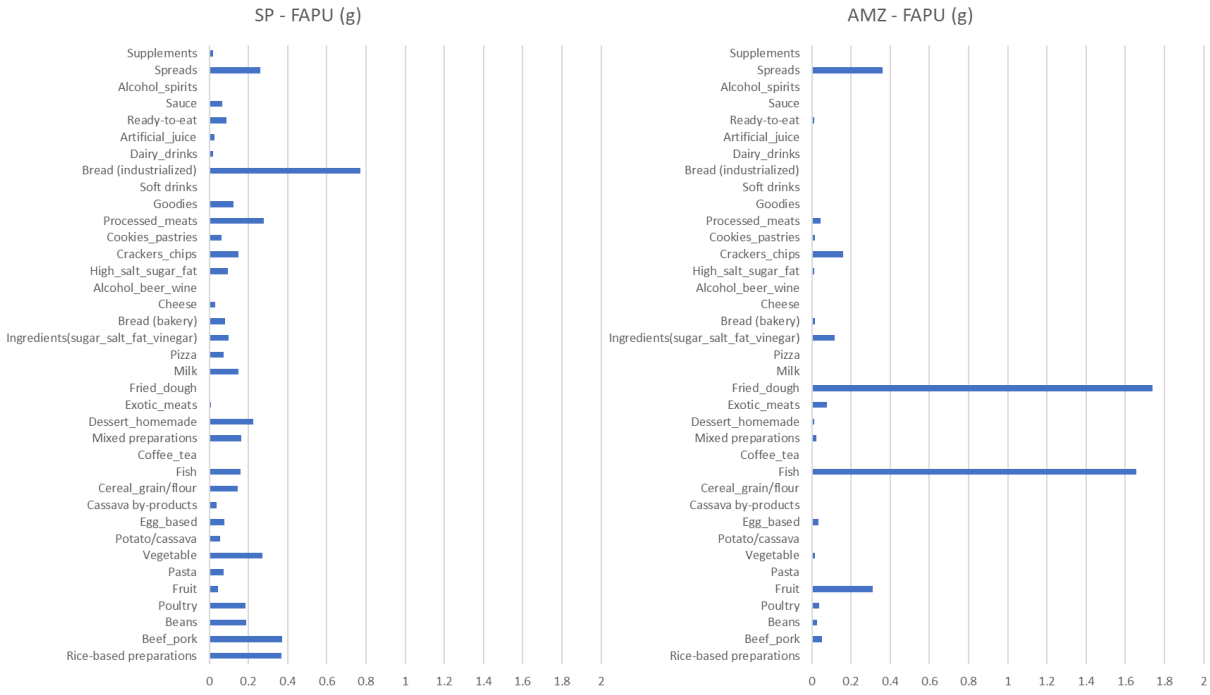
Source: Author.

Monounsaturated fat



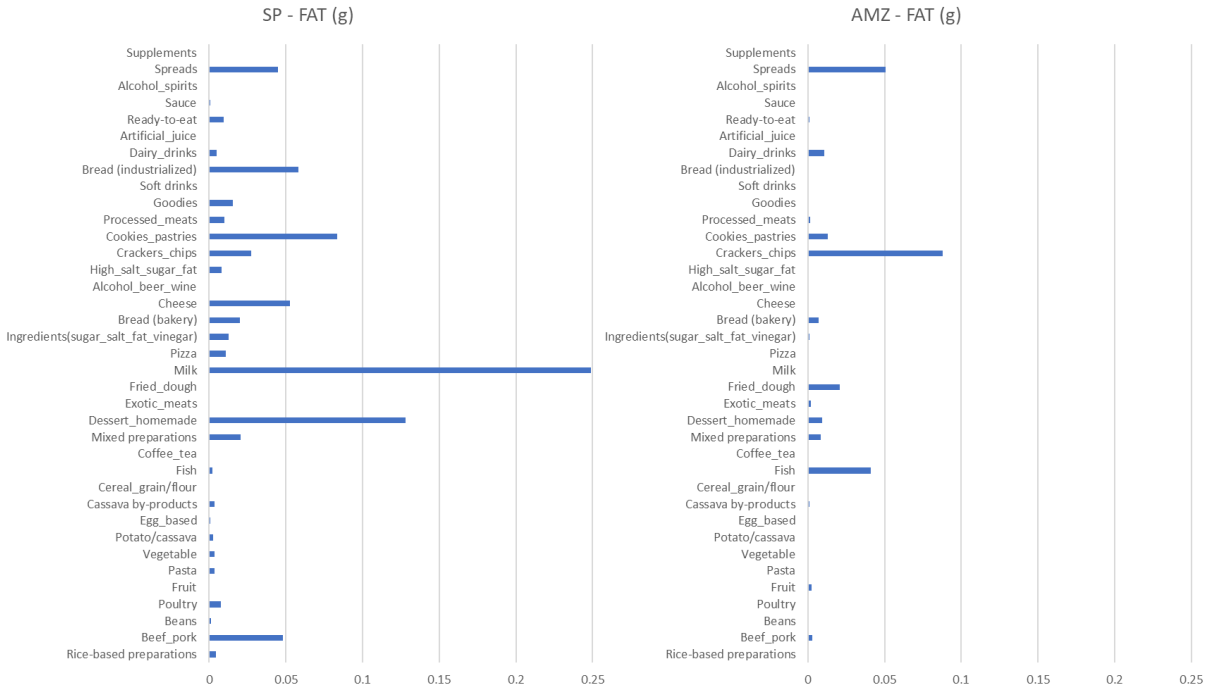
Source: Author.

Polyunsaturated fat



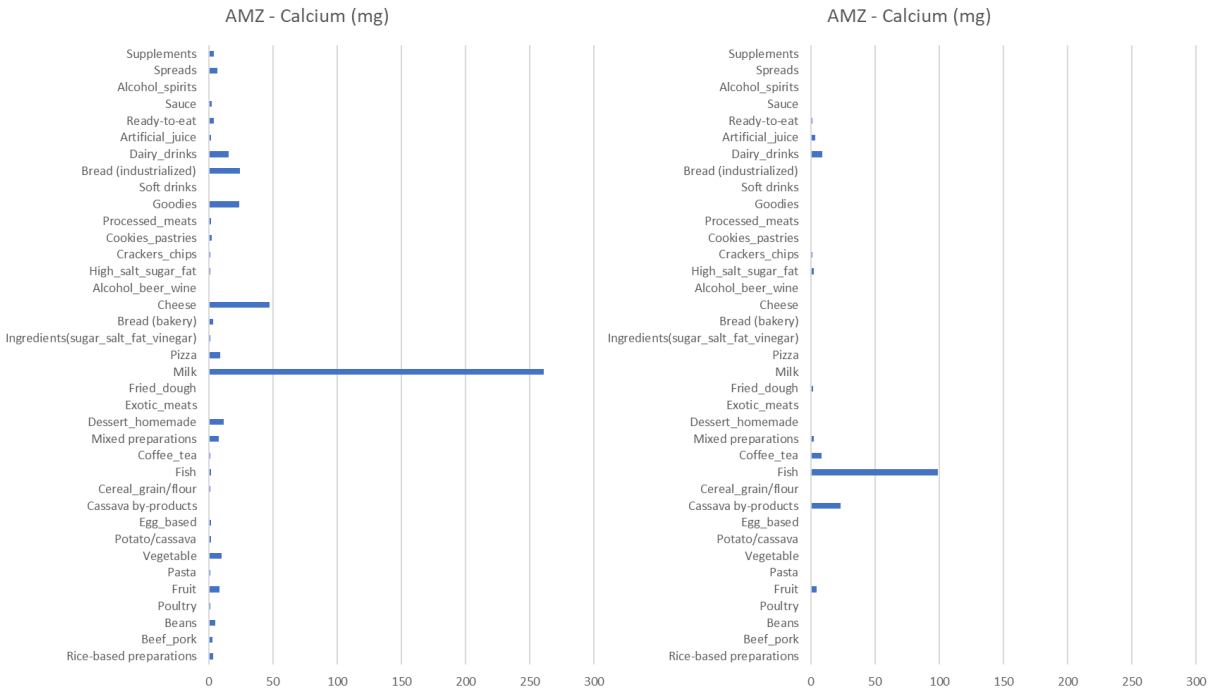
Source: Author.

Trans fat



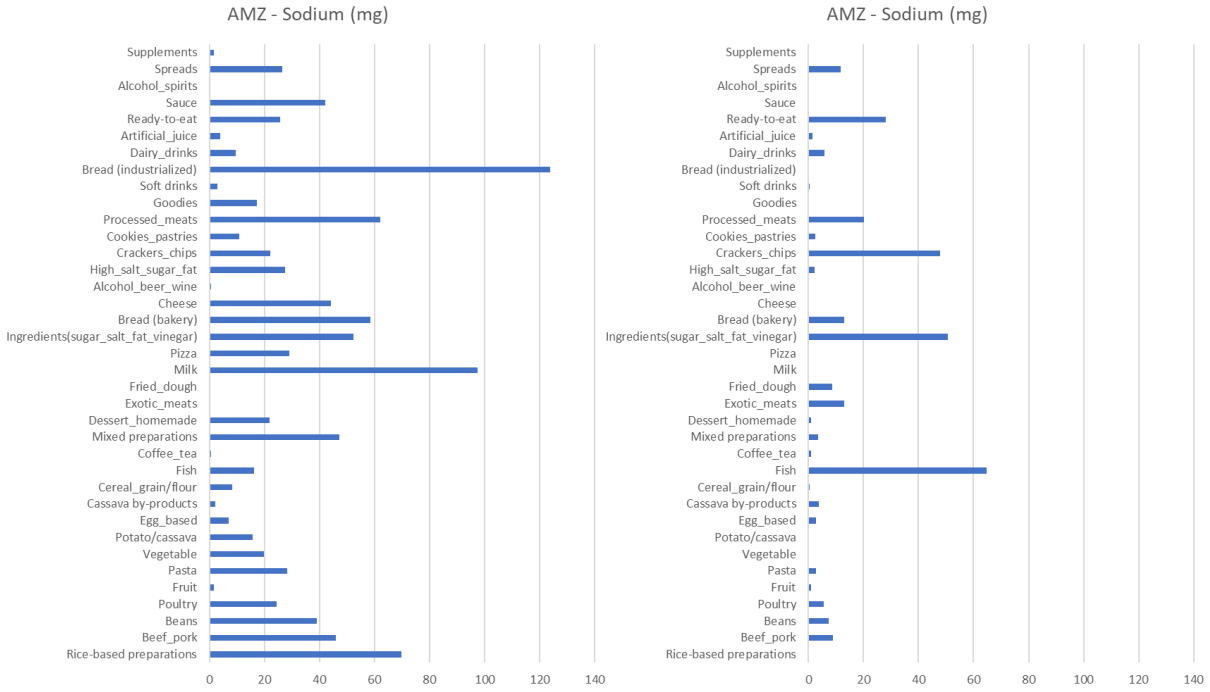
Source: Author.

Calcium



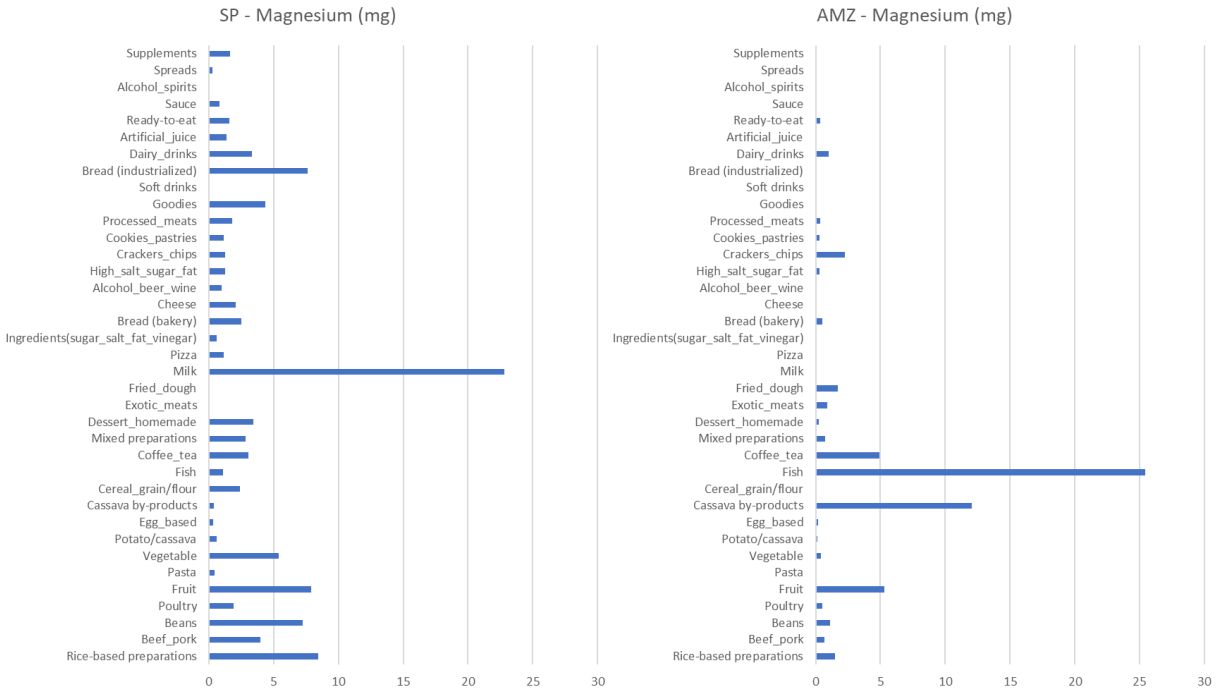
Source: Author.

Sodium



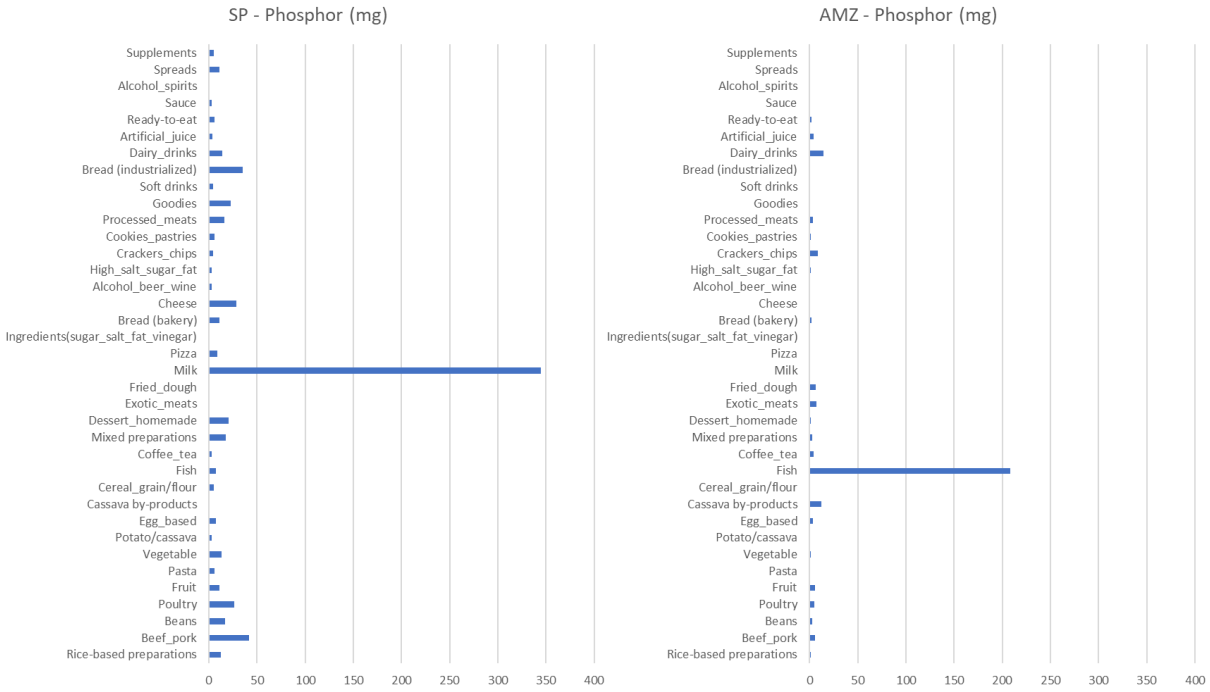
Source: Author.

Magnesium



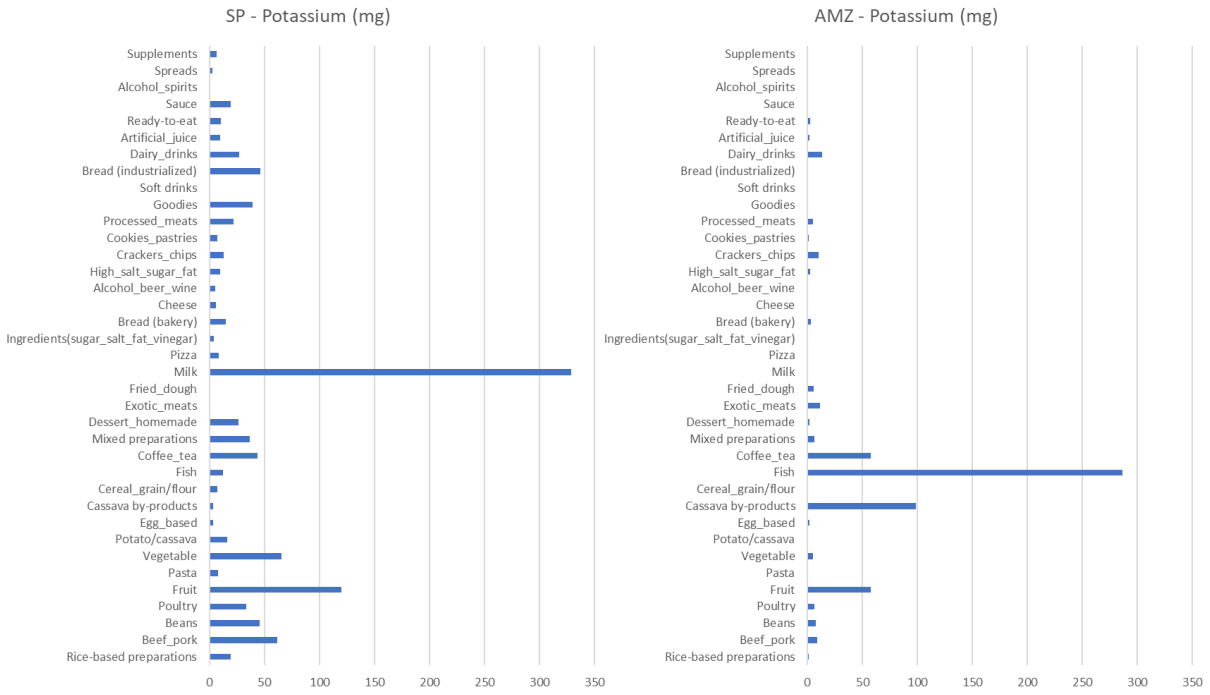
Source: Author.

Phosphor



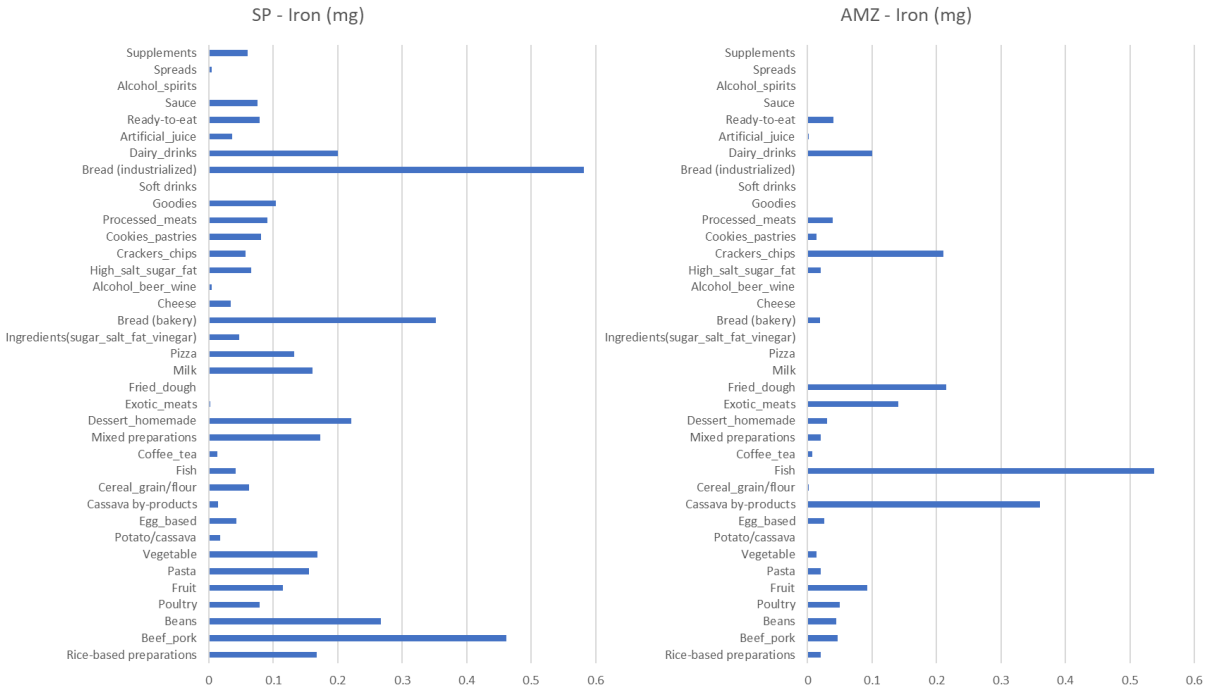
Source: Author.

Potassium



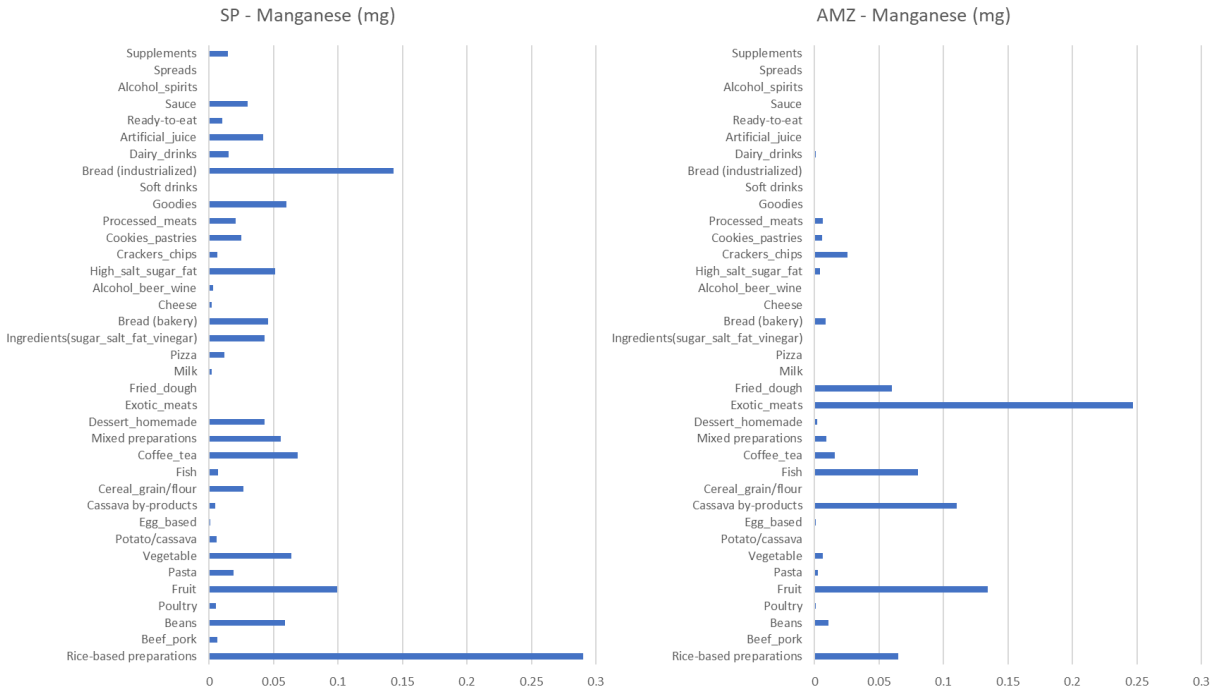
Source: Author.

Iron



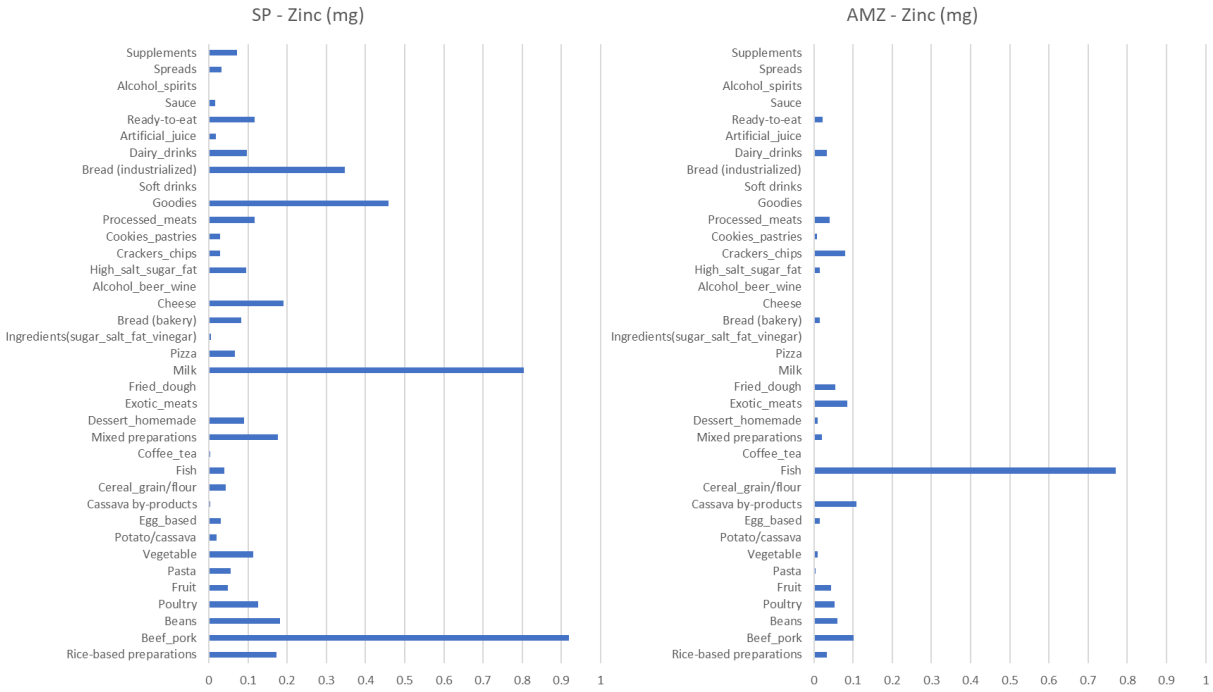
Source: Author.

Manganese



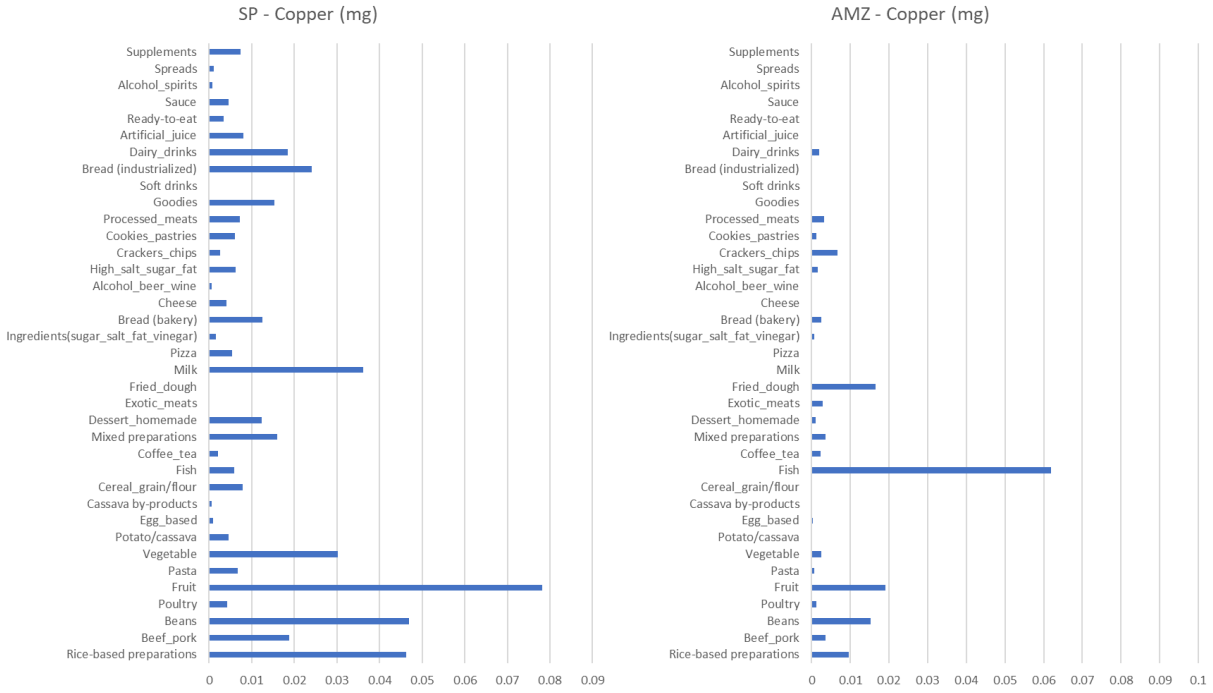
Source: Author.

Zinc



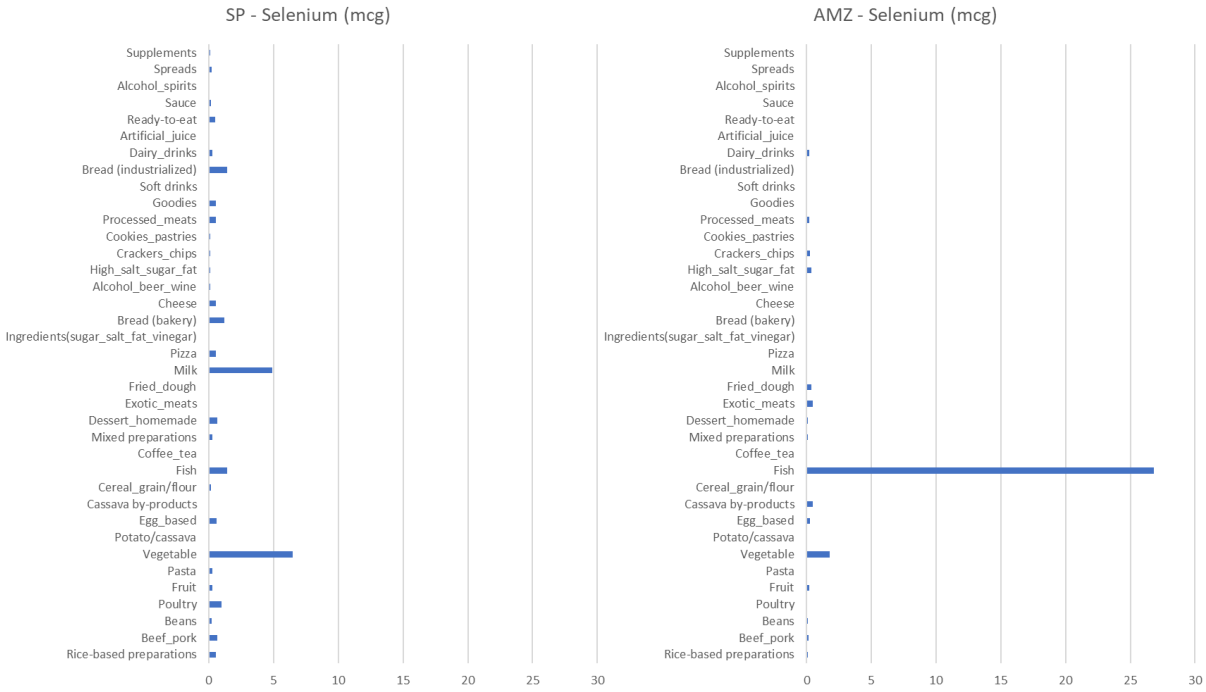
Source: Author.

Copper



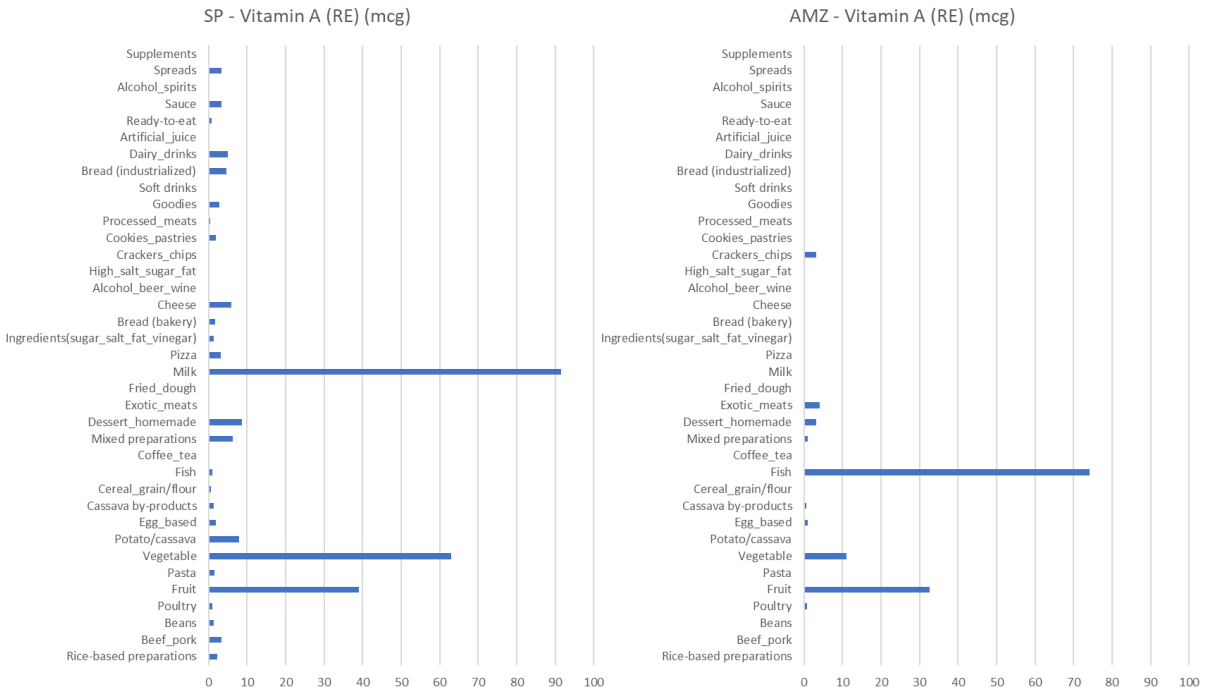
Source: Author.

Selenium



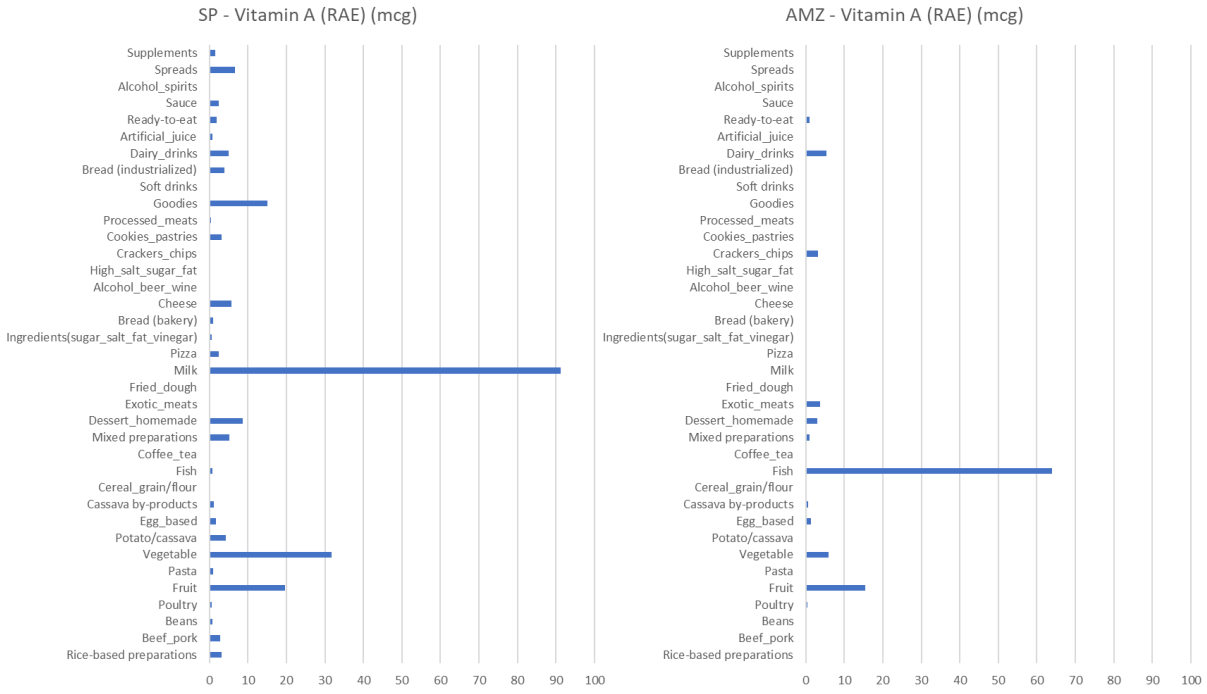
Source: Author.

Vitamin A (RE)



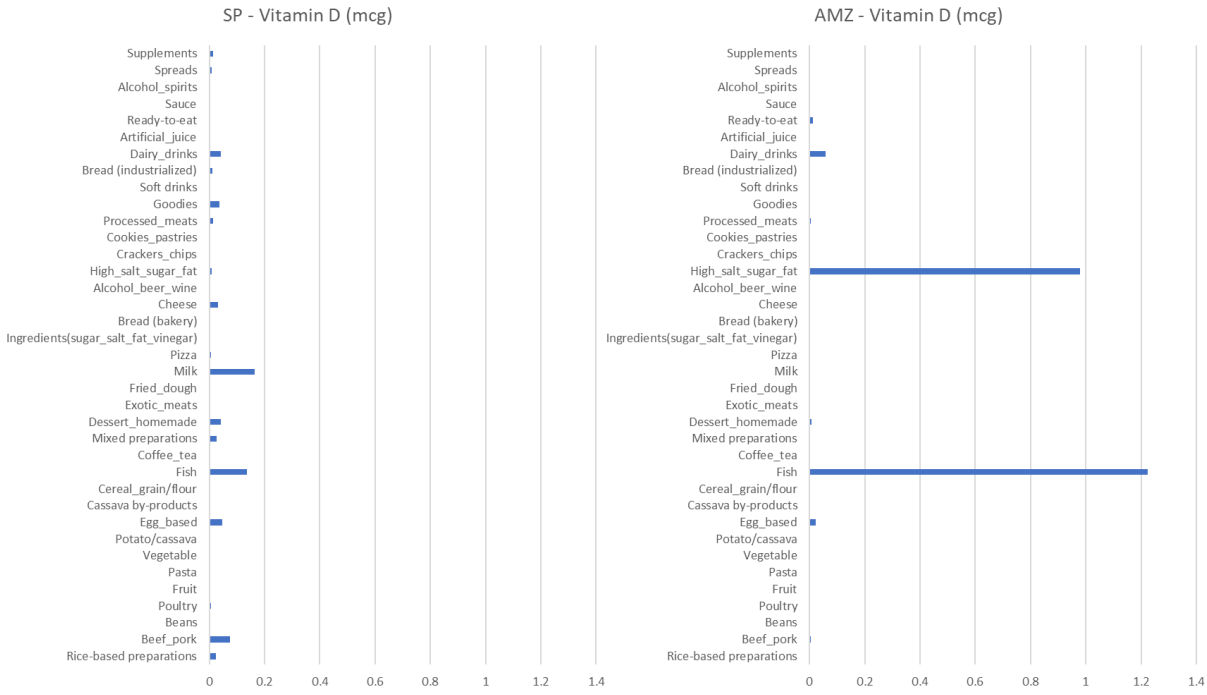
Source: Author.

Vitamin A (RAE)



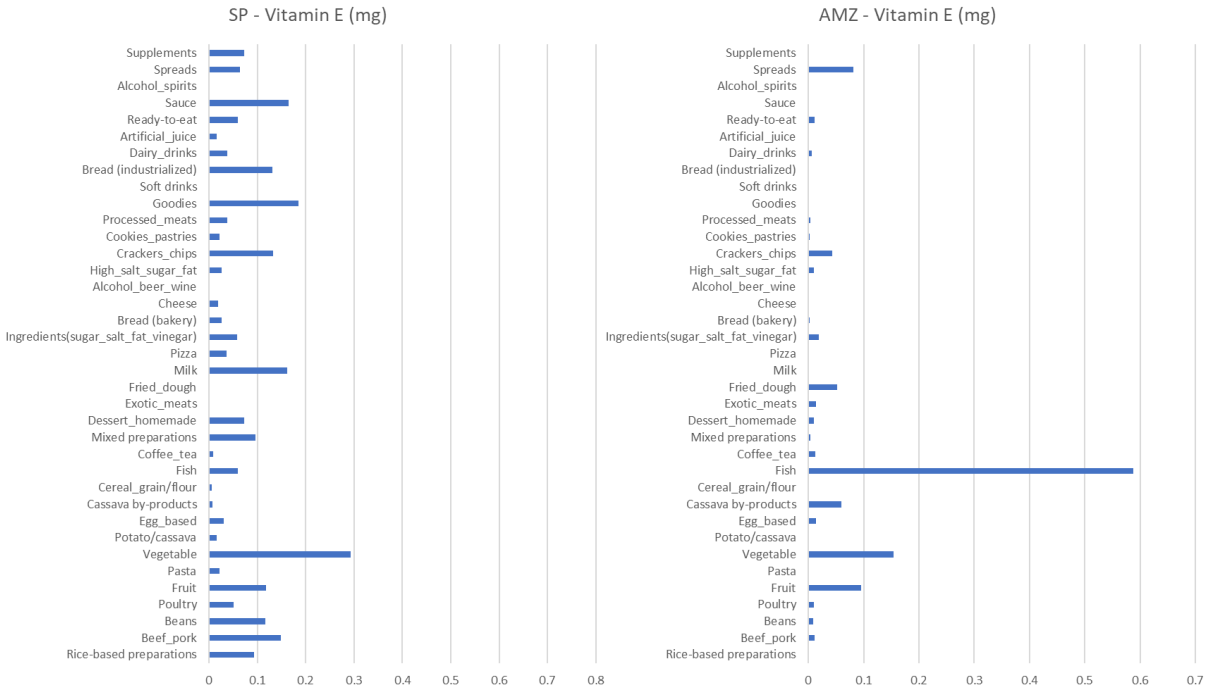
Source: Author.

Vitamin D



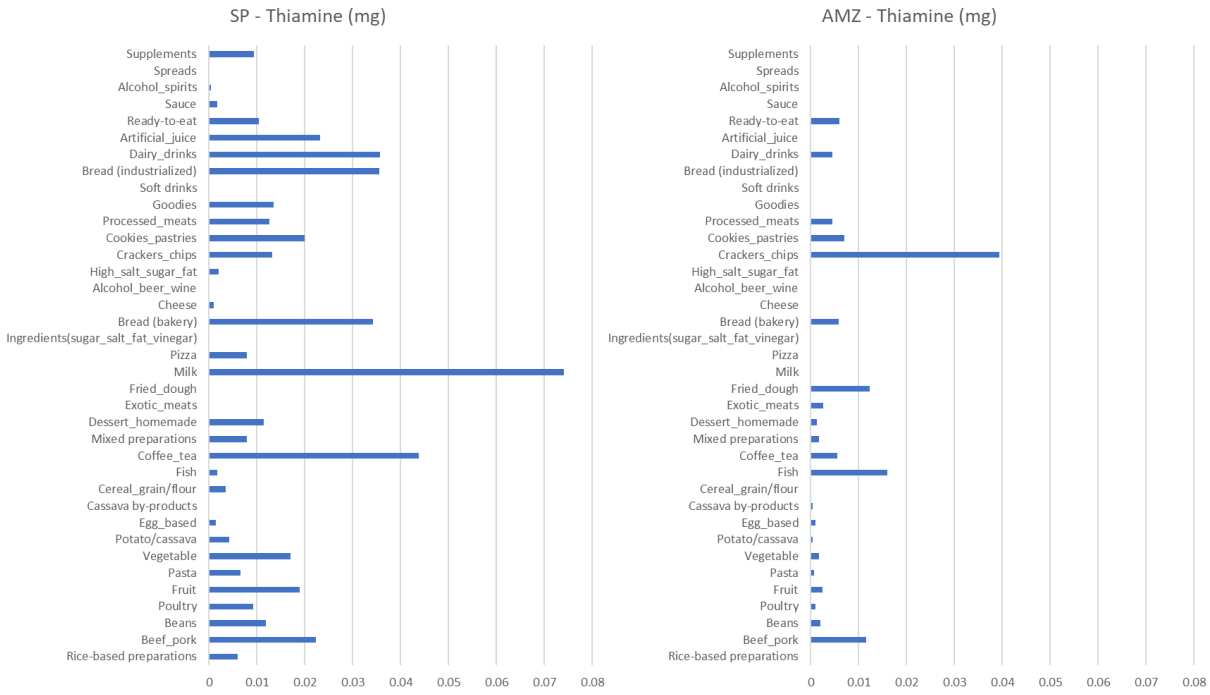
Source: Author.

Vitamin E



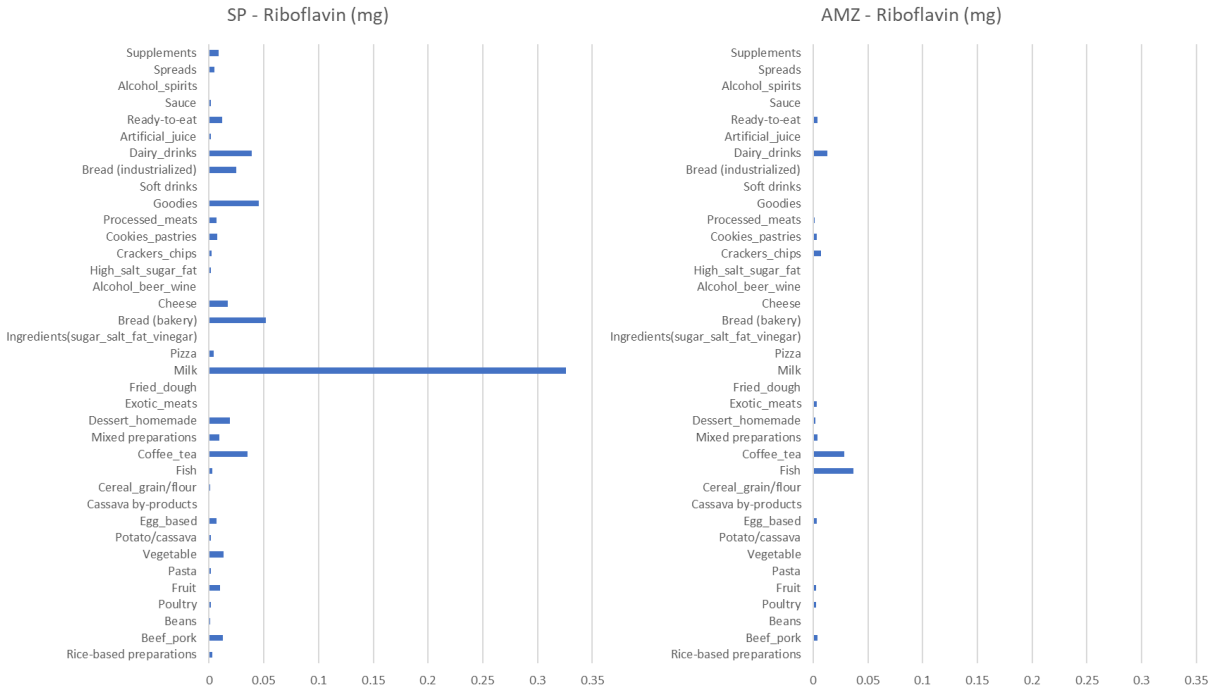
Source: Author.

Thiamine



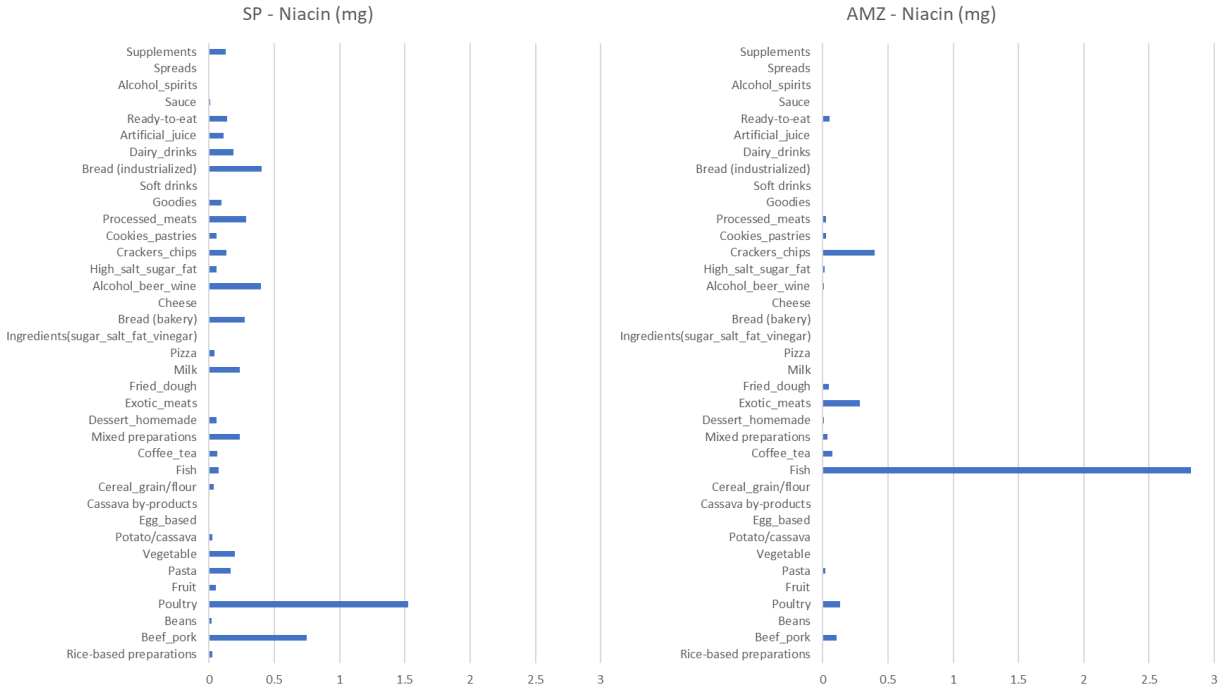
Source: Author.

Riboflavin



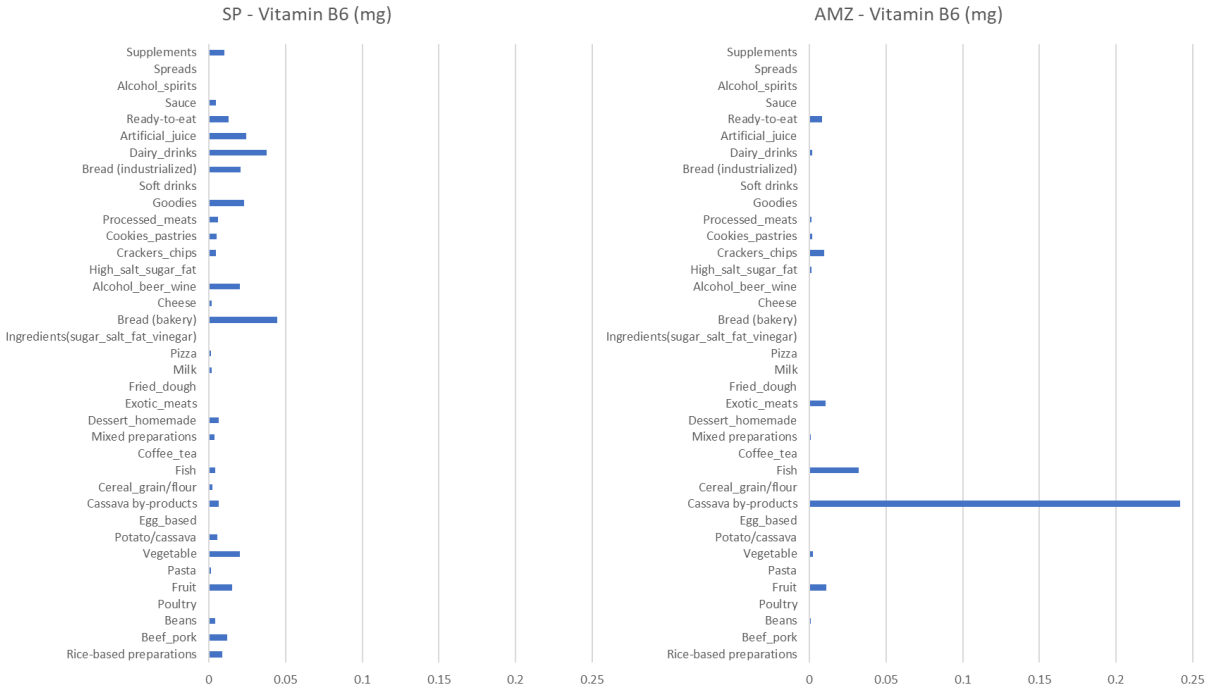
Source: Author.

Niacin



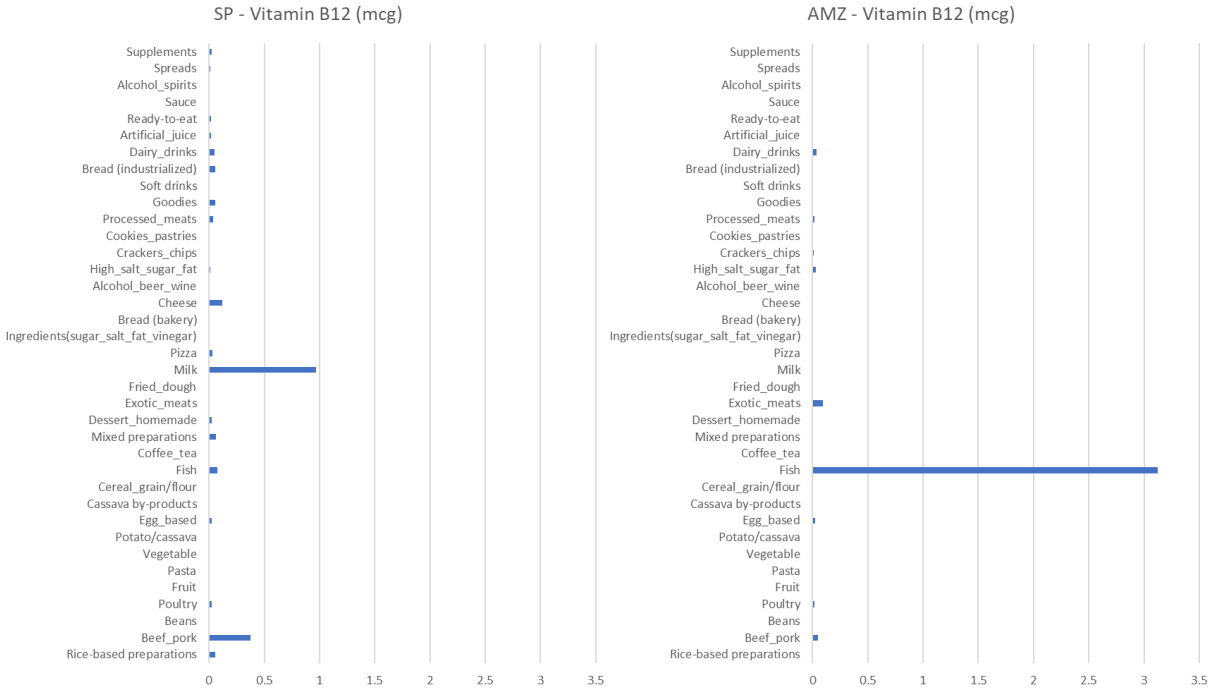
Source: Author.

Vitamin B6



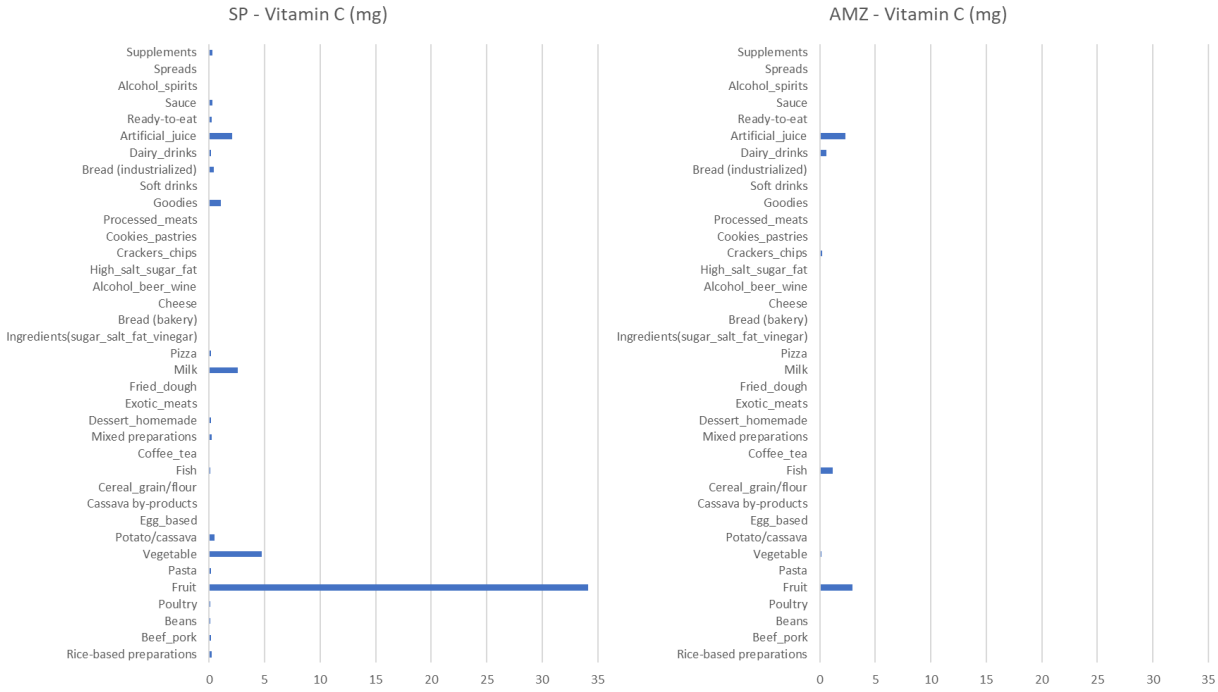
Source: Author.

Vitamin B12



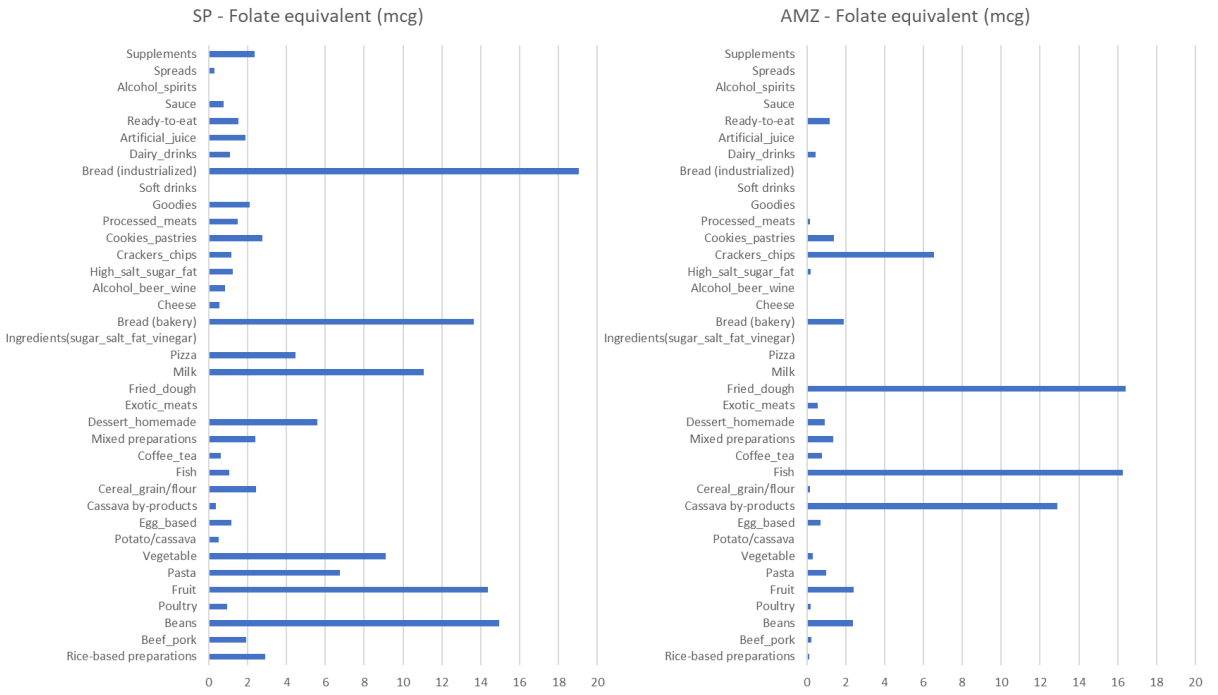
Source: Author.

Vitamin C



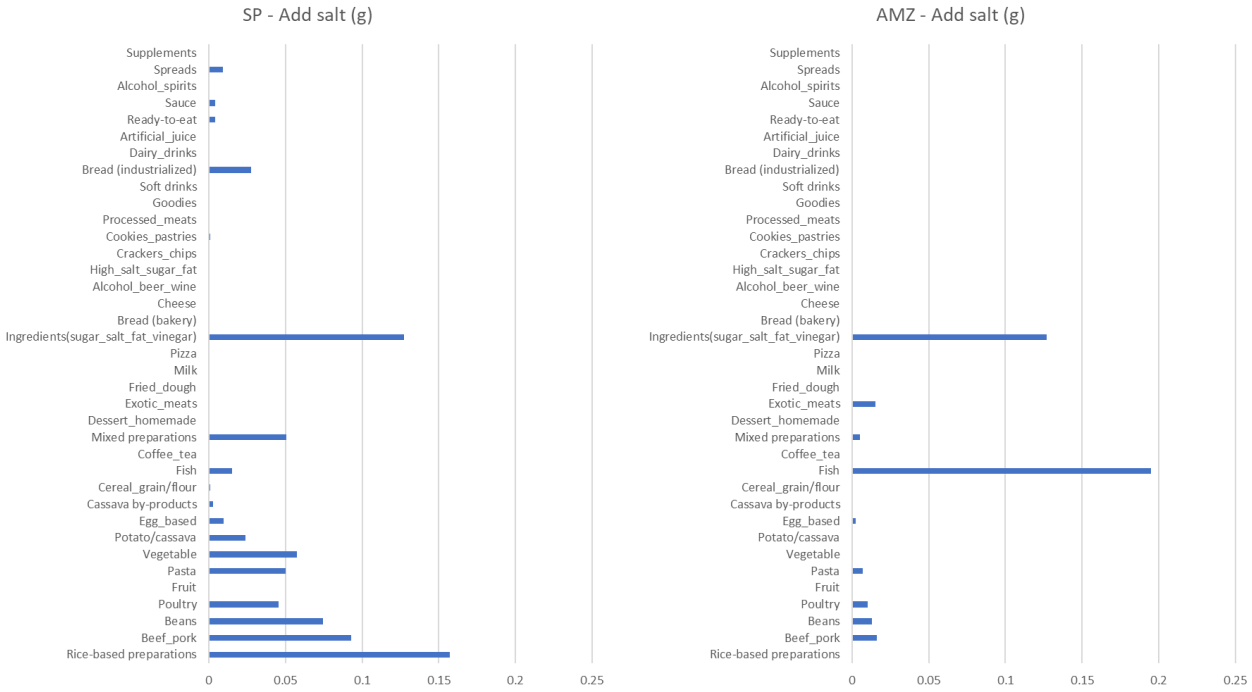
Source: Author.

Folate equivalent



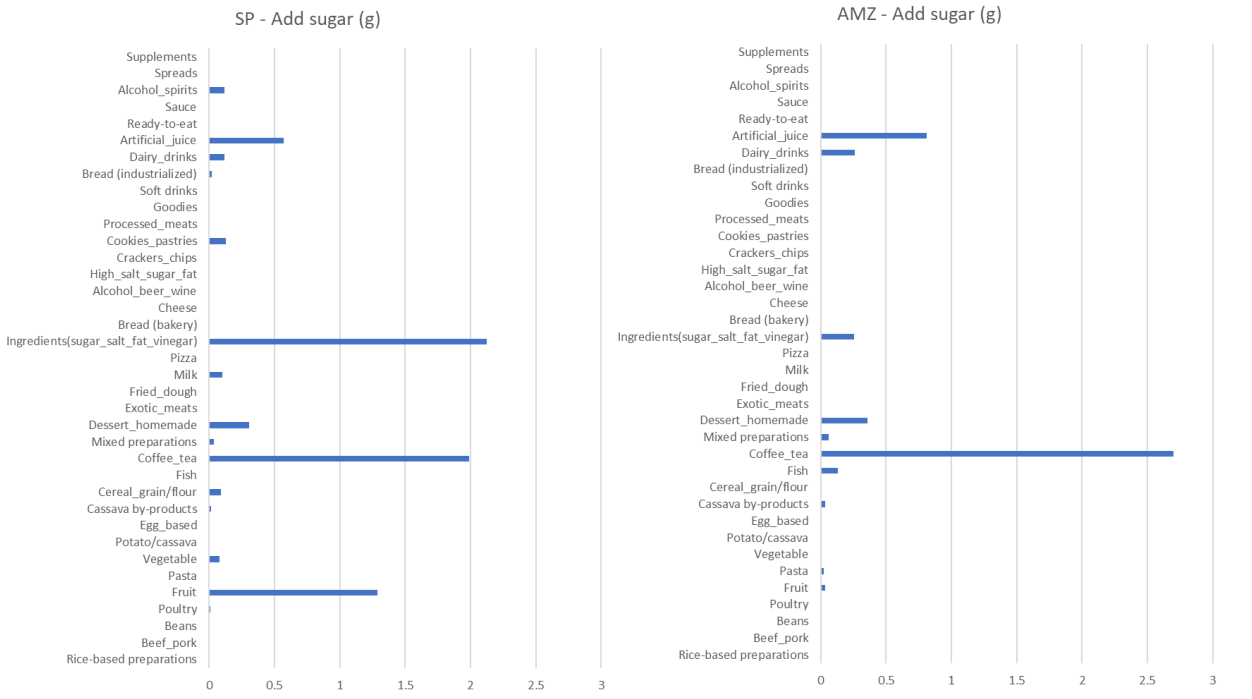
Source: Author.

Add salt



Source: Author.

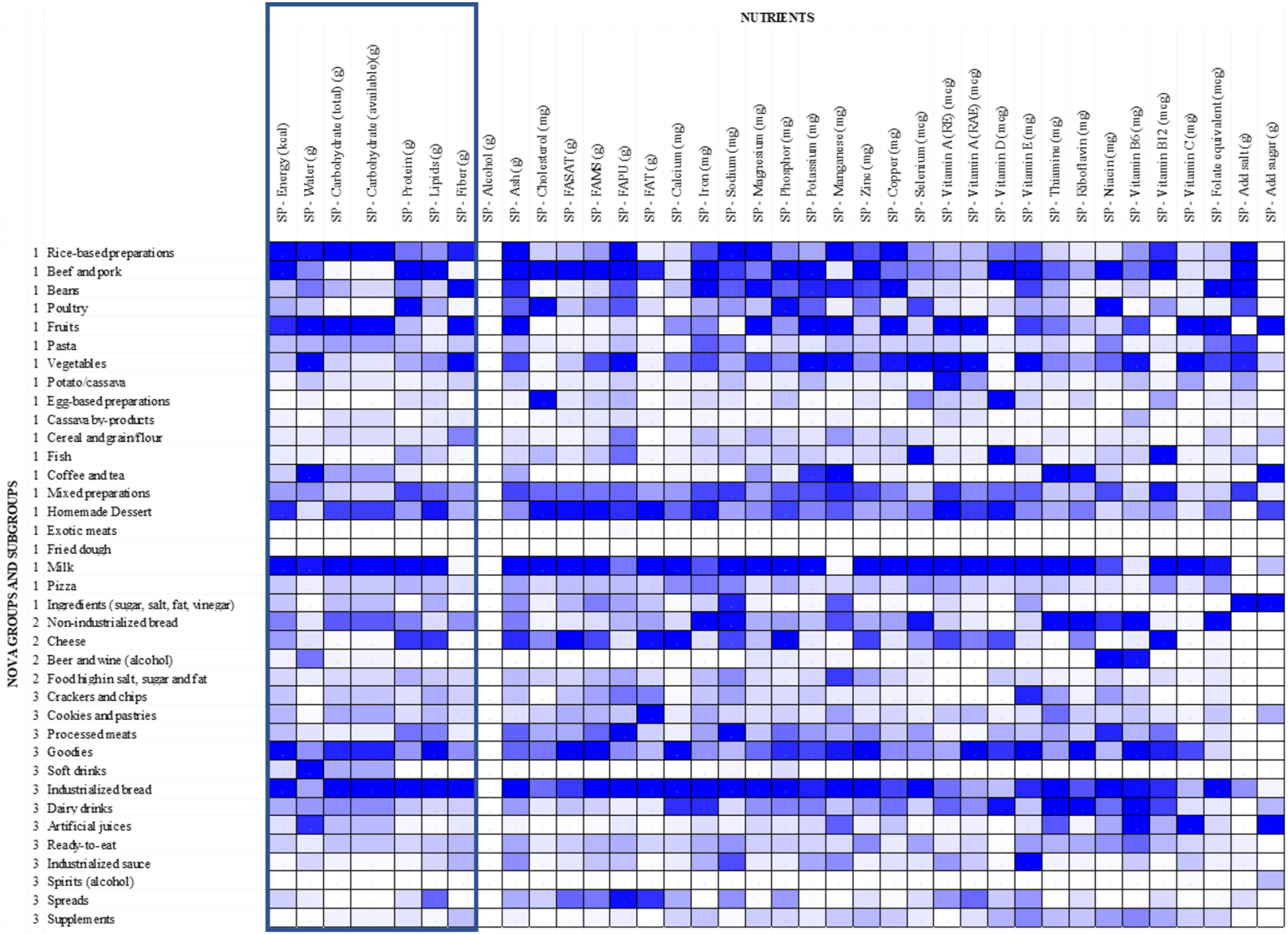
Add sugar



Source:

APPENDIX B

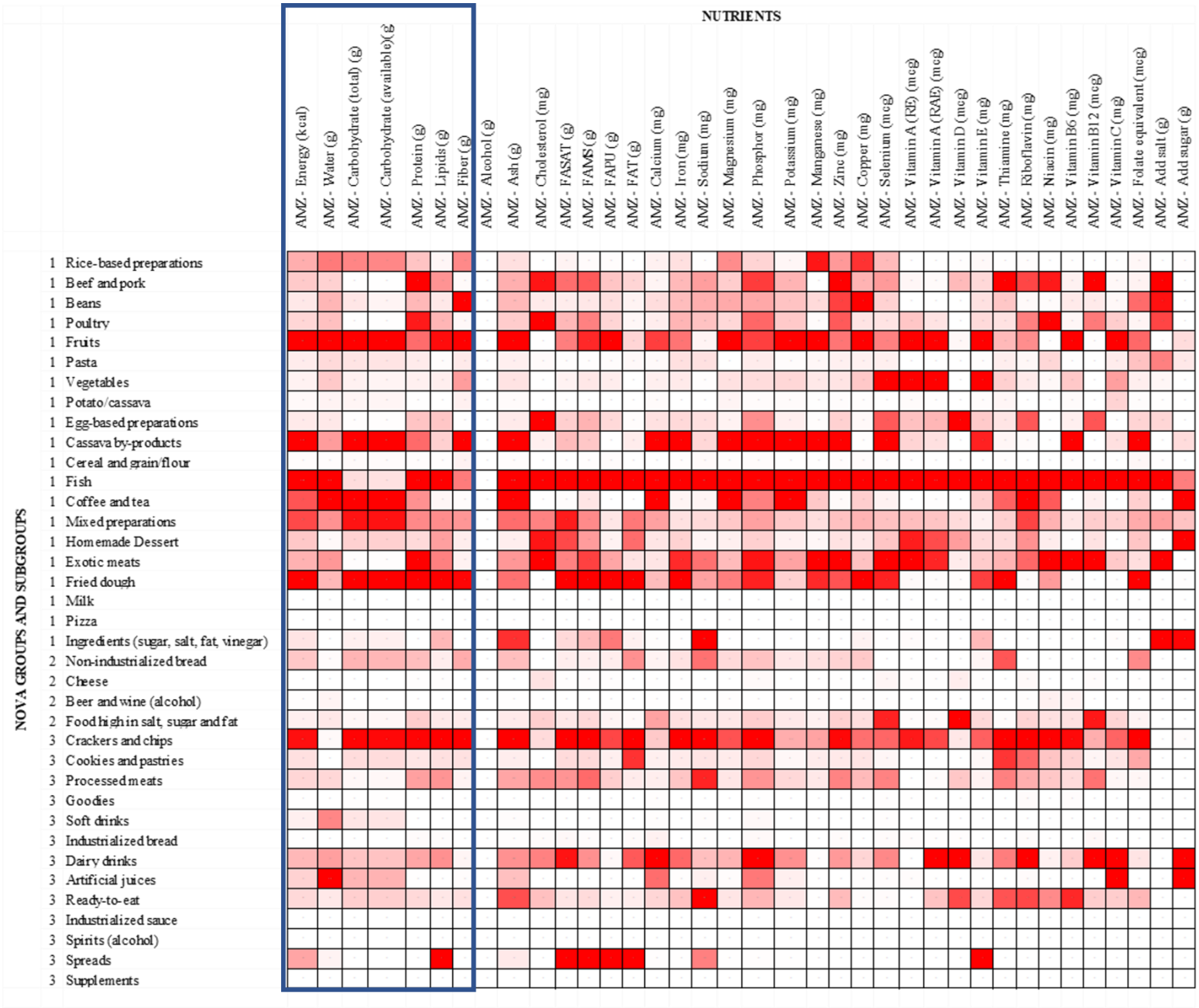
Percentile 90 (dark blue) and Percentile 10 (white) of NOVA subgroup contribution to nutrient intake among São Paulo Dwellers



Source: Author.

APPENDIX C

Percentile 90 (dark red) and Percentile 10 (white) of NOVA subgroup contribution to nutrient intake among Amazonian riverine



Source: Author.

APPENDIX D

Table below shows the main food contributing to NOVA subgroups among São Paulo dwellers and Amazonian riverine. Food names were kept in Portuguese to avoid loos accuracy with imperfect translation.

NOVA group and subgroup	São Paulo dwellers	Amazonian riverine
1.Rice-based preparations	Arroz branco, arroz integral.	Arroz banco.
1.Beef and pork[b]	Carne moída, bife, bife acebolado, lombo, carne em cubos, carne assada, estrogonofe de carne.	Carne bovina guisada.
1.Beans	Feijão carioca, feijão preto.	Feijão.
1.Poultry	Filé de frango grelhado, frango assado, frango desfiado.	Frango cozido.
1.Fruits	Suco de laranja, suco de uva, banana, mamão, maçã, melancia, laranja, manga, suco de maracujá, pera, meão, suco de tangerina, morango, suco de abacaxi.	Melancia, banana frita.
1.Pasta[a]	Macarrão.	Macarrão.
1.Vegetables	Alface, tomate, pepino, cenoura, repolho, agrião, castanha do Pará, brócolis, almeirão, couve refogada, repolho refogado, acelga, cebola.	Abóbora cabotian cozida, colorífico.
1.Potato/cassava[a,b]	Batata, purê de batata.	Tucupi (2).
1.Egg-based preparations[a,b]	Ovo frito.	Ovo frito.
1.Cassava products[a]	Farofa com bacon, farinha de mandioca.	Farinha de mandioca, farinha de tapioca, frito de goma.
1.Cereal and grain/flour[a,b]	Cuscuz, milho (4), aveia (4), pipoca (3).	Cuscuz (3).
1.Fish[a]	Filé de pescada à milanesa.	Peixe de água doce cozido, caldo de peixe, peixe frito, peixe assado.
1.Coffee and tea	Café infusão, café solúvel, chá mate, chá verde.	Café com açúcar, chá de capim santo, café com leite.
1.Mixed preparations[a,b]	Estrogonofe de frango, lasanha, tutu de feijão (3), molho bolonhesa (3), creme de espinafre (3), molho branco (3), baião de dois (3).	Mingau de arroz, feijão com macarrão.
1.Homemade Dessert[b]	Bolo simples, bolo com recheio e/ou cobertura, e tortas.	Bolo de trigo simples.
1.Exotic meats[a,b]	Koca burra (ave).	Tracajá, sarapatel de tracajá, mutum (ave).
1.Fried dough[a]	x	Frito de trigo.
1.Milk[b]	Leite (integral, desnatado e semidesnatado), leite em pó, iogurte natural, leite sem lactose.	Leite em pó (2).
1.Pizza[b]	Pizza.	x
1.Ingredients (sugar, salt, fat, vinegar) [b]	Açúcar, azeite de oliva, sal, vinagre, manteiga, óleos vegetais.	Sal.
2.Non-industrialized bread	Pão francês, pão baguete, pão italiano, sanduíche de frango (1), beirute de frango (1).	Pão torrado.
2.Cheese[b]	Queijo mussarella, minas e ricota, parmesão ralado e prato.	Queijo (1).
2.Beer and wine (alcohol) [a,b]	Cerveja.	Cerveja (1), vinho (1).
2.Food high in salt, sugar and fat[a,b]	Doce de banana, charque, palmito em conserva e chocolate amargo (Talento intense).	Charque (1), sardinha (1), bananada (1), almondega com farinha (1).

NOVA group and subgroup	São Paulo dwellers	Amazonian riverine
3.Crackers and chips	Batata palha, bolacha água e sal, salgadinho, bolacha club social.	Bolacha cream cracker, bolacha água e sal.
3.Cookies and pastries	Bolacha doce sem e com recheio/cobertura.	Bolacha doce simples, bolacha maria.
3.Processed meats[b]	Peito de peru, presunto, nuggets, calabresa, salame, salsicha, mortadela.	Salsicha frita, calabresa frita.
3.Goodies[b]	Achocolatado em pó, chocolate, brigadeiro/trufas, picolé/sorvete, sobremesas industrializadas, barra de cereal, bala, chicletes, adoçante.	Leite condensado (2).
3.Soft drinks	Coca cola, Guaraná.	Refrigerante de guaraná.
3.Industrialized bread[b]	Pão integral, pão de forma, bisnaguinha, pão de queijo, sanduíches tipo "Big Mc", batata frita, salgados assados.	Pão fatiado (1).
3.Dairy drinks	Iogurte, cappuccino, leite fermentado.	Composto lácteo, achocolatado.
3.Artificial juices	Suco de caju concentrado, suco de uva com açúcar, suco de pêssego UHT, suco de morango em pó, chá mate com limão.	Refresco industrializado com açúcar, refresco industrializado.
3.Ready-to-eat[a,b]	Farofa pronta, granola, cereal matinal, lasanha.	Mingau de nutrilon (3).
3.Industrialized sauce[b]	Molho de tomate industrializado, shoyu, catchup.	x
3.Spirits (alcohol) [a,b]	Caipirinha (1), amarula (1).	x
3.Spreads	Margarina, requeijão, maionese.	Margarina.
3.Supplements[a,b]	Sustagen, maltodextrina, fiber mais, whey.	x

Source: Author. x: no consumption. [a]: low consumption among São Paulo dwellers. [b]: low consumption among Amazonian riverine. The number in parentheses after the food name is the frequency that the food appeared in the database when this frequency was less than 5 times. Food in the sentence is ordered in decreasing order of frequency.

Source: Author.

APPENDIX E

Differential taxa in traditional and industrialized societies in different studies

	Traditional societies differential taxa		Industrialized societies differential taxa	
1	**ROSAS-PLAZA et al. (2022)**	**Phylum**	**ROSAS-PLAZA et al. (2022)**	**Phylum**
	Prevotellaceae (family)	Bacteroidetes	Bacteroidaceae (family)	Bacteroidetes
	Paraprevotellaceae	unknown	Lachnospiraceae (family)	Firmicutes
	Succinivibrionaceae (family)	Proteobacteria	Bifidobacteriaceae (family)	Actinobacteria
	Spirochaetaceae (family)	Spirochaetes	**Rikenellaceae (family)**	Bacteroidetes
2	**MCDONALD et al. (2018)**	**Phylum**	**MCDONALD et al. (2018)**	**Phylum**
	Mollicutes (class)	Tenericutes	**Rikenellaceae (family) (+ de 1)**	Bacteroidetes
	Muribaculaceae/S24-7 (family)	Bacteroidetes	Lachnospiraceae (family)	Firmicutes
	Prevotella (genus) (+ de 1)	Bacteroidetes	Bacteroides **(+ de 1)**	Bacteroidetes
	Ruminobacter (genus) - Succinivibrionaceae (family)	Proteobacteria	Blautia	Firmicutes
	Sarcina (genus)	Firmicutes	Coprococcus	Firmicutes
	Succinivibrio (genus) - Succinivibrionaceae (family)	Proteobacteria	Parabacteroides	Bacteroidetes
	Treponema (genus) (+ de 1)	Spirochaetes	Roseburia	Firmicutes
	Prevotella stercorrea (specie)	Bacteroidetes	Parabacteroides distasonis	Bacteroidetes
	Prevotella copri (specie)	Bacteroidetes	Bacteroides ovatus	Bacteroidetes
	Lactobacillus/Ligilactobacillus ruminis (specie)	Firmicutes		
3	**MANCABELLI et al. (2017)**	**Phylum**	**MANCABELLI et al. (2017)**	**Phylum**
	Brachyspira (genus)	Spirochaetes	Bacteroidales (order)	Bacteroidetes
	Treponema (genus) - lost	Spirochaetes	Barnesiella (genus) **- aquired**	Bacteroidetes
	Phascolarctobacterium (genus)	Firmicutes	Alistipes (genus)	Bacteroidetes
4	**DE FILIPPO et al. (2017)**	**Phylum**	**DE FILIPPO et al. (2017)**	**Phylum**
	Prevotellaceae (family)	Bacteroidetes	Barnesiella (genus)	Bacteroidetes
	Treponema (genus)	Spirochaetes	Alistipes	Bacteroidetes
	Succinivibrio (genus) - Succinivibrionaceae (family)	Proteobacteria	Sutterellaceae (family)	Proteobacteria
	Weissella (genus)	Firmicutes	Bacteroidaceae (family)	Bacteroidetes
			Lachnospiraceae (family)	Firmicutes
			Rikenellaceae (family)	Bacteroidetes
			Porphyromonadaceae (family)	Bacteroidetes

	Traditional societies differential taxa		Industrialized societies differential taxa	
			Enterobacteriaceae (family)	Proteobacteria
			Bifidobacteriaceae (family)	Actinobacteria
			Ruminococcaceae/Oscillospiraceae (family)	Firmicutes
			Bilophila (genus)	Proteobacteria
			Sutterella (genus)	Proteobacteria
			Parasutterella (genus)	Proteobacteria
			Odoribacter (genus)	Bacteroidetes
			Clostridium cluster XIVa (not formal taxonomy)	
5	**SCHNORR et al. (2014)**	**Phylum**	**SCHNORR et al. (2014)**	**Phylum**
	Prevotella (genus)	Bacteroidetes	Bifidobacterium (genus)	Actinobacteria
	Eubacterium (genus)	Firmicutes	Bacteroides (genus)	Bacteroidetes
	Oscillibacter (genus)	Firmicutes	Blautia (genus)	Firmicutes
	Butyricicoccus (genus)	Firmicutes	Dorea (genus)	Firmicutes
	Sporobacter (genus)	Firmicutes	Lachnospiraceae (unclassified) (family)	Firmicutes
	Succinivibrio (genus) - Succinivibrionaceae (family)	Proteobacteria	Roseburia	Firmicutes
	Treponema (genus)	Spirochaetes	Faecalibacterium (genus)	Firmicutes
			Ruminococcus (genus)	Firmicutes
			Erysipelotrichaceae (unclassified) (family)	Firmicutes
6	**DE FILIPPO et al. (2010)**	**Phylum**	**DE FILIPPO et al. (2010)**	**Phylum**
	Prevotella/Xylanibacter (genus)	Bacteroidetes		
	Treponema (genus)	Spirochaetes		
	Butyrivibrio (genus)	Firmicutes		

Source: Author.