REVIEW OF LITERATURE

The review of literature pertaining to the study entitled “Precision Nutrition Approach For Prevention and Management of Obesity”is discussed under the following heads:

2.1 Emerging science of nutritional genomics

2.2 Gene nutrient interactions: Connecting the dots between nutrients and the genome

2.3 Role of gut microbiome in diet and health

2.4 Gut microbiome & obesity

2.5 Defining a healthy microbiome

2.1 Emerging Science of Nutritional Genomics

2.1.1 Origin of Nutritional Genomics

The notion of nutrigenetics is not a novel concept; the influence of diet on health has ancient roots. With the advent of molecular genetics advancements in the latter part of the 20th century, researchers embarked on a quest to identify additional genes that interact with dietary constituents. By the 1980s, enterprises were commercializing the field of nutrigenomics. The Human Genome Project in the 1990s, which entailed the complete sequencing of human DNA, catalyzed the emergence of nutrigenomics as a scientific discipline. By 2007, scientists were uncovering myriad connections linking genes, nutrition, and pathological conditions. *(*Ahmed *et al., 2013)*

Nutritional genomics encompasses recognized intersections between food and hereditary genes, designated as 'inborn errors of metabolism,' that have been long managed through dietary manipulation. Illustrative instances include Phenylketonuria (PKU), traceable to a single gene mutation, prompting affected individuals to derive benefit from avoiding phenylalanine-containing foods. Galactosemia, arising from an inherited deficiency in one of three enzymes engaged in galactose metabolism, controlled with a milk-free diet, given that galactose is a metabolite derived from lactose or milk sugar breakdown. *(*Naser *et al.,2021)*

Recent methodological progressions in molecular biology and genetics have facilitated investigation into hereditary ailments at the DNA level and nutritional components

at the molecular scale. This exploration has spawned the formulation of concepts and investigations relating to genetic diversity and dietary reactions, denoted as nutrigenetics, along with evolutionary findings of diet and the influence of nutrients on gene expression, labeled as nutrigenomics. *(*Simopoulos*, 2010).*

The field of nutritional genomics holds significant potential for advancing personalized nutritional recommendations by elucidating the intricate interactions between genes and nutrients. Nutritional genomics encompasses two main branches: Nutrigenetics and Nutrigenomics. Nutrigenetics explores the impact of genetic variations on individual responses to diet, while Nutrigenomics investigates the influence of nutrients and bioactive compounds from food on gene expression patterns. To illustrate the distinction between nutrigenetics and nutrigenomics, consider the case of folate and the MTHFR gene. Folate, a vital micronutrient also known as vitamin B9, plays pivotal roles in DNA synthesis and the conversion of homocysteine to methionine, thereby contributing to cardiovascular health protection.*(Martinez, n.d.)*

The foundational principles underpinning genomic research can be summarized asfollows:

Common dietary components can directly or indirectly modulate human genetic material, leading to alterations in gene structure and expression.

Dietary factors may pose substantial risks for various diseases, particularly in specific circumstances and individuals.

Certain genes influenced by diet, along with their typical genetic variations, likely participate in the initiation, development, progression, and severity of chronic ailments.

The extent to which diet impacts the equilibrium between health and disease states may be contingent upon an individual's genetic makeup.

Precision dietary interventions based on an individual's nutritional needs, status, and genetic profile—referred to as "personalized nutrition"—can serve as preventive, palliative, or curative measures against chronic disorders. *(Farhud et al., 2017)*

2.1.2 What are Single Nucleotide Polymorphisms?

SNP, an acronym denoting Single Nucleotide Polymorphism, signifies instances wherein a solitary nucleotide is exchanged for another. Within the genomic framework, each SNP locus displays a potential quartet of nucleotide versions: A, C, G, and T. A depiction of SNP occurrence and its population-wide dissemination is depicted in the adjacent figures. Allelic disparities among SNPs manifest as minute differentials involving a solitary nucleotide alteration, primarily transitioning from A to G or C to T.

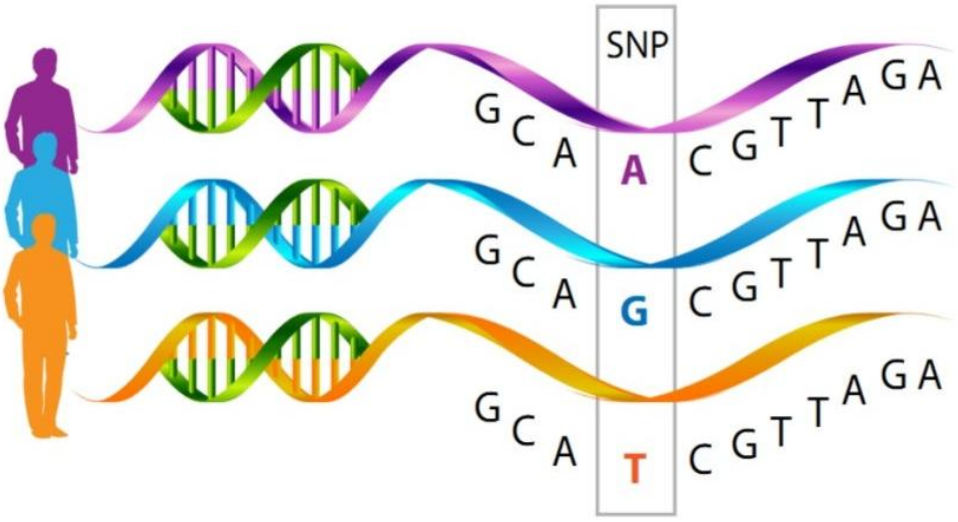

Figure.1 Single Nucleotide Polymorphisms (https://en.wikipedia.org)

It is noteworthy that not every solitary nucleotide alteration qualifies as an SNP. A classification as an SNP mandate that multiple iterations of a sequence exist, each being present in at least one percent of the overall populace. SNPs are widely dispersed throughout the human genome, manifesting approximately once every 300 nucleotide base pairs. This frequency equates to approximately 10 million SNPs within the comprehensive 3-billion-nucleotide human genome. The phenomenon of SNP is not a recent discovery; its recognition traces back to the advent of DNA sequencing in 1977.

SNPs hold the potential to prognosticate an individual's responsiveness to specific nutrients, pharmaceutical agents, vulnerabilities to environmental agents like toxins, and the

predisposition to ailments. Additionally, SNPs can be harnessed for tracing the transmission of disease-related genes within familial lineages. A paradigmatic instance of a prevalent SNP is observed in Ireland in relation to Cystic Fibrosis, a condition predominantly affecting the pulmonary and digestive systems. This SNP is situated on chromosome 7, influencing the CFTR gene. Dysregulation of chloride channels stemming from the SNP on chromosome 7 results in the accumulation of mucus and constricted air passages.

2.1.3 The new path to personalized nutrition

The notion of personalized, genotype-driven nutrition entails the integration of genotyping with specific dietary guidance to enhance the prevention of chronic illnesses associated with nutrition. Difference in genetic makeup among individuals and distinct ethnic groups influence the demands for nutrients, metabolic processes and reactions to dietary and nutritional interventions, thereby resulting in the variability in metabolic responses to specific diets among different individuals. The essence of personalized nutrition is to formulate comprehensive and easily adaptable nutritional recommendations by considering the interconnected parameters within an individual's internal and external milieu over their lifespan. In essence, personalized nutrition strategies encompass not only genetics but also encompass other factors such as eating patterns, dietary behaviors, physical activity, the composition of microorganisms in the body, and the chemical fingerprints of metabolism. The enhancement of healthcare can be realized by tailoring nutritional guidance in accordance with an individual's genetic constitution, observable traits, health status, dietary preferences, and environmental circumstances. *(Joost et al, 2006)*

Four primary factors substantiate the rationale for personalized nutrition:

(i) Genetic variation within the human genome, which influences how an individual responds to nutrients, their availability, and metabolic processes.

(ii) Cultural, economic, geographical, and taste-related distinctions among individuals that significantly impact food choices and availability.

(iii) Malnutrition, encompassing both excessive and deficient nutrient intake, can independently influence the expression of genes and the stability of the genome, leading to divergent physical characteristics during various life stages.

(iv) Generalized dietary guidelines for the population at large, such as recommended dietary

allowances (RDAs) or upper safety limits, which are predicated on diverse metabolic outcomes, might not be appropriate for individuals with distinct genetic compositions.
According to the International Society of Nutrigenetics/Nutrigenomics (ISNN, 2019), the future trajectory of precision nutrition should be deliberated upon at three tiers:

• Segmentation of traditional nutritional guidelines into subcategories within the population based on age, gender, and other social determinants.
• Tailored approaches derived from detailed and refined phenotypic characterization.
• Genetically guided nutrition rooted in uncommon genetic variations exhibiting pronounced penetrance and impact on an individual's response to specific foods.

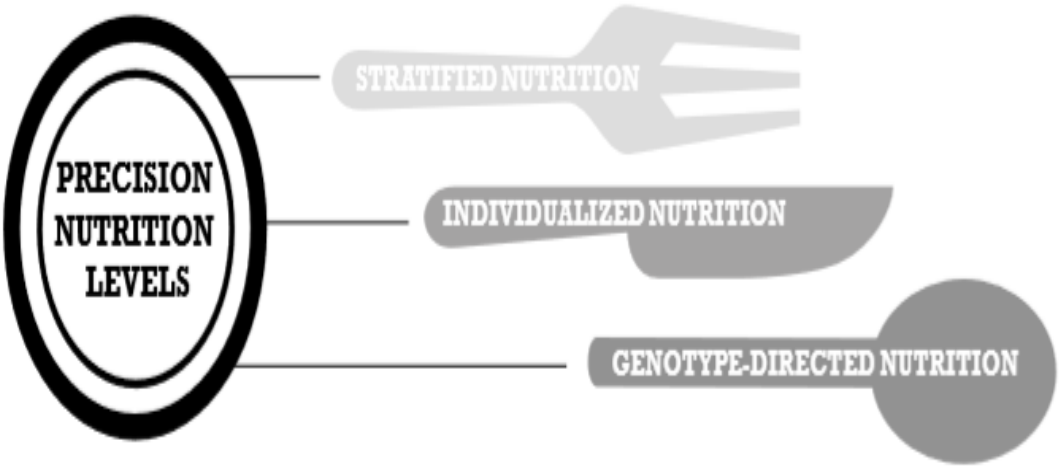

Figure 2. Different Levels of Precision Nutrition (Toro-Martin.,2017)

The American Society of Nutrition (ASN, 2020) has recently identified the understanding of the inter- individual variability in the response to diet as one of the six top research priorities in nutrition sciences. Moreover, the ASN has identified the required tools to attain these research needs such as omics technologies for enabling an accurate nutritional impact prediction on health, bioinformatics and database management for an enhanced patient information survey and the use of biomarkers, metabolomics for suitable assessment of disease progression and patient response to a nutritional treatment.

2.2 Gene Nutrient Interactions: An overview

2.2.1 Understanding Gene- environment interactions

Chronic diseases represent the phenotype of altered gene expression, as a result of interactions between environmental factors and genetic make-up (i.e. the inherited collection of 'susceptibility' and 'protective' genes). These interactions are conceptualised in the 'health pendulum'.

This summarizes the major influences, including genetic makeup that determine health outcome. Hence it is therefore a reasonable assumption that knowledge of interaction between gene and diet and other lifestyle factors will be of major help when assessing disease risk and when initiating preventive measure. For a given individual, the position along the health-disease continuum from which the pendulum is suspended depends on genetic make-up (indicated by the inherited collection of 'susceptibility' and 'protective' genes). Nutrition in utero and postnatal lifestyle interacts with genetic make-up to further modify the risk; i.e. each of these factors pushes the individual's pendulum to the right or the left. The net effect of these 'forces' will determine whether an individual is, or is not, healthy. Factors that enhance risk are shown in red, whereas those reducing risk appear in green. For emphasis, time is shown in a black box and has an arrow pointing to the right to indicate that, for most common non-communicable diseases, risk increases with age. (Arumugam *et al*., 2011).

2.2.2 Gene- Nutrient Interaction & Evolution

Human health is the result of constant interaction between genes and environmental factors. The most significant environmental factors are our diets and daily lifestyles. Of the over 3 billion base pairs of the human genome, 97 to 99% are identical among any two given individuals. Therefore, the fundamental processes of food metabolism in every human body are largely the same. This is why some general practices, such as eating healthy and staying active, are beneficial to everyone. However, the 1 to 3% genome difference among us makes us respond differently to different types of food. For example, descendants of hunting tribes are better-suited for high-protein diets while descendants of farming tribes are better-suited for high-carbohydrate diets. This is why personalized diets are necessary.

The genetic variations responsible for food metabolism are the result of millions of years of evolution during which there have been several major dietary transitions. During each transition, human genes were subject to natural selection to better suit the foods

available for survival.

About 2.5 million years ago, our human ancestors began to use stone tools, which led to increased hunting and meat consumption. During these hunter-gatherer years, food resources were limited and the human genome developed so-called “thrifty genes.” These genes promoted more efficient food utilization, fat deposition, and rapid weight gain during times of food surplus in order to give carriers a higher chance of survival during food shortage.

Around 100 to 200 thousand years ago, modern humans began to domesticate plants and animals. This transition made food more available but nutrient sources less diverse since diets were comprised of only a few domesticated plants and animals. Crops and livestock varied by region and, in response, genetic variations that suited regional diets were preferentially selected. (Azad *et al.*, 2013).The most dramatic transition of the human diet occurred within the last century. Industrialized food production made all kinds of food available in excess at extremely low prices. Since then, overeating has become an epidemic, especially in affluent Western countries. The advances of modern technology have also led to an increase in sedentary lifestyles and overall lower energy expenditure. This combination has resulted in rapid weight gain among human populations.Regardless of these dietary changes, the human genome has remained almost the same over the last 100 years. The 200 or so “thrifty genes” that were once advantageous are incompatible with modern diets and cause the “diseases of civilization” — chronic conditions.

A gene-culture coevolutionary perspective helps us to understand the process in which culture is shaped by biological imperatives while biological properties are simultaneously altered by genetic evolution in response to cultural history. Fascinating examples of such gene-culture coevolution can be found in the evolution of human diets.

Major events in hominid evolution can be viewed from a gene-culture coevolution perspective. More recently, the dietary shifts following the Neolithic Revolution provide fascinating examples of the interplay of cultural change and biological evolution. Contrary to popular belief, bipedality did not evolve to free hands for manufacturing and use of tools (an example of old teleological thinking not accepted by scientists). In fact, upright posture preceded tool-making by at least 2 million years. Indeed, Ardi, the celebrated and well-preserved specimen of Ardipithicus ramidus, seems to have moved upright already 4.4 million years ago, and the same may have been true for the much older Sahelanthropus

tchadensis. Bipedality, increasingly complex social behavior, tool-making, increased body size and dietary changes formed an adaptive complex that enhanced survival and reproduction in the changing African environment. Controlled use of fire had a great impact on the diet of our ancestors and helped colonization of all main continents by our species.

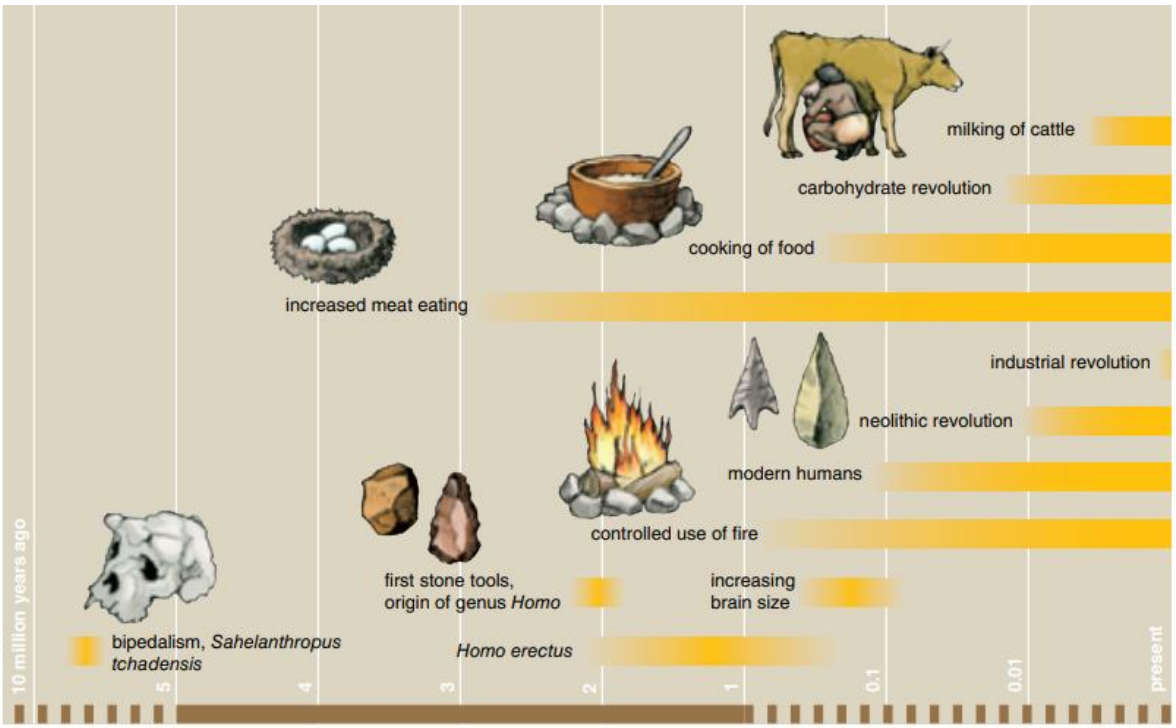

Figure 3. Major events in hominid evolution (Boyd., 2012)

The Neolithic or Agricultural Revolution, a gradual shift to plant and animal domestication, started around 12,000 years ago. For our species this cultural innovation meant, among many other things, that the proportion of carbohydrates in our diet increased considerably. Cereal grains have accounted for about 35 percent of the energy intake of hunter-gatherer societies, whereas it makes up one-half of energy intake in modern agricultural societies. Diets prior to the Neolithic differed considerably from what most people eat today. The contribution of protein to caloric intake declined significantly as evident from the data given in figure 3, which elicits the dietary intakes of Finnish young adults. In place of the missing protein came carbohydrates such as potatoes. This may have driven an increase in the copies of the human amylase salivary enzyme gene. (Boyd, 2012).

The Neolithic Revolution also included domestication of mammals, which in favorable conditions guaranteed a constant supply of meat and other sources of animal protein. Although fire likely played a role in the early utilization of carbohydrates, the big

shift in diet brought about by plant domestication has its roots in the interplay of cultural change and biological evolution. Sweet-tasting carbohydrates are energy rich and therefore vital for humans.

In the environment of Paleolithic hunter-gatherer populations, carbohydrates were scarce, and therefore it was important to effectively find and taste sweet foods. When eaten, large polymers such as starch are partly hydrolyzed by the enzyme amylase in the mouth and further cleaved into sugars, the sweet taste of which might have functioned as a signal for identifying nutritious food sources. (It is interesting to note that the fruit fly Drosophila melanogaster perceives the same compounds as sweet that we do.) Later, in the Neolithic agriculture, during which humans shifted to consumption of a starch-rich diet, the role of the amylase enzyme in the digestive tract became even more important in breaking down starch.

AMY1 gene makes salivary amylase (α-amylase), an enzyme in your saliva that starts the digestion of starch. The gene that makes amylase, AMY1, varies in copy number from person to person. And AMY1 genes have a huge copy number variant, from two to sixteen copies. More AMY1 genes mean more salivary amylase. More salivary amylase means you break down carbs more effectively, immediately.

Analyses of copy number variation in the human salivary amylase gene (Amy1) found that the copy number correlated with the protein level and that isolated human populations with a high-starch diet had more copies of Amy1. Furthermore, the copy number and diet did not share a common ancestry; local diets created a strong positive selection on the copy number variation of amylase, and this evolutionary sweep may have been coincident with the dietary change during early stages of agriculture in our species. It is interesting to note that the copy number variation appears to have increased in the evolution of human lineage: The salivary protein levels are about six to eight times higher in humans than in chimpanzees and in bonobos, which are mostly frugivorous and ingest little starch compared to humans.

Research studies found that salivary amylase gene (AMY1) copy number is correlated positively with salivary amylase protein levels, and that individuals from populations with high-starch diets have on average more AMY1 copies than those with traditionally low-starch diets. Comparisons with other loci in a subset of these populations suggest that the level of AMY1copy number differentiation is unusual. This example of positive selection on a copy number variable gene is one of the first in the human genome. Higher AMY1 copy numbers

and protein levels likely improve the digestion of starchy foods and may buffer against the fitness-reducing effects of intestinal disease. (De Filippo *et al*., 2010).

In 2007, researchers learned that people living in cultures that traditionally ate high starch diets had more AMY1 copy numbers and more amylase enzyme in their saliva. People living in historically agricultural societies like Japan had, on average, seven copies of AMY1, while people near the arctic circle in places like Yakut, Russia had, on average, four copies of AMY1.

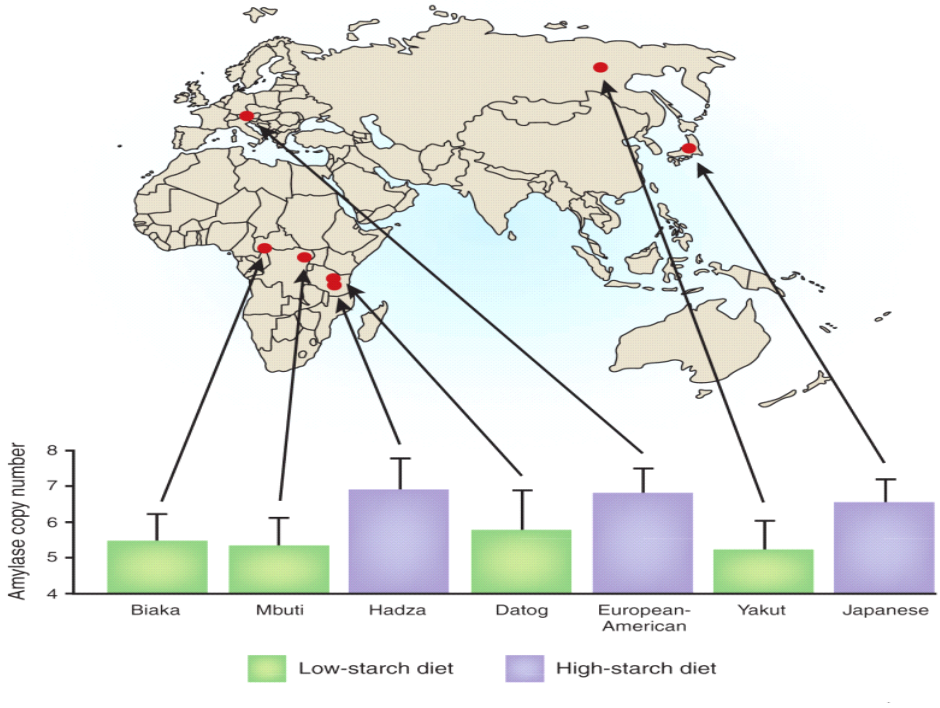

Figure.4 Copy number variations in Amylase gene and its interaction with high and low starch diet consumption pattern in various tribal populations (De Filippo *et al*., 2010).

A classic example of gene-culture coevolution is lactase persistence (LP) in human adults. Milk contains a sugar named lactose, which must be digested by the enzyme lactase before it can be absorbed in the intestine. The ability to digest milk as adults (lactose tolerance) is common in inhabitants of Northern Europe where ancient populations are assumed to have used milk products as an energy source to survive the cold and dark winters, whereas in southern Europe and much of Asia, drinking milk after childhood often results in gastrointestinal problems.

If the intestine is unable to break down lactose to glucose and galactose—due to lack of lactase or lactase-phlorizin hydrolase (LPH) enzyme, normally located in the villi of enterocytes of the small intestine—bacterial procession of lactose causes diarrhea, bloating and flatulence that can lead to fatal dehydration in infants. On the other hand, milk provides adults with a fluid and rich source of energy without bacterial contamination, enhancing their survivaland fitness. Therefore, in the past the phenotype of lactase persistence undoubtedly increased the relative reproductive success of its carriers.

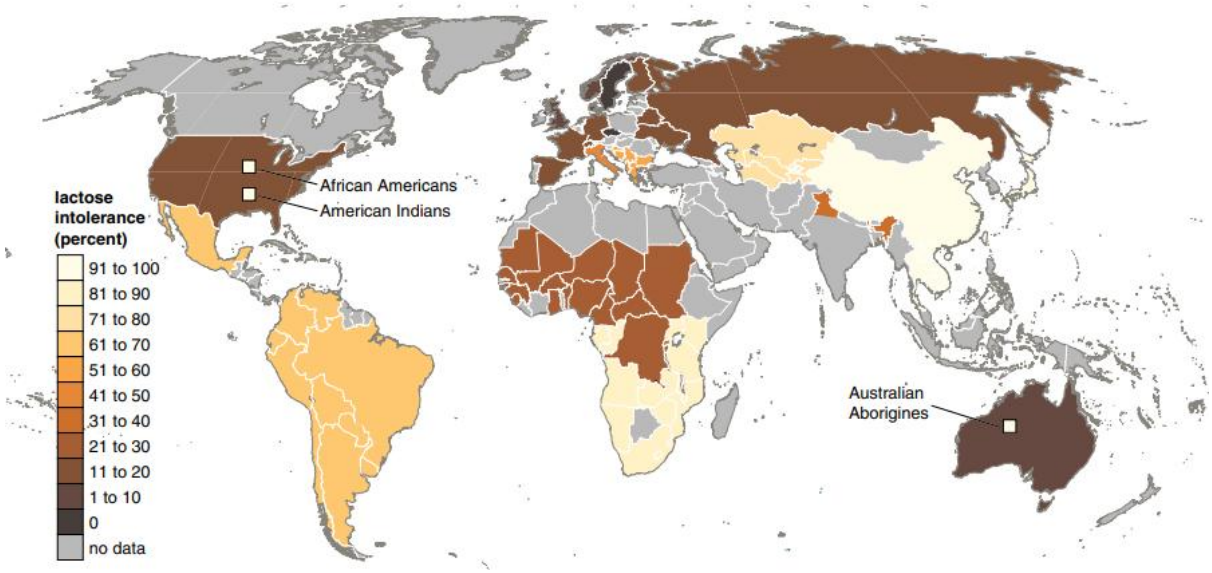

Figure 5. Global Prevalence of lactase persistence among adults (Itan *et* al., 2010)

Lactose intolerance in adult human beings is, in fact, the rule rather than the exception, although its prevalence may well be declining as the single nucleotide polymorphism that causes lactase persistence spreads. Note the wide variation in lactose intolerance over short geographic distances. Particularly in African cultures, the prevalence of dairy farming is strongly correlated to lactose tolerance. Gray areas indicated areas where no data are available.

Lactase persistence emerged independently about 10,000 to 6,000 years ago in Europe and in the Middle East, two areas with a different history of adaptation to the utilization of milk.

- The earliest historical evidence for the use of cattle as providers of milk comes from ancient Egypt and Mesopotamia and dates from the 4th millennium b.c. Still today

there are large areas of central Africa and eastern Asia without any tradition of milking, and many adults in these countries are physiologically unable to absorb lactose. The ancient Romans did not drink milk, and this is reflected in the physiology of their Mediterranean descendants today.

- The first evidence for a SNP as a causative factor in LP came from a group of Finnish families. A haplotype analysis of nine extended Finnish families revealed that a DNA variant (C/T-13910) located in the enhancer element upstream of the lactase gene associated perfectly with lactose intolerance and, because it was observed in distantly related populations, suggested that this variant was very old. Later it was shown that this allele had emerged independently in two geographically restricted populations in the Urals and in the Caucasus, the first time between 12,000 and 5,000 years ago and the second time 3,000 to 1,400 years ago.
- Saudi Arabian populations that have a high prevalence of LP have two different variants introduced in association with the domestication of the Arabian camel about 6,000 years ago.
- In Africa, a strong selective sweep in lactase persistence produced three new SNPs about 7,000 years ago in Tanzanians, Kenyans and Sudanese, reflecting convergent evolution during a similar type of animal domestication and adult milk consumption.

All these facts indicate that there has been a strong positive selection pressure in isolated populations at different times to introduce lactose tolerance, and this has taken place through several independent mutations, implying adaptation to different types of milking culture.

Different biological processes influence our personal response to carbohydrates when ingested. Accordingly, different genes related to these processes determine how carbohydrates affect our energetic balance and well-being. In this sense, carbohydrates are absorbed in different ways to reach the bloodstream. Oligosaccharides and polysaccharides must be hydrolyzed into their component disaccharidases (i.e., lactase, maltase, etc.). Then specific transporter proteins play essential roles in facilitating the diffusion (GLUTs proteins) or the active transport (SGLTs proteins) of the molecular units across the apical membrane of enterocytes. Namely, fructose transport is assisted by fructose transporter 2 and 5 (GLUT2, GLUT5) while glucose and galactose are preferably transported by the sodium/glucose transporter 1 (SGLT1). This process ends with the delivery of carbohydrates in the bloodstream.

2.2.3 Genetic Polymorphisms related to Appetite and Satiety

Energy intake is mainly influenced by your appetite (the desire to eat) and satiety (the sensation of fullness). Many signalling molecules and hormones control appetite and satiety in the cellular, peripheral and central nervous systems which in turn are affected by our genes. Genetic variations that cause increased appetite or reduced satiety are the major contributors to overeating or excess carbohydrate intake. In an environment of food surplus, people carrying these genetic variants are at a much greater risk for overweight and obesity.

(i) For instance, the agouti-related protein (AgRP) is a powerful orexigenic molecule. It promotes food consumption when ubiquitously overexpressed or when it is systematically administered. Interestingly, polymorphisms affecting AgRP have shown to modulate the appetite and to increase carbohydrate consumption at the expense of fat intake. Namely, lower saturated and monounsaturated fats were consumed by individuals' Ala67Thr higher when compared to Ala67Ala homozygotes. On the other hand, there are AgRP polymorphisms strongly linked to resistance to fatness and to resistance for developing type 2 diabetes in people with African ancestry.

(ii) Another factor related to obesity and carbohydrateintake is the dopamine receptor D2 (DRD2) gene, whichhas been already linked to food addiction. It seems thatone of the main reasons for that contribution is related tothe function of DRD2 as a key element in the regulationof the rewarding effects of foods in response to a dietwith high content of carbohydrates. In this sense, theC957T single-nucleotide polymorphism (SNP) in theDRD2 gene has been linked to lower sucrose consumption.

(iii) In contrast, higher sugar intakehas been linked to a TUB gene variant, also associatedwith higher glycemic load. TUB gene encodes the tubby protein homolog that has been linked to obesity, eating behaviour, andsensorineural degradation processes.

Genetic mutations in the appetite and satiety signaling systems have also been reported to cause extreme obesity due to an abnormally large appetite. For example, mutations in the LEP gene which makes the tonic satiety signal leptin, often lead to infants constantly feeling hungry and demanding food. These children often become

morbidly obese before their teens and require clinical attention. Similar traits have also been reported for mutations in the LEPR, PC1, and POMC genes, which are all involved in the leptin signaling pathway. However, these kinds of mutations are relatively rare in the general population.

In comparison, many overweight and obesity risk genes are widely distributed in the human population. These risk genes predispose their carriers to overweight and obesity if they live in an obesogenic environment with easy access to food and limited physical activity. Many of them are associated with overeating behaviour due to their effect on satiety. People who carry the risk gene variants often overeat without being aware of it. For example, people carrying one or two risk alleles of the FTO gene are less sensitive to satiety signals and may not sense fullness even when they have already eaten more than enough. Studies have shown that people carrying at least one FTO risk allele are 30% more likely to become obese in an environment of excess food. Carriers of risk variants of the MC4R, BDNF, and SH2B1 genes are similarly insensitive to satiety signals. Ironically, these so called “risk variants” were once beneficial to their carriers during time of food shortage over the course of human evolution. However, in our current state of constant food surplus, there is less opportunity to expend excess stored energy and these variants become a health hazard. (Flint *et al*.,2012)

Although there are many genes that influences the way we respond to carbohydrates. AMY1 gene makes salivary amylase (α-amylase), an enzyme in your saliva that starts the digestion of starch. The gene that makes amylase, AMY1, varies in copy number from person to person. And AMY1 genes have a huge copy number variant, from two to sixteen copies. More AMY1 genes mean more salivary amylase. More salivary amylase means you break down carbs more effectively, immediately.

Starch consumption is a prominent characteristic of agricultural societies and hunter-gatherers in arid environments. In contrast, rainforest and circum-arctic hunter-gatherers and some pastoralists consume much less starch. This behavioural variation raises the possibility that different selective pressures have acted on amylase, the enzyme responsible for starch hydrolysis.

Research studies found that salivary amylase gene (AMY1) copy number is correlated positively with salivary amylase protein levels, and that individuals from

populations with high-starch diets have on average more AMY1 copies than those with traditionally low-starch diets. Comparisons with other loci in a subset of these populations suggest that the level of AMY1copy number differentiation is unusual. This example of positive selection on a copy number variable gene is one of the first in the human genome. Higher AMY1 copy numbers and protein levels likely improve the digestion of starchy foods and may buffer against the fitness-reducing effects of intestinal disease. In 2007, researchers learned that people living in cultures that traditionally ate high starch diets had more AMY1 copy numbers and more amylase enzyme in their saliva. People living in historically agricultural societies like Japan had, on average, seven copies of AMY1, while people near the arctic circle in places like Yakut, Russia had, on average, four copies of AMY1. (Franzago*et al.*, 2022)

2.2.4 Genetic polymorphisms linked to taste preferences

The sense of taste has probably evolved to allow animals to choose and consume appropriate food. The most common natural taste stimuli that humans describe as sweet are sugars. Sugars are important nutrients that are recognized by the taste system and evoke appetitive consummatory response. It is well known that genetic factors influence taste perception. Genes encoding taste receptors have been identified and genetic variability of sweet, umami, and bitter perceptions have been intensely investigated, although knowledge gaps exist for sour and salty perception.

Numerous scientific studies have shown that moderate alcohol consumption (defined as 1-2 drinks per day) is associated with reduced risk for heart disease. Remarkably, these results have remained consistent over the years and are true for both men and women regardless of obesity and other risk factors. Recent findings indicated that modest drinking may only benefit those who carry the A allele at SNP# rs708272 (also known at the B2 allele of TaqIB SNP) within the CETP gene. About 40% of the general population carries this heart-protective A variant**.**

Alcohol consumption can also be particularly dangerous to individuals of Asian descent who are more likely to carry a variant in their ALDH2 gene (A allele at rs671) that hinders their ability to breakdown alcohol. This trait is commonly referred to as the “Asian Flush.” This reduced ability to breakdown alcohol leads to an increased risk of certain cancers in “flushed” individuals who consume alcohol.

Other variants in genes that are involved in the brain's emotion and reward centres increase an individual's chances of forming addictive tendencies and may lead to alcoholism. These SNPs are: the G allele at rs1799971 within the opioid receptor (OPRM1) or the A allele at rs1042173 within the SLC6A4 gene (associated with Caucasians only) (Caledron*et al.*, 2022).

2.3 Role of gut microbiota in diet and health

The microbiota of human gut contains a plethora of microbes, providing a platform for metabolic interaction between the host and microbiota. The gut microbiota produces metabolites that act as a link between gut microbiota and its host. These metabolic interactions happened to be decoded due to recent advances in the defining the gut microbiota and its symbiotic relationship with the host. A crucial component for dietary metabolism is human gut microbiota and is characterized by the genetic, epigenetic and dietary factors. The metabolic potential of gut microbiota explains its significance in host health and diseases.(Yadav et al., 2018)Various factors influence the gut microbiota composition which includes, mode of birth, age, life style, health status and genetics, but diet is considered among the most crucial factors impacting on the human gut microbiota *(Oriach et al., 2016).*

One of the most topical areas of human nutrition is the role of the gut microbiota in diet and health. In particular, this involves interactions between the in-habitant microbiota and dietary ingredients. Recent studies shows that the gut microbiota consists of pathogenic, commensal and beneficial microbiome. Many studies convince that the gastro intestinal disorders such as irritable bowel syndrome, bowel cancer, neonatal necrotising enterocolitis and ulcerative colitis are induced by pathogenic gut microbiota. It is apparent that the composition of gut microbiota can be altered through diet. In view of the fact of their perceived health-promoting status, bifidobacteria and lactobacilli are the commonest microbes used as probiotics. Probiotics involve the use of live microorganisms in food; prebiotics are carbohydrates selectively metabolized by desirable moieties of the indigenous flora; synbiotics combine the two approaches *(Steer et al., 2000).* A strong evidence has provided by current researches for the role of the commensal gut microbiota in brain function and behaviour. Many potential pathways are involved in this bidirectional communication between the gut microbiota and the brain such as immune mechanisms, the vagus nerve and microbial neurometabolite production. Dysbiosis of gut microbial function has been

associated with behavioural and neurophysical deficits *(Oriach et al., 2016).*

Microbial communities colonize different regions of the human gut , it impacts many aspects of health. In the healthy state, they bestow many functions such as (i) providing nutrients and energy to the host by fermenting non-digestible dietary components (ii) vitamins, essential amino acids biosynthesis and (iii) perpetuating balance with the host's metabolism and immune system. An imbalance of these microbial communities results in involvement in gastrointestinal diseases like inflammation and infection of gut, and possible contributions to diabetes mellitus and obesity *(Flint et al., 2012).* The equilibrium of healthy and unhealthy gut microbial communities depends on factors like distribution, diversity, species composition and metabolic outputs as illustrated in figure 6.

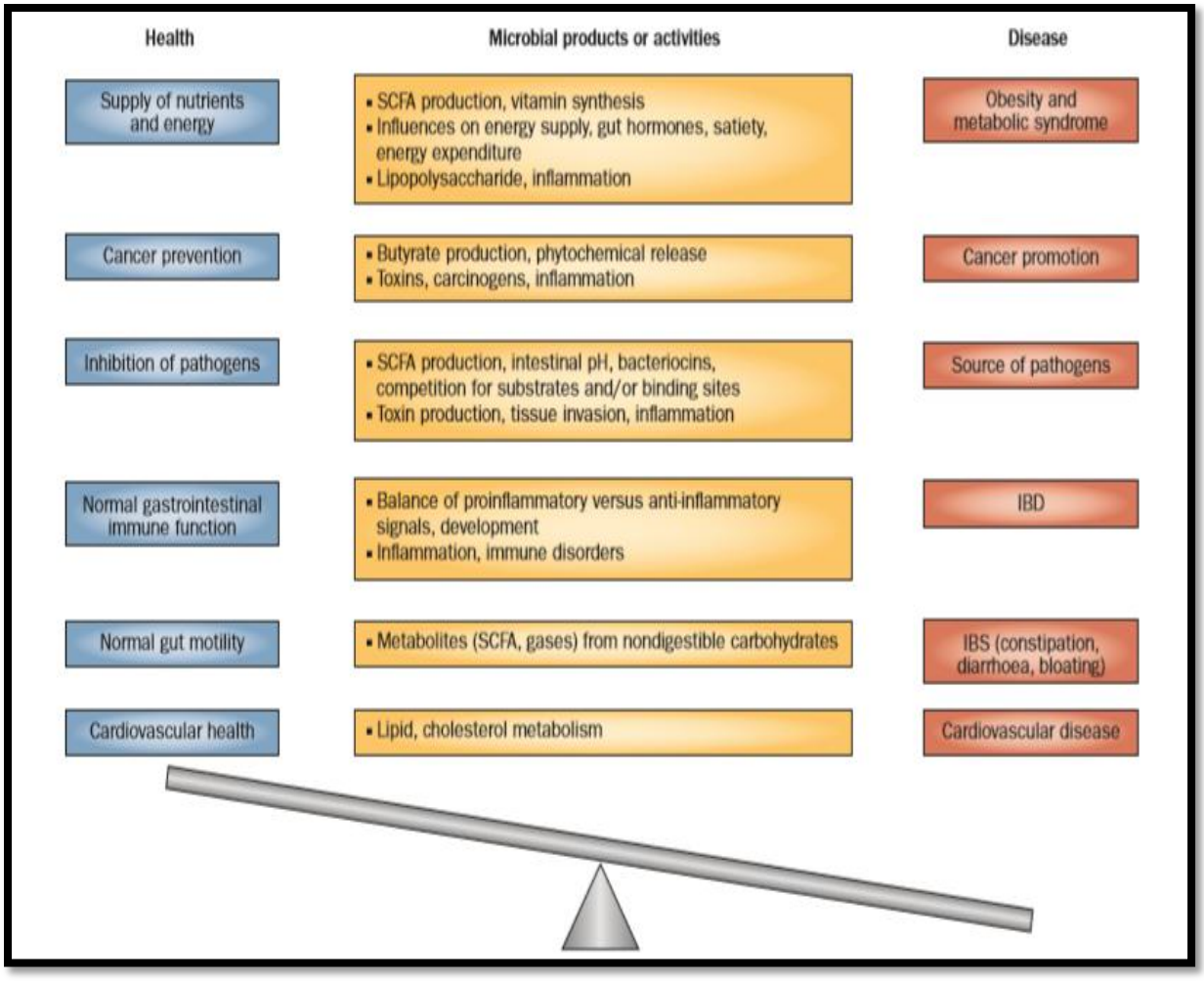

Figure: 6 Functions of gut microbiome and factors effecting the balance of gut microbiome *(Flint et al., 2012)*.

In recent years, our understanding on the importance of the human gut microbiota and their role in human diet and health has greatly expanded because of the availability of molecular methods to study the gut microbiota *(Ramakrishna, 2007).*

2.3.1 Composition of the gut microbiota

Earlier, the gut microbiota was assumed to be composed of 400–500 species of microbes, but the availability of molecular methods suggest that there are greater than 1000 species in the gut of each individual and that the number of species and its diversity increases with age *(Yatsunenko et al., 2012*). The predominant phyla of gut bacteria are the Firmicutes, the Bacteroidetes, and the Proteobacteria, while Actinobacteria contribute to a small fraction of the total bacteria. The phyla Firmicutes include an enormous number of Clostridium genera, followed by some Eubacterium, Faecalibacterium, Roseburia, and Ruminococcus. The phyla Bacteroidetes include bacteria belonging to genus Bacteroides and genus Prevotella. The major genus belonging to phylum Actinobacteria in the human gut is Bifidobacterium (*Arumugam et al., 2011).*

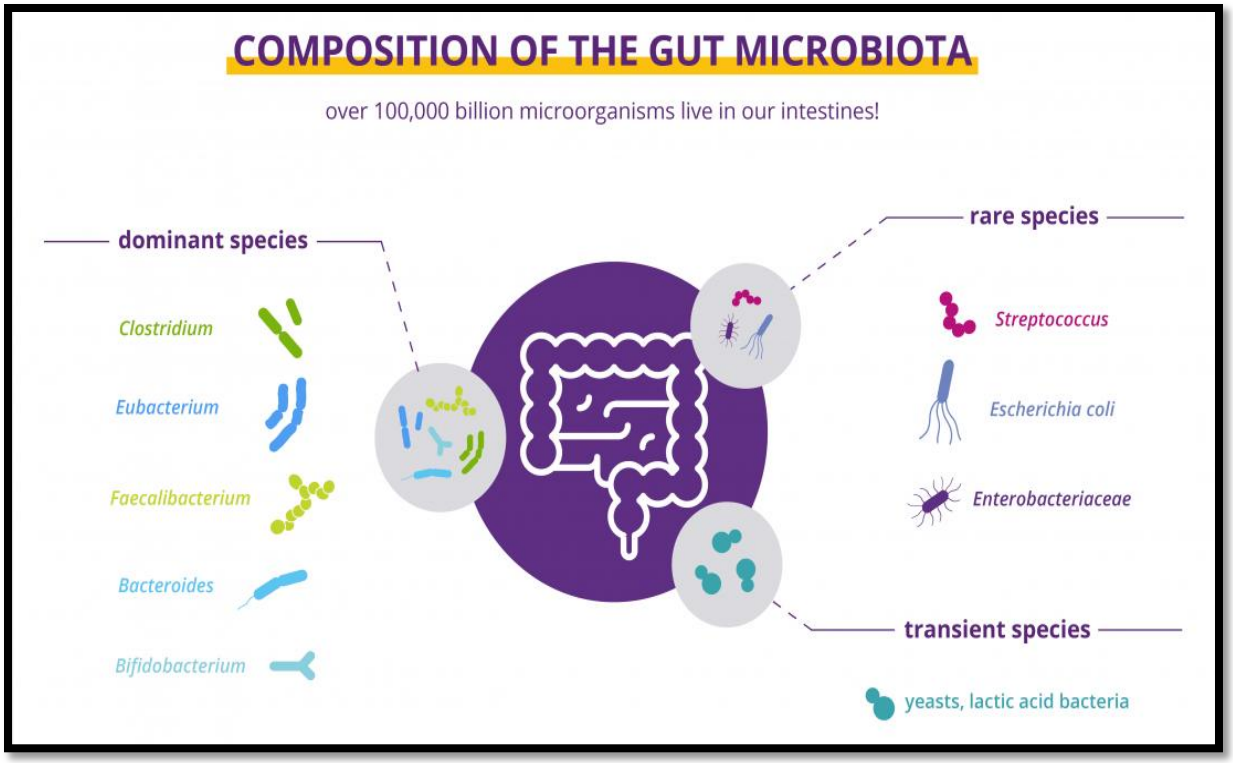

Figure 7: Composition of gut microbiota showing dominant, rare and transient species (Biocodex Microbiota Institute Presentation).

The infant gut is believed to be sterile in utero and acquires microbes during the process of birth but the main source of an infant's gut microbiota is the maternal gut. During the last decade, it has become obvious that maternal commensal microbes or their products are transferred to the foetus through the placenta in utero and/or postnatally *(Miko et al., 2022).* Almost immediately microbial colonization of the gut appears to reach maximal levels.The diversity of the various phyla of the gut microbiota changes presumably in response to changing in dietary patterns. Remarkable numbers of carbohydrate-fermenting bacteria appear at the time of weaning, that includes Bacteroides-Prevotella and Clostridium coccoides-Eubacterium rectale *(Kabeerdoss et al., 2013).* The diversity of gut microbiota continues to change during childhood and adolescence. The genus Bifidobacterium is abundant in children and declines in abundance with age,the genus Bacteroides increases through childhood and adolescence and became very abundant in adults, while E. rectale is most abundant in adolescents and declined in adults. Diet is presumed to be the primary factor for these changes in microbial diversity with increase in age *(Balamurugan et al., 2008).*

2.3.2 Gut Microbiota Metabolism and formation of SCFA

The human gut contains numerous mutualistic microbes that provides various specialized metabolites, and bioactive molecules that triggers immune system and host metabolic pathways. Hence, the gut microbiota is named as a "metabolic organ" with a metabolic potential same as that which the liver (O'Hara & Shanahan, 2006). The gut microbiota metabolizes indigestible complex carbohydrates leading to the formation of short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate *(Olofsson &Bäckhed, 2022*). The indigestible dietary carbohydrates includes certain forms of resistant starch and non-starch polysaccharides *(Kumar et al., 2012).* These indigestible dietary carbohydrates fermented by gut microbiota to SCFA, lactate, and gases such as CO_2, H_2, and methane (Fig. **8**).

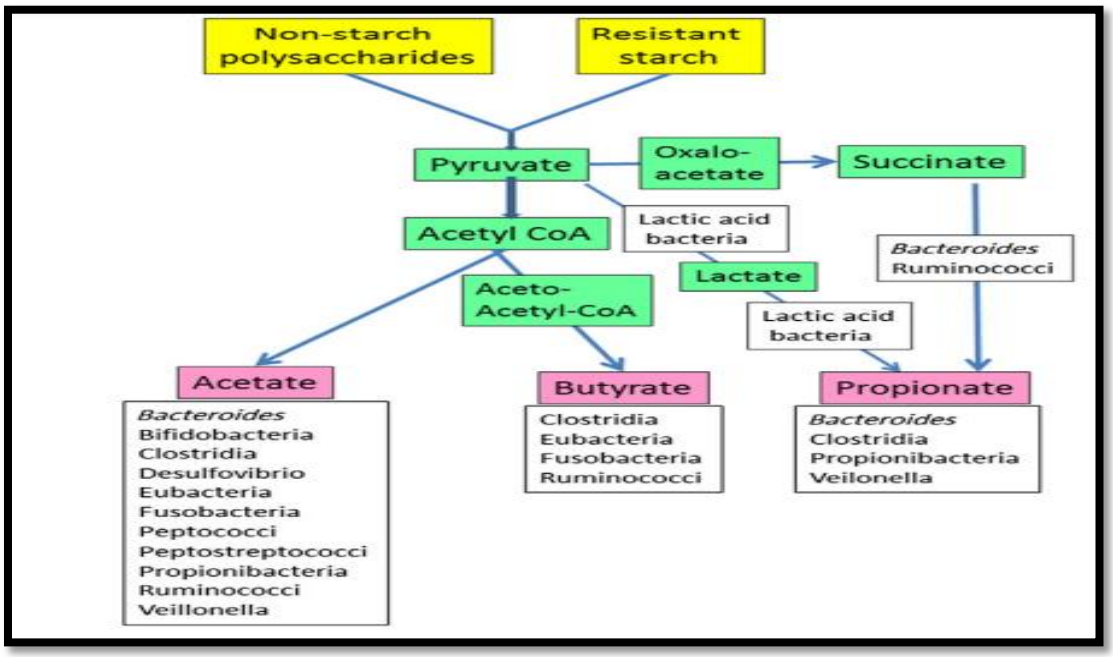

Figure 8: Formation of the three major short-chain fatty acids - acetate, propionate, and butyrate by gut microbial fermentation of resistant starch and non-starch polysaccharide (Hosseini *et* al., 2011)

Butyrate provides the major energy source for colonic epithelial cells *(Ramakrishna & Roediger, 1990).* Acetate and propionate are absorbed into the portal circulation and metabolized in the liver. A proportion of acetate produced in the colon by bacterial fermentation reaches the peripheral circulation as detected by elevation in circulating blood levels of acetate following oral administration of non-digestible carbohydrate *(Muir et al., 1995)*. Propionate is metabolized in the liver, and acts in reducing serum cholesterol and blood glucose *(Hosseini et al., 2011).*

2.3.4 Gut microbiota and glucose metabolism

The gut microbiota plays a fundamental role in human nutrition and metabolism, presumed to have direct implications for type 2 diabetes, and associated preconditions *(Palmnäs-Bédard et al., 2022*).Human observational studies show significant differences in the composition and function of the gut microbiota between healthy individuals and people with prevalent type 2 diabetes *(Koh &Bäckhed, 2020).* The main proposed molecular mechanisms by which the gut microbiota modulates and interferes with host glycemic control includes : modulation of incretin secretion, short chain fatty acid production, bile acid transformation, and regulation of adipose tissue inflammation.

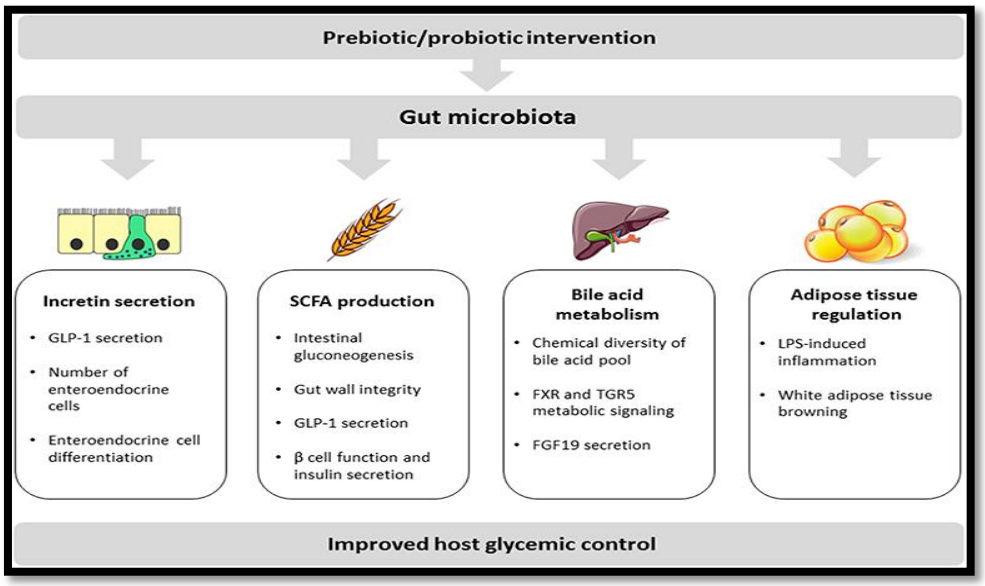

Figure 9: Key mechanisms linking the gut microbiota with host glycemic regulation. (1) Increase of incretinsecretion. (2) SCFA production. (3) Bacterial metabolism of bile acids. (4) Adipose tissue regulation. (Gérard, C., & Vidal, H. (2019).

Incretin hormones, are gut peptides released from enteroendocrine cells.They are mainly represented by glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). These incretin hormones are secreted into the blood stream and rapidly stimulates insulin secretion from beta cells *(Drucker, 2018).*

Short chain fatty acids (SCFA) are organic fatty acids that are produced in the human gut following the anaerobic fermentation of non-digestible dietary fibres by gut microbiota. Acetate, propionate, and butyrate represent 95% of SCFA, and are among the most abundant microbiota-derived compounds (Macfarlane & Macfarlane, 2012). Propionate and butyrate have been described to stimulate intestinal gluconeogenesis, via different mechanisms at a local level. In particular, butyrate induces the expression of genes involved in intestinal gluconeogenesis through a cAMP-dependent mechanism, while propionate acts itself a substrate of intestinal gluconeogenesis and activates gene expression via a gut-brain neural circuit *(De Vadder et al., 2014).*

2.3.5 Gut microbiota and lipid metabolism

Given its regulatory role in host lipid metabolism, gut microbiota has been highly associated with hyperlipidemia and related diseases *(Jia et al., 2021*).Certain gut microbiota,

particularly lactobacilli, have the ability tohydrolyze bile salts by producing the enzyme bile salt hydrolases. This interferes with the enterohepatic cycle of bile salt reabsorption, leading to increased fecal bile salt loss and secondary reduction of serum cholesterol due to diversion of cholesterol to bile acid synthesis *(Hosseini et al., 1995)*. The other mechanism being the inhibitory effect of propionic acid (synthesized by gut bacteria) on 3-Hydroxy-3-Methyl Glutaryl-Coenzyme A synthase activity in the liver leading to reduction in cholesterol synthesis *(Lin et al., 1995).*

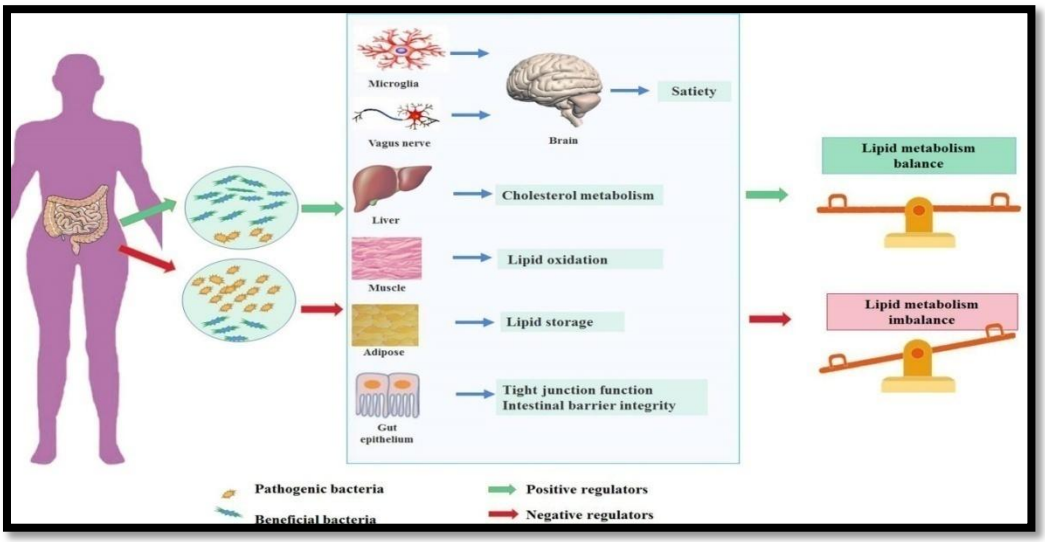

Figure 10: Impact of gut microbiota in the lipid metabolism. *(Jia et al., 2021*)

2.3.6 Gut microbiota and protein metabolism

Dietary amino acids are not only absorbed and metabolized by enterocytes but also available to the microbiota in the gut in mammals.Besides host physiological factors, recent studies demonstrated that human gut microbiota in the small and large intestine plays a role in host dietary protein metabolism. Metabolites produced through fermenting amino acids by gut microbiota can affect host protein/amino acid uptake and metabolism, as well as can affect host cell physiology *(Davila et al., 2013*). Gut microbiota can also synthesize amino acids that can be provided to the host (Metges, 2000). Amino acids produced by gut microbiota that are accessible to the host may be useful to compensate indispensable amino acid deficiency in low quality protein diets *(Portune et al., 2016).* The protein entering the colon and subject to microbial metabolism is more likely to be host derived with some contribution from unabsorbed dietary protein. Protein fermentation leads to the production of branched-chain amino acids and to a variety of phenolic and other metabolites that may be toxic to the host. These are largely detoxified in the intestinal wall and the liver *(Ramakrishna et al., 1989).*

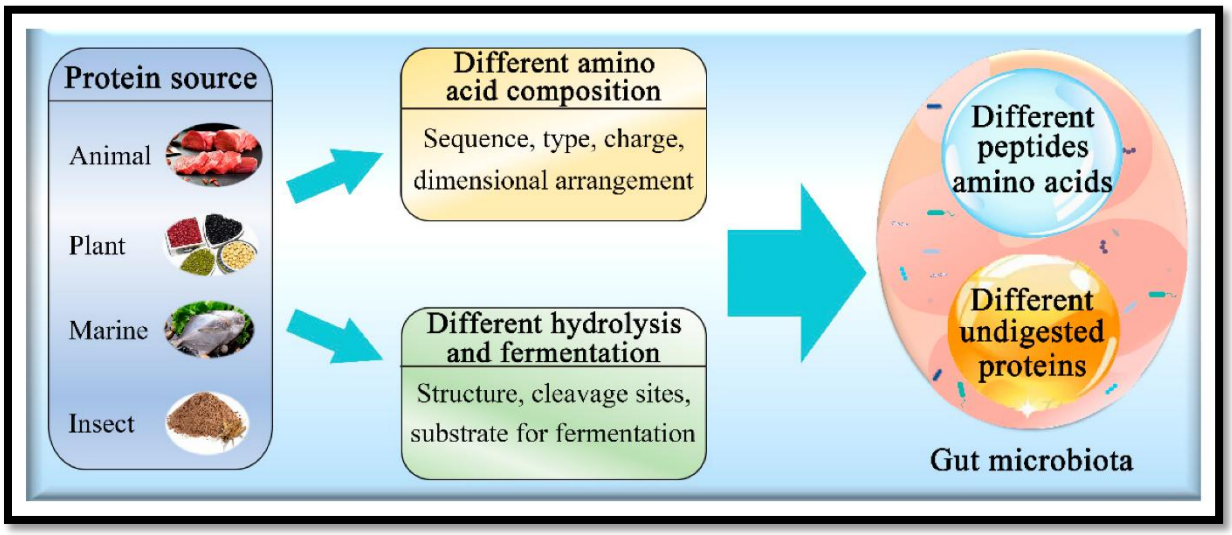

Figure 11. The effect of different protein sources on gut microbiota.

***(Portune et al., 2016*)**

2.3.7 Gut microbiota and mineral absorption

The human gut microbiome comprises several bacteria that possess the ability to affect the host mineral status. Gut microbiota synthesise a wide range of enzymes that helps in the release of minerals from dietary sources. Gut microbiota also influence the mineral absorption rate at the gastrointestinal level directly *(Bielik &Kolisek, 2021).* Among bacterial enzymes, enzyme phytases hydrolysis phytic acid present in many plant-based foods consumed with the diet and release bioavailable forms of inorganic minerals, such as calcium, magnesium, iron, and phosphorous (Bohn et al., 2007). On the other hand, carbohydrate-fermenting bacteria produce SCFA and reduce the luminal pH in the right colon, effects that stimulate the absorption of divalent cations through transporters in the cecum *(Scholz-Ahrens &Schrezenmeir, 2007).* As lactobacilli are involved in the conversion of lactate to propionate in fermentation systems,this provides a plausible explanation for a causal link between reduction of lactobacilli and iron-deficiency anemia.

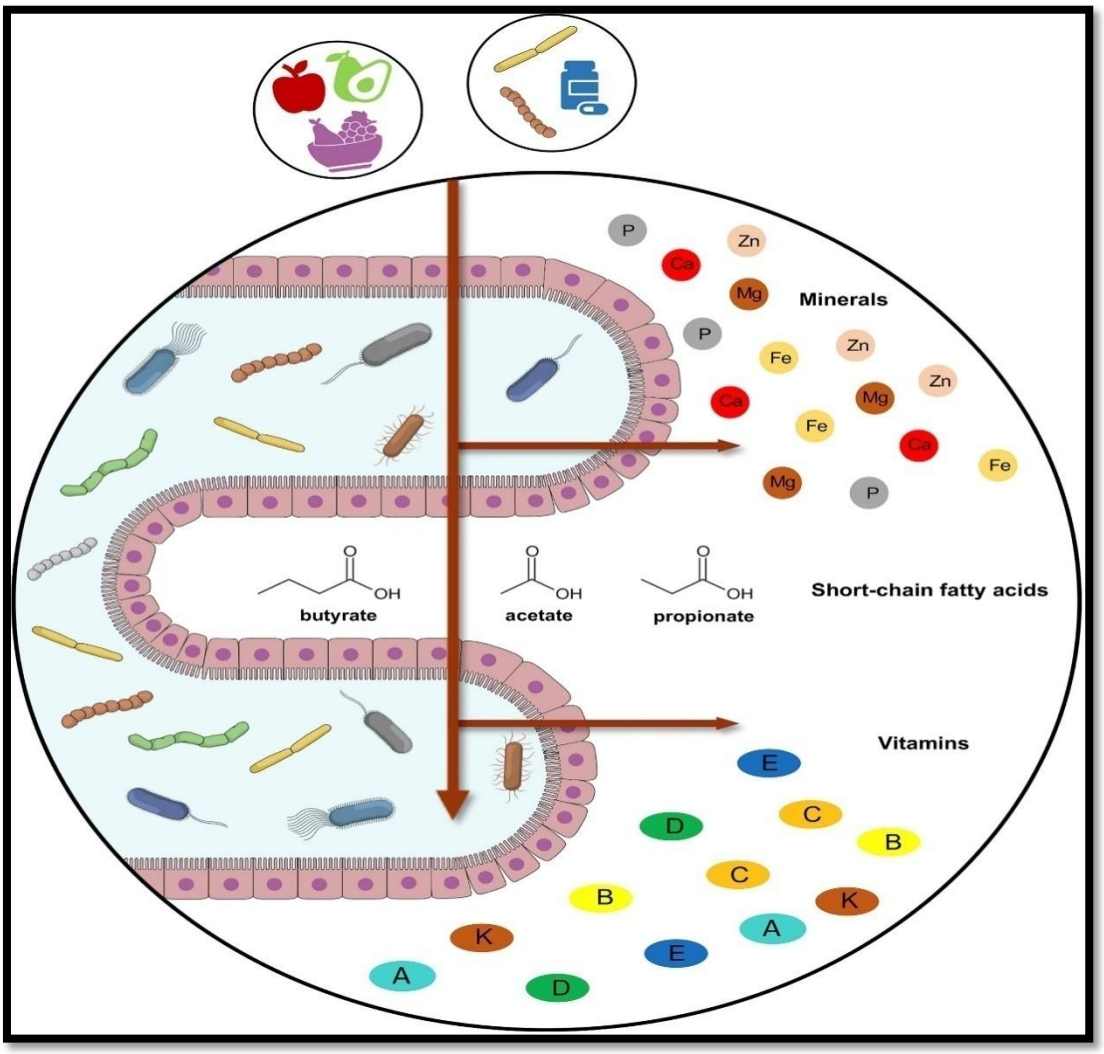

Figure 12 : Micronutrient interchange between the gut microbiome and the host.

(D'Amico et al., 2023)

Micronutrients and the gut microbiome interact along a bidirectional axis. Dietary micronutrients affect the composition and functionality of the microbiome, and the latter can influence the bioavailability of micronutrients, for example, by synthesizing vitamins and controlling the absorption rate. In particular, the absorption seems to be favored by the generation of short-chain fatty acids, end-products of the microbial fermentation of polysaccharides *(D'Amico et al., 2023).*

2.4 Role of gut microbiota in obesity

Exponential increase in obesity rates cause concern about health risks associated with rising obesity has become nearly universal. During the previous three decades, the mean body mass index (BMI) and the prevalence of obese and overweight individuals increasing worldwide. Unfortunately, prevention and treatment of obesity and related complications have proven complex, and successful strategies to tackle this pathology remain limited. Epidemiological studies have highlighted potential environmental exposures, including - diet, energy expenditure, early life influences, sleep deprivation, endocrine disruptors, chronic inflammation, and gut microbiome status, is contributing to higher risk of obesity *(Franks & McCarthy, 2016).* Among these, the microbiome has received extensive attention during the previous decade.

Variation in gut microorganisms might play an important role in the pathogenesis of obesity. Although the composition of intestinal microbiota is highly diverse in healthy individuals, those exhibiting overall adiposity, insulin resistance and dyslipidemia are characterized by low bacterial richness *(Le Chatelier et al., 2013*). Moreover, composition of gut microbiota in obesity individuals differs from that in lean individuals, although inconsistent changes have been reported. *Bacteroidetes* prevalence is lower in obese people, with this proportion increasing along with weight loss based on a low-calorie diet *(Ley et al., 2006a). Lactobacillus* and *Clostridium* species are associated with insulin resistance, with *Lactobacillus* positively correlated with fasting glucose and HbA1c levels, whereas *Clostridium* showed a negative correlation with these parameters (Karlsson et al., 2013). These data suggest that specific bacterial phyla, class, or species or bacterial metabolic activities could be beneficial or detrimental to the onset of obesity.

Impact of gut microbiota on local and distant organs contributes to obesity development and progression. In local tissues, obesity-associated gut microbiota have an increased capacity to harvest energy from the diet, stimulate gene reprogramming in the colon, change polypeptide hormones and other bioactive molecules released by EC cells, decrease the intestinal barrier, and disturb immune homeostasis. Gut microbiota also communicate with host adipose tissue and the liver and brain. Microbiota-fat-signaling axis. Gut microbiota participates in the regulation of adipogenesis through distinct mechanisms. LPS triggers an immune response along with inflammation and immune-cell infiltration.

SCFAs also participate in insulin-mediated fat accumulation in adipocytes via activation their receptors GPR43 and GPR41, which inhibits lipolysis and encourages adipocyte differentiation *(Sun et al., 2018).*

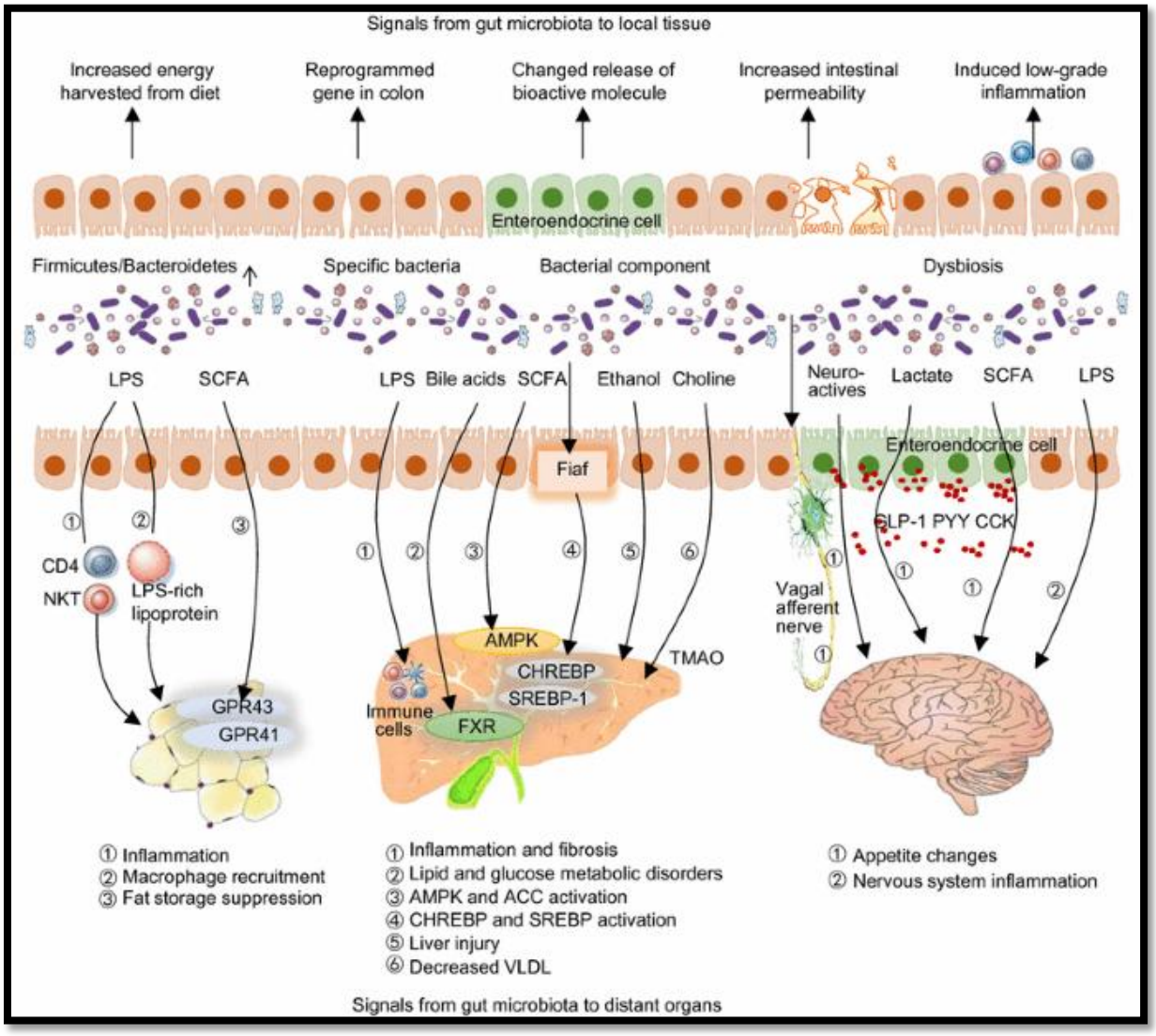

Figure 13: Changes in molecular signalling chemicals released by bacteria in contact with local tissue or distant organs. *(Sun et al., 2018)*

Some mechanisms have been proposed to explain the role of gut microbiota in obesity development.

2.4.1 Short Chain Fatty Acids

The gut microbiota metabolizes energy from the diet, e.g., indigestible dietary fibers, which are chemically polysaccharides and oligosaccharides. They are converted into short chain fatty acids (SCFA), such as acetate, propionate, and butyrate. After absorption, SCFAs can induce lipogenesis and increase triglyceride stores through molecular pathways. They activate the carbohydrate-responsive element-binding protein and the sterol regulatory element-binding transcription factor 1, both involved in the process of lipogenesis. The rate of SCFA metabolism can establish the direction of host energy balance by increasing the effectivity of calorie uptake. Moreover, SCFAs suppress the fasting-induced adipocyte factor, which inhibits lipoprotein lipase, inducing triglycerides accumulation in adipocytes (Rosenbaum et al., 2015). Dietary fibers, which are the main source of SCFAs, are suggested to have a protective effect for maintaining a healthy body weight. Several mechanisms have been suggested for how SCFAs may participate in the development of obesity:

(1) SCFAs provide an extra energy source (approximately 10% of daily energy requirement) and contribute to extra fat deposition in the body;
(2) SCFAs are ligands for G protein-coupled receptor GPR 41 and GPR43, which are expressed in the intestinal epithelium, immune cells, and adipocytes and are responsible for regulating energy expenditure;
(3) Regulation of fasting-induced adipose factor;
(4) de novo lipogenesis;
(5) Regulation of glucose homeostasis;
(6) Regulation of leptin secretion via free fatty acid receptor; and
(7) Modulation of satiety response *(Cuevas-Sierra et al., 2019).*

2.4.2 Adenosine monophosphate kinase (AMPK) and fasting-induced adipose factor

Adenosine monophosphate kinase (AMPK) and fasting-induced adipose factor (Fiaf) are circulating lipoprotein lipase inhibitors. Gut microbiota can decrease liver fatty acid oxidation by suppressing AMPK and Fiaf , which causes increased fat accumulation (38). The bacterial suppression of the expression of Fiaf and AMPK in the liver and skeletal muscle, leads to weight gain from a carbohydrate and fat rich diet. Fiaf is produced by the intestine, liver, and adipose tissue. Inhibition of Fiaf results in increased activity of LPL,

which mediates cellular uptake of triglycerides and accumulation of triglycerides in adipocytes.

2.4.3 Bile Acids

A reduced bile acid concentration in the gut has been associated with bacterial overgrowth and inflammation *(Cerdó et al., 2019).* Recent studies suggest farnesoid X receptor (FXR) signalling as an important pathway for the interaction between the gut microbiota and bile acids. The FXR pathway through which bile acids and gut microbiota contribute to host metabolism is by metabolizing bile acids into primary and secondary bile acids, which then bind to the FXR receptor and stimulate secretion of gut-derived hormones, such as fibroblast growth factor FGF19. In turn, FGF-19 regulates bile acid synthesis as well as lipid and glucose metabolism. Increased bile acid synthesis contributes to increased energy expenditure in the host by stimulating the brown adipose tissue and skeletal muscle *(Lee et al., 2020).*

2.4.4 LPS Lipopolysaccharides (LPS)

LPS contain lipid A, which can cross the intestinal mucosa through tight junctions or with the aid of chylomicrons. LPS are responsible for the absorption and transport of dietary triglycerides and initiate an inflammatory process that result in the insulin resistance often observed in obesity. LPS concentrations are low in healthy people but may reach high concentrations in obese individuals and cause metabolic endotoxemia. Metabolic endotoxemia increases adipocyte hyperplasia and recruitment of macrophages into adipose tissue in a CD14-dependent pathway and increases the production of activin A, which activated the proliferation of adipocyte precursor cells (Gomes et al., 2018). Gut microbiota also may contribute to metabolic disturbances observed in obese patients by triggering systemic inflammation.

Overall, currently available evidence suggests that changes in the gut microbiota could contribute to the pathogenesis of obesity and to the development of obesity-related metabolic disorders, including type 2 diabetes, NAFLD, metabolic syndrome, and cardiovascular disease. Obesity treatments such as calorie reduced diets and/or bariatric surgery modify the gut microbiota in ways that are associated with health benefits, supporting

the hypothesis that changing gut microbiota composition has the potential to provide an additional mechanism for achieving stable weight loss *(Muscogiuri et al., 2019).*

2.5 Defining Healthy Gut Microbiome

Each individual has a unique gut microbiota that depicts fingerprint of an individual. Gut microbiota plays many specific functions in host like nutrient metabolism, maintenance of structural integrity of the gut mucosal barrier, immunomodulation, and protection against pathogens. Different bacteria species composes gut microbiota that is taxonomically classified by genus, family, order, and phyla. Each and every human's gut microbiota are shaped in early life as their composition depends on birth, type of delivery, methods of milk feeding, weaning period. This personal and healthy core native gut microbiota remain relatively stable in adulthood but differ between individuals due to many factors like lifestyle, enterotypes, body mass index (BMI) level, cultural and dietary habits and physical exercise. Therefore, there is no distinguishable gut microbiota composition since it is different for each individual. However, a healthy gut microbial balance has to be maintained in order to perform metabolic and immune functions optimally and prevent disease development *(Singhvi et al., 2020).*

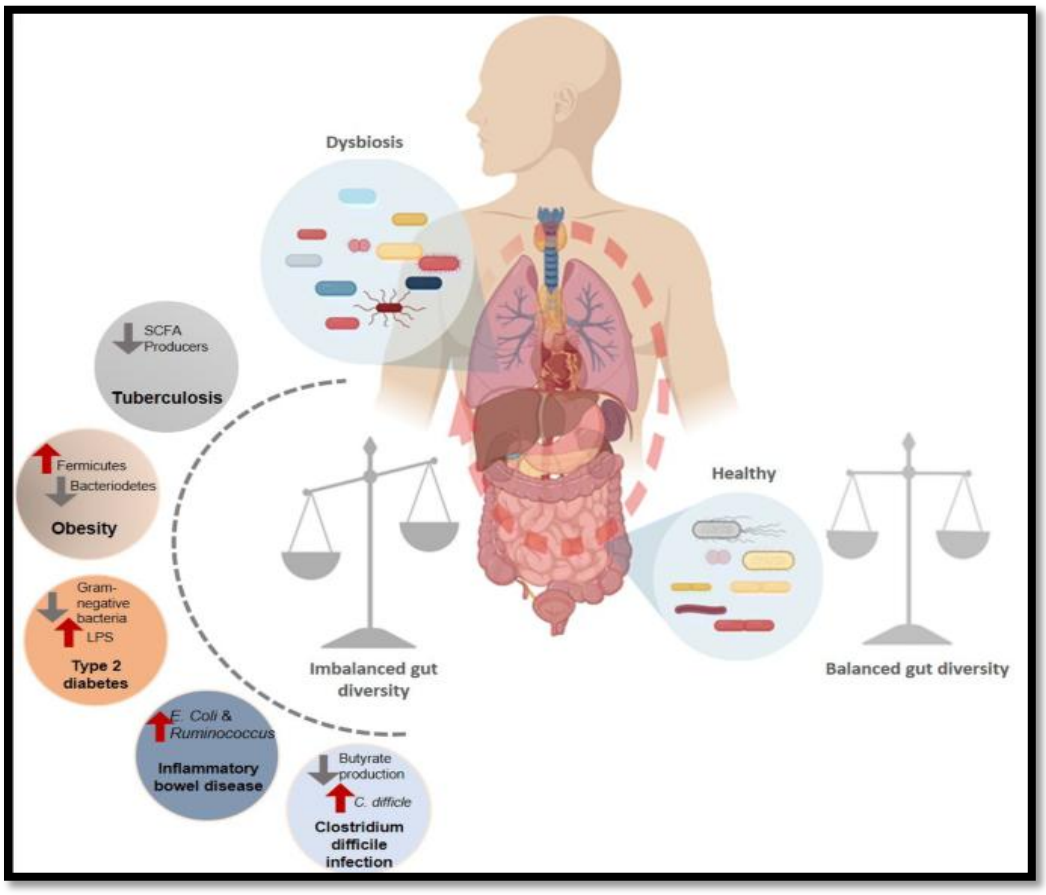

Figure 14: Balance and imbalance of gut microbiome(*Singhvi et al., 2020).)*

2.5.1 Variations in gut microbiota

Gut microbiota is composed of several species of microorganisms, including bacteria, yeast, and viruses. Taxonomically, bacteria is classified according to phyla, classes, orders, families, genera, and species. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. The two phyla Firmicutes and Bacteroidetes represents 90% of gut microbiota *(Arumugam et al., 2011)*. The phylum Firmicutes is composed of more than 200 different genera such as *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus*, and *Ruminicoccus*. *Clostridium* genera represent 95% of the Firmicutes phyla. Phyla Bacteroidetes consists of predominant genera such as *Bacteroides* and *Prevotella*. The phylum Actinobacteria is proportionally less abundant and mainly represented by the *Bifidobacterium* genus (Arumugam et al., 2011).

2.5.2 Variations in the Same Individual

Human gut microbiota vary taxonomically and functionally in each part of the GI tract and undergo variations in the same individual due to factors like infant transitions, age, and environmental factors such as antibiotic use.

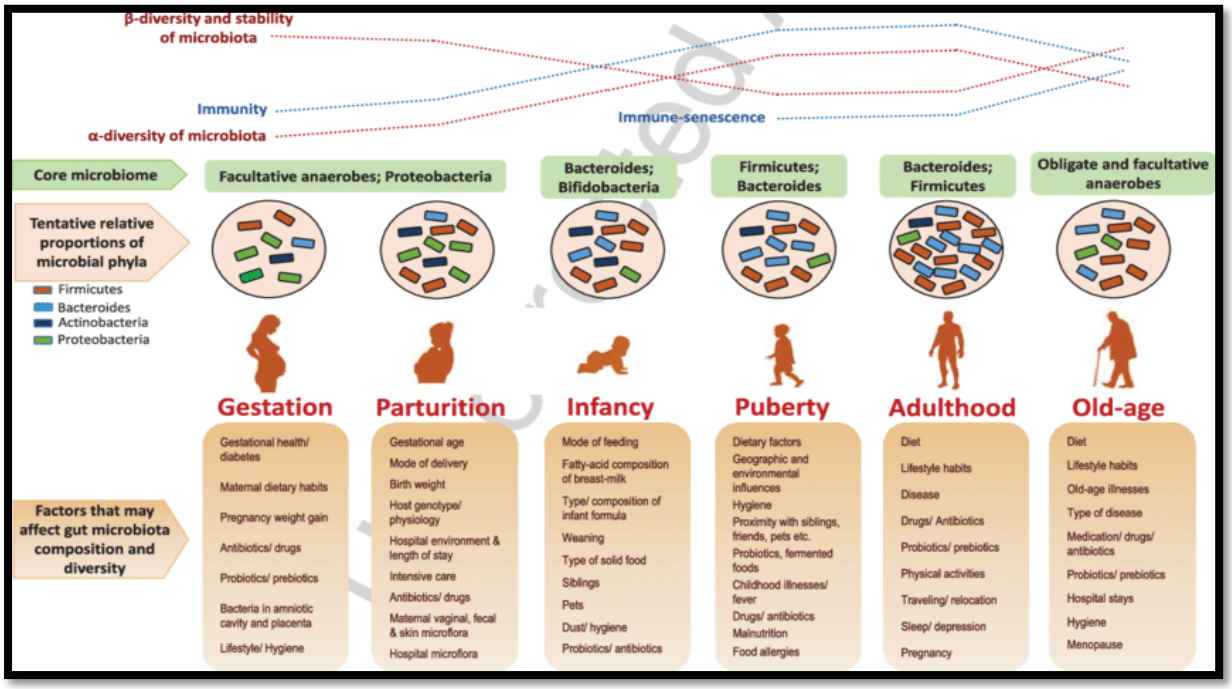

Figure 15. Potential factors that could affect microbiota composition at different stages of lifediversityspecies (taxa) richness within a single host.(Nagpal *et al.*, 2017)

Gut microbiota vary in the different anatomical regions of gut. This may be due to difference in terms of physiology, pH and O2 tension, digestive flow rates which is rapid in the mouth to the caecum, slower colon and rectum, substrate availability, and host secretions. The small intestine provides a more challenging environment for gut microbial colonizers whereas the large intestine, which has slow flow rates and neutral to mildly acidic pH, harbors by far the largest microbial community dominated by obligate anaerobic bacteria *(Flint et al., 2012).*

Birth and gestational age is a major determinant of gut microbiota colonization. The microbiota composition of preterm infants is different from full term infants. In preterm infants, the organ immaturity and environmental factors such as antibiotic use, hospital stay and enteral feeding impacts microbiota colonization of gut (*Ren et al., 2018).*

After birth, a rich and dynamic microbial ecosystem develops in infant gut from mother's skin, vaginal and fecal microbiota, and environment microbiota contacts. Gut microbial colonization differs according to the type of delivery *(Salminen et al., 2004).* In vaginal delivery, new-borns acquire a gut microbial composition resembling their mother's vaginal microbiota (*Lactobacillus, Prevotella)* On the contrary, infants born by cesarean section acquire bacteria derived from hospital environment and mother's skin (*Staphylococcus, Corynebacterium, Propionibacterium* spp.) *(Dominguez-Bello et al., 2010)*. The gut microbiota are less diverse in terms of bacteria species of neonates delivered by cesarean delivery than that of microbiota of vaginally delivered infants.

Various studies have demonstrated that breastfed infants generally harbour a more complex and diverse *Bifidobacterium* microbiota than formula-fed infants. Breastfed infants have more beneficial gut microbiota, with a higher richness and diversity of *Bifidobacterium* spp. and a lower number of *Clostridium difficile* and *Escherichia coli* than formula-fed infants *(Penders et al., 2006*). *Bifidobacterium* spp. ferments galactooligosaccharide (GOS), one of the main components of breast milk and produce SCFAs (*Tanaka & Nakayama, 2017).* However, the formula-fed infants are more often colonized with *Escherichia coli*, *Bacteroides,* and *Clostridium difficile* compared with breastfed infants *(Tidjani Alou et al., 2016).*

Dietary habits, infant weaning, and feeding practices play a crucial role in gut microbiota variations. Introducing traditional and high-fiber foods increases the colonization of Firmicutes and *Prevotella*, whereas the introduction of high-fiber and animal protein foods causes an increase in colonization of Bacteroidetes*(Iizumi et al., 2017)*. Microbiota diversity increases with age until it becomes a stable adult. Impact of genetics, environment, diet, lifestyle, and gut physiology results in the high microbial diversity. The gut microbial composition is dominated by three bacterial phyla: Firmicutes, Bacteroidetes, and Actinobacteria *(Yun et al., 2017*). Gut microbiota composition can be affected With regard to older people over the age of 70, by digestion and nutrient absorption changes and immune activity weakness.

Gut microbiota composition can be more or less affected by antibiotic use. Broad-spectrum antibiotics lead to an imbalance between Firmicutes and Bacteroidetes. During antibiotic treatments the bacterial diversity and the abundance of these bacteria decreases. The alteration of the gut microbiome composition depends on the factors like antibiotic class, dose, and period of exposure, pharmacological action, and target bacteria *(Bervoets et al., 2013).*

2.5.6 Variations in the different individuals

These inter-individual variations are principally due to enterotypes, body mass index (BMI) level, and external factors such as lifestyle, exercise frequency, ethnicity, and dietary and cultural habits.

Gut microbiota of each individual are specifically characterized by clusters of bacteria named enterotypes *(Arumugam et al., 2011)*. Three enterotypes are characterized by three dominant
Bacteriaclusters: *Bacteroides* (enterotypeI), *Prevotella* (enterotypeII),or *Ruminococcus* (enter otype III). Each enterotype harbors different bacteria genera. These three enterotypes are specifically regrouped by functions and enumerations of bacteria. Bacteria clusters of enterotype I derive energy primarily from carbohydrates using principally glycolysis and pentose phosphate pathways, whereas bacteria clusters of enterotypes II and III degrade mucin glycoproteins of the gut mucosal layer.

Various studies have examined the impact of childhood BMI on gut microbiota composition. Children with overweight or normal BMI are demonstrated with a higher microbial diversity than underweight children *(Wu et al., 201*1). The gut microbiota of obese children have elevated Firmicutes-to-Bacteroidetes ratio compared to the microbiota of lean children. Furthermore, low relative proportions of *Bifidobacterium vulgatus* and high concentrations of *Lactobacillus* spp. are observed in the obese microbiota (*De Filippo et al., 2010*). SCFAs are higher in obese children suggesting elevated substrate utilization. Studies have demonstrated that increased or depleted production of SCFAs correlates gut microbiota variatons that may respectively contribute to the pathophysiology of obesity.

Lifestyle and dietary cultural choices certainly influence the gut microbial dynamics *(Bai et al., 2018).* A study of European children (fed with the Western diet) and African children (fed with a diet rich in millet/sorghum + local vegetables containing very few lipids and animal proteins), revealed that African children's microbiota have a remarkable abundance of *Prevotella* and *Xylanibacter*.Where, *Shigella* and *Escherichia* arewidely under-represented *(Patterson et al., 2014).*

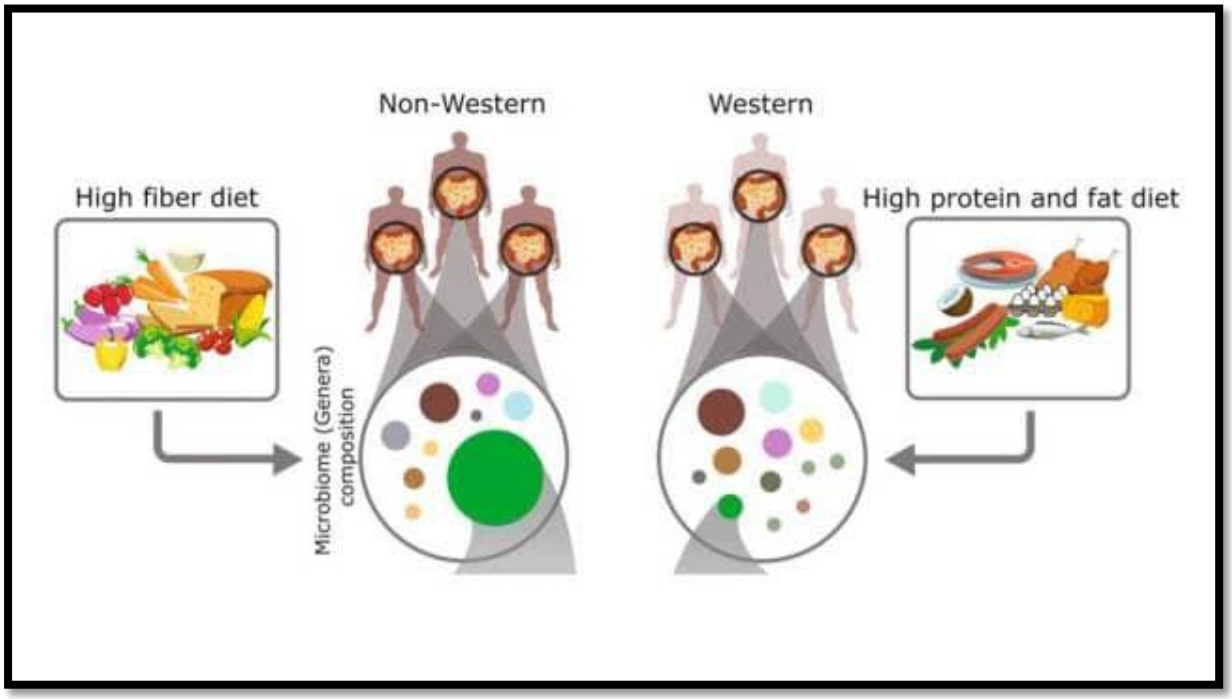

Figure 16: Variation in gut microbial population in western and non-western populations. Bai *et* al., 2018

Bai et al. suggested associations of exercise frequency with gut microbiota composition of young children and adolescents. Daily exercise increases gut microbial diversity with a Firmicutes enrichment microbiota: *Clostridiales*, *Roseburia*, *Lachnospiraceae*, and *Erysipelotrichaceae* by producing more SCFAs which may increase the expression of tight junction proteins in colon epithelia to heighten the resistance of the intestinal barrier, reduce mucosal permeability, and inhibit inflammatory cytokines (Bai *et* al., 2018).

Throughout our life, the richer and more diverse the microbiota, the better they will withstand external threats. Infact, gut microbiota represent a changing ecosystem that is influenced by many factors such as unbalanced diet, stress, antibiotic use, or diseases. A healthy host–microorganism balance must be respected in order to optimally perform metabolic and immune functions and prevent disease development. However, imbalance of host–microbe relationship may disrupt the development of the immune system, which may in turn result in diseases (Patterson *et* al., 2014).