Introduction

Globally 800 million people are obese, with a billion more at risk of becoming overweight or obesity, according to the data in the World Obesity Atlas, published by the World Obesity Federation (2023). It is estimated that the global prevalence of obesity nearly tripled between 1975 and 2020. The World Health Organisation (2021) predicts that almost half of the world's adult population will be overweight or obese by 2030, if the prevalence of obesity continues on its current trend.

The rising prevalence of obesity represents a growing public health challenge worldwide in terms of economic burdenon the individual, and on families and nations. Though there is a considerable health care cost attributable in preventing and treating obesity, the cost of failing to prevent and treat obesity will be far higher. Currently the global economic impact from obesity is estimated to be $4 trillion of potential income or three per cent of the global gross domestic product (GDP) (World Obesity Federation, 2022).

The COVID-19 pandemic has further fuelled the obesity epidemic during the period from 2020 to 2022. Extensive restrictions or lockdowns have curtailedthe movements outside home, paved way for sedentary behaviours that has led to increased weight gain. This rise in obesity prevalence clearly indicated a side- effect of preventing and managing the COVID-19 pandemic which has further worsened the obesity pandemic. (Clemmensen *etal*.,2020).

Obesity is a complex, multifactorial preventable disease, characterised by positive energy imbalance resulting in excess body weight. The growing epidemic of obesity has coincided with a distinct shift in the environment, such as sedentary life, physical inactivity, poor sleeping habits, stress, pollution, unhealthy dietary patterns, eating behaviour. (Townshend *et al*., 2017).

The completion of the human genome project in 2003 accelerated the advancements in the field of genetics and utilisation of the genetic information in clinical settings. Similarly, Genome- Wide Association Studies (GWAS) (2007) contributed to the identification of specific genetic variations associated with certain diseases. Currently, there are more than 740 genes associated with obesity (Akiyama *et al*., 2017) (Turcot *et al*.,2018).Single Nucleotide Polymorphisms, SNPs are the most common genetic variation, that occur throughout the human genome and found in at least one percent of the population.

With the discovery of genetic variants associated with obesity, there is an increased use of genetic information to identify individuals at risk of obesity. Knowing an individual's genetic susceptibility for obesity will help to identify who is at more risk for gaining weight and this would allow for earlier interventions in the prevention of obesity in an effective manner. (Loos *et al*., 2022).

According to the 12th update of the Human Obesity Gene Map (2005), nearly 253 QTLs (Quantitative Trait Loci) have been identified for obesity related phenotypes from large scale genome-wide association studies (Rankinen*et al*.,2006). Several research studies have established not only the genetic basis for obesity and body composition but also provided the evidence for an individual's response to weight loss or gain. To name a few genes that are involved in the molecular pathways linked to obesity are those affecting neural regulation of feeding and body weight- BDNF, MC4R, NEGR1, genes associated with fasting insulin secretion and action, energy metabolism, lipid metabolism, and/or adipogenesis - FTO, TCF7L2, IRS1, FOXO3, RPTOR, PTBP2, MAP2K5, MAPK3 (Mahmoud *et al*., 2022).

Several research studies has helped to clarify molecular mechanisms involved in obesity. Emerging evidence also suggested that genetic variants may have an impact on the efficacy of the behavioural weight loss interventions (Thaker *et* al.,2017) These studies have enabled to gain an in-depth understanding about the molecular mechanisms involved in obesity and provides new insights into the genetic prediction of weight loss.

Numerous evidence suggested that gene environment interactions play an important role in the regulation of body weight and energy balance. (Crovesy*et al*., 2019). Thus, we can summarise body weight regulation as a complex interaction between genetic, behavioural, environmental, socioeconomic, sociocultural and psychosocial factors (Qi *et al*., 2008). Currently, the biggest gap in knowledge is how these interactions confluence to produce obesity.

Despite living in an obesogenic environment, a significant proportion of the world's population remains of normal weight, suggesting the influence of genetic factors. The heritability of obesity is estimated at approximately 40-70% (Elks *et al.*, 2012) suggesting that half of the interindividual variability in body weight is due to genes and the other half is due to environmental factors.

A growing number of research studies has begun to examine the role of epigenetics as a key regulator of gene-environment interactions and its contribution to the development of obesity. The science of epigenetics focuses on the heritable changes in gene expression without any changes in the DNA sequence. The main epigenetic mechanisms include DNA methylation, histone modifications, non-coding RNAs and chromatin remodelling mediates the body weight regulation and the associated gene expression. This has led to the identification of many genes and various biological markers. Research findings on epigenome and its link to obesity expands our possibilities for prediction of obesity risk and targeted prevention strategies (Mahmoud, 2022).

The rapid rise in the number of obese individuals globally has been attributed to the presence of "thrifty genes", almost 200 of these genes are involved in fat storage and metabolism. These genes were previously an evolutionary advantage in times of food scarcity and famines for our ancestors, have now become a huge burden amidst the obesogenic environment. This highlights that there is a constant interaction between the genetic variations and the environmental factors, which plays an important causative role in obesity (McGarvey,1994).

Nutrients are one of the environmental factors that constantly interact with the human genome. Various nutrients present in the food acts as cofactors in various metabolic pathways, thus seem to influence the processes involved in DNA repair and metabolism. The individual's genotype determines the response to a particular nutrient whereas the nutrient present in food influences the development of phenotype.

Microarray studies show that 7 to 21% of the genes expressed in adipose tissue shows a specific rhythmic pattern. (Wozniak *et al.*,2009). Clock genes expressed in the adipose tissue regulates various physiological processes and functions of adipose tissues in response to the changes in the environment (Ptitsyn*et al.*,2006) Recent molecular studies suggest that circadian biology may influence expression of various genes and hormones involved in body weight regulation and plays an important role in the pathogenesis of obesity. (Cheung *et al.,* 2012)

The current obesity treatment strategies for obesity relies on a "one-size-fits-all" approach despite the heterogeneity of the pathophysiology that exists among different obese

individuals. (Hurtado *et al*., 2020). This is mainly contributed by the diseaseaetiology, clinical manifestation of the condition and its associated comorbidities. The existing health care system follows the current obesity guidelines that starts with behavioural and lifestyle modification and progresses to the use of pharmacological treatment, endoscopy and/or bariatric surgery based on the individual's response. The variability in weight loss response to the current obesity treatment approaches continues to be a hit- or- miss phenomenon, suggesting it is not effective in delivering a comprehensive and individualized care that is needed by an individual who is obese (Yanovski*et al*.,2018)

Contrary to the one-size- fits- all approach, precision medicine focuses on understanding the human metabolic individual variabilityfor disease prevention, management and treatment. The completion of the human genome project and rapid developments in the field of genetics and genomics has laid the foundation of precision medicine. This has led to the identification of hundreds of gene variants and genetics of intermediate phenotypes such as circulating metabolites (metabolomics), proteins (proteomics), messenger RNA or transcripts (transcriptomics), DNA modifications (epigenomics), lipids (lipidomics), gut microbiome (microbiota) and food (foodomics) that are associated with obesity and related traits. The precision nutrition approach, which is a critical component of the precision medicine brings in a new dimension for food and health that tries to explain the human metabolic individual variability of the response to specific diets (Livingstone *et al*.,2022).

A systems biology approach refers to combining different omics areas allows to create larger pool of information which upon computational integration allows a more extensive analysis of the individual response to a specific diet, thus providing an in-depth understanding of how food and nutrients present in food may influence health and disease (Badimon*et al.*, 2017).

Nutrigenetics: Nutrigenetics focuses on understanding how different SNPs may affect individual variations in response to diet provides a scientific basis to personalise dietary interventions for individuals based on their genetic make-up by linking specific dietary components to health outcomes. (Pang *et al.*,2010).

Nutrigenomics: Food, nutrients present in food and bioactive compounds present in food can affect the gene function directly and indirectly, by turning "on" and "off" certain genes. Nutrigenomics focuses on how food influence gene expression and also the resulting changes in the protein and other metabolites.

Transcriptomics: The transcriptomics refers to the study of the complete set of RNA transcripts. This requires the understanding about the cells in which genes are expressed because gene expression is tissue specific. Such analysis can help in understanding about the changes in gene expression in response to different diets and help in establishing the new biomarkers for diagnosis of diseases.

Proteomics: It seeks to understand about the protein expressed and focusses on identifying the effect of food and nutrients on the genome.

Lipidomics: Lipidomics refers to the identification of the lipids found in cells, tissues and fluids and studies about lipids and its interactions between genes and human metabolism. It may be used as a tool to determine the individual variability in response to individual's dietary intake.

Metabolomics: Metabolomics studies about different intermediary metabolites in human systems such as blood, urine, biological fluids, saliva, cells and tissues. This focuses on studies about the metabolites and the related molecular pathway thus helps to understand about how the body responds to different diets.

Epigenomics: Epigenomics studies about different direct chemical alterations, including DNA methylation, histone modifications, chromatin remodelling and micro RNA's and how these mechanisms regulate gene expression.

Understanding and applying the information from various omics related studies either separately or in an integrated manner could provide new insights in the precision prevention and management of obesity (Trujillo *et al.*,2006). In the recent years, there has been a growing interest to utilise the precision nutrition approach for the prevention, management and treatment of obesity, which takes into consideration the interaction between food and the genome. Food and the nutrients present in the food is one of the important environmental factors that constantly interacts with the genes (Barrea *et al*., 2020).

With the advancements in the area of omics technologies, the term nutrient-gene interactions has been replaced with the term nutritional genomics. The bigger term nutritional genomics comprises of nutrigenetics and nutrigenomics. Nutrigenomics refers to the study of interaction between the food and the genome and nutrigenetics refers to the study of how the

genes determines the response to nutrients present in the food. Quite a good number of research studies have showed the interaction between the SNPs present in various genes and its influence on the metabolic response of the nutrients present in the food. Therefore, analysing these SNPs provides more information about an individual to optimise nutrition for health and disease and to customise diets according to the genetic make- up. (Farhud *et al.*, 2010)

Single Nucleotide Polymorphisms (SNPs) determines the response to certain nutrients present in the food and some of the specific examples are, lactase-phlorizin hydrolase gene (LPH) polymorphisms, associated with hypolactasia, that changes the tolerance to dietary lactose (milk sugar, LPH hydrolyzes lactose into glucose and galactose) and allows different expression of the LPH. Another example related to the taste perception genes is TAS2R38 gene which determines the individual's response to bitter taste. Likewise, the MTHFR (5,10-methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms influences the folate status of an individual. Decoding information about an individual's genotype and its effects on the nutrient- gene interactions is essential for the development of personalised and clinically useful dietary recommendations for preventing and treating obesity (Qi *et al.*, 2012).

The study of gene-nutrient interaction is a developing area of science. The concept of treating and managing a genetic condition using dietary modification is not something new and it existed in the past as seen from examples of Phenyl Ketonuria (PKU), defects associated with long chain fatty acid oxidation, iron absorption (haemochromatosis), which can be reasonably well managed with dietary restrictions (Marcum *et al.*, 2020).

Phenylketonuria (PKU) is a classic example of gene- diet interaction, characterised by elevated levels of phenylalanine in the blood that causes mental retardation and related symptoms. This is caused due to the defective gene that encodes for the enzyme responsible for the conversion of phenylalanine into tyrosine. This condition is treated by lowering the amount of phenylalanine in the diet. Another example is glucose-6- phosphate 1-dehydrogenase enzyme deficiency caused by genetic defects result in hemolytic anemia in response to the consumption of fava beans. These examples explains the genetic susceptibility of a disease in the presence of gene diet interactions at the molecular level. (Phillips, 2013).

The rapidly burgeoning direct-to-consumer (DTC) genetic testing industry has made it easier to access individual's personal genetic data. Qualitative and exploratory research studies have concluded that there is substantial interest among consumers for genetic testing and personalised nutrition, especially to learn about different genetic variants and their response to diet on various health and disease outcomes. One of the advantages of commercial applications of nutrigenetics has enabled to develop individualised gene- based dietary recommendations that are more precise in nature.

The Food4Me study is one of the largest personalised nutrition intervention randomized control trial till date which tested for genetic variants present in five genes,FTO, FADS1, TCF7L2, ApoE, and MTHFR , provides strong evidence for the effectiveness of personalised nutrition on dietary intake among European consumers from seven different countries. The results from the study revealed that the participants of this study improved their dietary intake over 6 months period. Participants receiving personalised nutrition advice based on genetic make-up consumed less red meat (8.5%) and less salt (6.3%) and had higher Healthy Eating Index scores (2.6%) compared to the group that didn't receive personalised nutrition advice. This clearly shows that personalised nutrition advice based on genotype helps in improving dietary intake and improves the compliance to personalised dietary recommendations. The use of multi-omics in personalised nutrition approach thus requires integration of machine learning and artificial intelligence to study the impact of personalised nutrition randomized controlled trials. (Celis-Morales*et* al., 2015, 2016,2017)

A recently appreciated factor that influence the inter-individual human variability is the huge micro-organismal ecosystem and its genetic material, collectively known as the microbiome. The gut microbiome, often referred to as our 'second genome' (a total of up to 100 trillion cells), contains almost equal number as our own cells are unique to each individual. (Roager *et al*.,2022). The gut microbiome contains a plethora of microbes such as viruses, fungi, archaea, protozoas forming a large ecosystem that is increasingly recognized to impact the human physiology, modulating our metabolism and disease risk. The millions of microorganisms present in the gut, "superorganisms" performs a number of functions that includes breakdown and metabolism of nutrients, synthesis of essential vitamins, improves immunity, promotes intestinal cell integrity and regulation of body weight. (Bull *et al.*, 2022)

Recent studies have suggested the gut microbiome to be a potential environmental factor involved in the control of body weight and energy balance. In recent years, it is well documented that gut microbiome plays a role in energy harvest and consequently obesity.Human and animal model studies reveal that obese subjects have altered gut microbiota composition, specifically, a greater representation of firmicutes and fewer bacteroidetes, reduced bacterial diversity in obese individuals than their leaner counterparts, where the altered bacterial representation is found to be the causal factor affecting the metabolic pathways (Sarfraz *et al.*, 2022)

It is well established that the host microbiome changes in response to dietary patterns, diet consumption and in response to weight loss. Diet induced weight loss promotes alteration in the gut composition, that can impact the efficacy of the nutritional interventions. Some gut bacteria are also influenced by themselves. For example, the archaeon Methanobrevibactersmithii, has a tendency tometabolise the intermediary dietary substrates and utilises the end products of the metabolism of other bacteria which results in increasing the host energy intake and subsequently resulting in weight gain. (Cani, 2018)

In another dietary intervention study of reduced carbohydrate and increased protein intake, Duncan et al., found reduced abundance of Bifidobacterium, Roseburia spp., and Eubacterium rectale subgroups of clostridial cluster XIVa. This shows marked and significant changes in the gut microbial composition of the gut with diet induced weight loss (Hernández-Calderón *et al.*,2022)

With the rapid technological advances in the field of omics research, our insights into interindividual variability and its effect on disease risk are increasing. It is well established that the human genome and the microbial ‘second genome’ influences our response to the diet. In the recent years, several “consumer genomics” companies have started offering commercialised nutrigenetic and gut microbiome tests to design tailored dietary advice for promoting health and treating disease conditions. Nutrigenetic testing focuses on understanding the specific genetic variations of the individual, whereas the gut microbiome testing provides information on the microbial composition, abundance and diversity to provide personalised nutrition advice that are designed to be genetically appropriate dietary and lifestyle recommendations. Thus offering a tailored dietary advice based on the individual’s genetic susceptibility and gut microbiome could be a promising strategy for the prevention and treatment of obesity.

Research studies have examined the usefulness of nutrigenetic testing and gut microbiome testing in weight management in different populations. (Franzago*et al*.,2022) (Zeinalian*et al.,* 2022). There is a huge potential in improving the health outcomes of the individuals complying to the personalised dietary recommendations based on their genetics in treating and managing obesity. Few Indian genetic testing companies offer personalised, targeted nutrition recommendations for obesity-related polymorphisms based on the particular pattern of genetic variation and the gut microbiome composition. A need for developing new tools will allow us to utilise the potential of individual microbiome and genetic fingerprints for the benefit of precision nutrition approach in the prevention and management of obesity.

Recent evidence show that this concept of precision nutrition will provide new insights into the pathogenesis of obesity, elucidate the role of gene-host-microbiome-environment interactions in obesity thus contributing to a precision approach in prevention and management of obesity. This study is first of its kind in India, based on the results of the previous research findings, attempts to examine the use of precision nutrition approach in combining the genetic make-up and gut microbiome profile of individuals in designing personalised diet recommendations and its potential in improving long term weight loss maintenance.

Rapid progress in the field of genetics and genomics along with developments in sequencing technologies have led to in-depth understanding of pathogenesis of obesity. Genetic testing for obesity have facilitated early diagnosis and prediction and thereby have led to personalised intervention based strategies for the treatment and management of obesity. Various health care professionals need to work together to understand and explain the risk of obesity and to manage it holistically. So far, the knowledge related to genetic contribution to obesity is only a small proportion and needs more validation through systematic research studies. Identification of genetic predictors that are easy to measure and less expensive will improve the clinical validity and utility of these risk assessment predictors in the treatment and management of obesity. Lifestyle modifications that includes healthy diet and physically active lifestyle still remains the key to manage body weight irrespective of an individual's susceptibility to obesity.

With this in view, the objectives of the present studyare

Primary Objective:

- Determine whether nutrigenetically tailored, gut-microbiome based diet helps in the prevention and management of obesity.

Secondary Objectives

- Examine the factors influencing consumer acceptance of genetic testing for personalised nutrition.
- Develop & design an algorithm for formulating a genetic based diet & gut microbiome-based diet.
- Evaluate the impact of precision dietary recommendations on long term weight management among obese adults.

Hypothesis

H1: Precision nutrition approach that includes nutrigenetics and gut-microbiome based dietary advice is more effective than generic dietary advice.

H2: Precision nutrition approach results in better compliance and long-term weight loss maintenance.