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A Review of Obesity, Metabolic Syndrome and Epigenetics in South Asian (SA) Communities

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ABSTRACT

South Asia is home to a remarkable portion of the world's population, with about 1.9 billion people, making up nearly 24% of the global total. This region, which includes countries like India, Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka, and the Maldives, plays a vital role in shaping global demographics. One of the striking characteristics of South Asia's population is its youthful nature, setting it apart from many other parts of the world.

In South Asia, roughly 28-30% of the population is under the age of 14, a larger proportion than the global average of 25%. This reflects a region with a high birth rate and a significant number of young people entering the workforce and education systems. Meanwhile, about 65% of South Asians fall within the working-age group (15-64 years), aligning with global trends. However, only 5-7% of the region's population is over 65, compared to around 10% globally. This indicates that South Asia has a smaller elderly population, in contrast to many developed countries where longer life expectancy and lower birth rates are creating aging populations. These dynamics suggest that South Asia's youthful demographic will be central to its future development and economic growth.

Introduction: *South Asia is one of the most populous regions globally, and its population statistics are significant when compared to the global population. As of recent estimates:*

Percentage of Global Population from South Asia

- *South Asia accounts for about 25% of the global population. The region includes countries like India, Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka, and the Maldives.*
- *The total population of South Asia is around 1.9 to 2 billion people, with India alone contributing to a large portion (about 1.4 billion).*

Age Distribution

South Asia has a relatively young population compared to the global average, with a higher proportion of younger age groups. Here's a comparison of the age distribution in South Asia vs the rest of the world.

South Asia

- *0–14 years: About 30% of the population.*
- *15–24 years: Around 20% of the population.*
- *25–64 years: Approximately 45%.*
- *65 years and older: Around 5%.*

Global Average

- *0–14 years: About 25% of the global population.*
- *15–24 years: Roughly 15%.*
- *25–64 years: Around 50%.*
- *65 years and older: Around 10%.*

Key Points

- *South Asia has a younger population, with a higher percentage in the 0–24 age bracket compared to the global average.*
- *The rest of the world, particularly regions like Europe and North America, tends to have a more aging population, with higher percentages in the 65+ age group.*

These demographic trends have significant implications for future economic development, healthcare needs, and social policies in South Asia and globally.

Obesity is increasing globally, and South Asians (SA's) are particularly vulnerable due to a combination of genetic, environmental, and lifestyle factors. Central obesity is prevalent among South Asians, leading to metabolic issues like insulin resistance and hypertension, even at lower body mass index (BMI) levels than seen in Western populations. This has prompted organizations such as the International Diabetes Federation (IDF) to adopt ethnic-specific waist circumference cut-offs for SAs.

The "thin fat" phenotype, common in this group, refers to individuals who appear lean but carry excess visceral fat, raising their cardiovascular risk. Despite identifying some obesity-related genes like FTO and MC4R, research on South Asian populations remains limited compared to studies on Europeans. Traditional BMI cut-offs often underestimate health risks in this population, highlighting the need for targeted public health interventions to address rising obesity and metabolic disorders among South Asians.

Keywords

BMI, Obesity, South Asian, Metabolic disorders.

Introduction

Obesity is a rapidly growing global health challenge among South Asians, which denotes residents of India, Pakistan, Bangladesh, Iran, Afghanistan, Sri Lanka, Nepal, Bhutan and Maldives, constituting 25.29% of the world's population [1].

The worldwide prevalence of obesity has nearly tripled since 1975, mainly due to the adoption of a progressively more sedentary lifestyle and the consumption of less healthy diets. According to the WHO, there are about 2 billion adults who are overweight, whilst 650 million are obese. If these rates do not slow down, it is expected that 2.7 billion adults will be overweight and over 1 billion will be obese by 2025 [2].

Obesity is linked to other co-morbid illnesses, including dyslipidaemia, hypertension, diabetes, and a cluster of disorders referred to as metabolic syndrome [2]. The rising prevalence of obesity and dyslipidaemia among South Asians is driven by nutritional, lifestyle, and demographic shifts, coupled with suboptimal diets and sedentary behaviour, against a background of epigenetics. Central obesity is hereditary among South Asians, indicating a significant genetic influence. Genetic research primarily conducted on individuals of European descent has pinpointed genetic loci associated with central obesity; however, few studies have explored the genetic determinants of central obesity in South Asians.

Aim of the Review

To investigate this, we conducted South Asian-specific genetic association data analyses to determine if genetic variation contributes to the higher risk of central obesity in South Asians relative to Europeans, correlating our findings with existing European research.

Definitions

"South Asians" and 'Asians' refer to residents of India, Pakistan, Bangladesh, Iran, Afghanistan, Sri Lanka, Nepal, Bhutan, and the Maldives, constituting 25.29% of the world's population.

Methods

The medical search engines Pub med (National Library of Medicine) and Google Scholar were used for literature search using the keywords "Obesity, central obesity, overweight, dyslipidaemia, metabolic syndrome, metabolic risks, Body Mass Index, waist circumference, obesity-related genes, FT0, MC4R, TMEM18, thin-fat phenotype, polymorphism, epigenetics, South Asians, and Asians'

Guidelines for Diagnosis of Obesity

Body Mass Index (BMI), a ratio of height to weight stated in kg/m², is frequently utilised to outline overweight and obesity, derived from morbidity and death statistics from Caucasian populations. An individual with a BMI of ≥25 kg/m² is classified as overweight, while a BMI of ≥30 kg/m² is classified as obese. These thresholds for identifying overweight and obesity have been universally endorsed [3].

Several studies have found that at the same BMI levels, Asian populations tend to have a higher body fat percentage relative to their weight compared to white populations, even when their absolute body fat mass is not higher. The research concluded that

BMI cut-off points for overweight and obesity should be lower for Asian populations to more accurately reflect their health risks and therefore indicates that BMI alone may not be a sufficient indicator of obesity-related health risks in Asian populations [4,5].

A World Health Organisation (WHO) expert consultation addressed the notions around interpreting suggested body-mass index (BMI) cut-off points for identifying overweight and obesity in Asian populations. It evaluated the necessity of population-specific BMI cut-off values. Their analysis of scientific evidence indicates that Asian populations exhibit distinct correlations between BMI, body fat percentage, and health concerns compared to European populations. The consultation determined that a significant number of Asian individuals show a high risk of type 2 diabetes and cardiovascular disease with BMIs below the current WHO threshold for overweight (≥ 25 kg/m²). Nonetheless, the existing data do not definitively establish a specific BMI threshold for overweight or obesity applicable to all Asians as the BMIs were variable. The threshold for observed risk ranges from 22 kg/m2 to 25 kg/m^2 among various Asian cultures; for high risk, it spans from 26 kg/m^2 to 31 kg/m^2. Consequently, no effort was undertaken to establish distinct cut-off values for each population. The consultation concurred that the WHO BMI cut-off points should be maintained and not changed as worldwide classifications [6].

A separate study highlighted that those of South Asian heritage possess an increased susceptibility to cardiovascular problems attributable to their body fat distribution. Central adiposity (abdominal fat) presents a considerable risk, and the incidence of cardiovascular risk factors, including hypertension and diabetes, is notably high, even among those deemed to have an average weight [7].

The importance of ethnic-specific cut-off points for waist circumference (WC) in defining metabolic syndrome has been recognised in the guidelines established by both the International Diabetes Federation (IDF) and the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) [8]. It is important to note that these organisations have tailored their definitions to accommodate variations in body composition and cardiovascular risk among different ethnic groups, particularly in Asian populations. For instance, the IDF defines central obesity for Asian populations with a waist circumference of ≥90 cm for men and ≥80 cm for women, recognising the higher prevalence of metabolic syndrome at lower levels of obesity compared to Western populations, which typically use higher cut-offs (≥102 cm for men and ≥88 cm for women) [9]. This adjustment reflects the understanding that Asian individuals may experience increased cardiometabolic risk at lower levels of adiposity.

Genetics

Genetic predisposition plays a significant role in South Asians' higher susceptibility to obesity and related metabolic disorders. Several gene variants have been identified in South Asians that predispose them to fat accumulation, particularly in the abdominal region, where fat is more metabolically active and harmful than in other body areas.

Single nucleotide polymorphisms (SNPs) are prevalent genetic differences in human genomes. As of now, 23,715 susceptibility SNPs, including 283 index SNPs, have been identified inside the enhancer regions of obesity-related cell lines, implicating numerous genes such as LEP, LEPR, NPY, ADIPOQ, FTO, MC4R, PCSK1 and POMCin the aetiology of obesity [10].

One of the first studies using data from 16,157 Pakistani adults was the Pakistan Risk of Myocardial Infarction (PROMIS) study and studied the interactions between 95 BMI-associated genetic variants with physical activity for the risk of obesity. The authors reported that out of 95 BMI-associated genetic variants discovered in Europeans, 73 were directionally related to the risk of BMI in South Asians [11].

The fat mass-associated gene (FTO) is the primary and most significant gene linked to obesity across many populations worldwide [10]. In 2007, FTO was described as the first gene associated with common obesity. The FTO gene has been linked to increased obesity risk in several populations, including South Asians. Studies showed that variants of this gene, such as the rs8050136 C/A variant, are associated with obesity [12]. A meta-analysis of published research involving Asians indicated that the minor allele for the variant rs9939609 considerably elevated the risk of obesity [13]. Limited research on South Asians has been documented. Different FTO SNPs cause fat accumulation in various body parts, most notably around the abdomen, associated with a greater risk of insulin resistance, diabetes, and cardiovascular diseases. Obese patients are influenced by diet intakes and living habits, which are generally related to specific FTO polymorphisms. Studies also show FTO is associated with an increased risk of obesity and type 2 diabetes, with effect sizes similar in East and South Asians and like those observed in Europeans. Furthermore, FTO is also associated with type 2 diabetes independently of BMI.

Another gene associated with obesity is the melanocortin-4 receptor (MC4R), which regulates energy balance. Mutations in this gene can disrupt the body's ability to regulate appetite and energy expenditure and reduce energy burn. MC4R gene mutations have also been associated with childhood-onset obesity, hyperphagia and hyperinsulinism [14]. In South Asians, variations in the MC4R gene have been linked to higher fat mass, greater risk of obesity, and related metabolic disorders. Research indicates that the MC4R gene is linked to a heightened risk of obesity in South Asian populations [15]. Alterations in this gene are associated with an increased risk of metabolic syndrome and obesity, particularly when coupled with dietary habits. Studies show that South Asians possessing specific variants of the MC4R, such as the rs17782313 polymorphism, display an increased vulnerability to obesity and associated disorders, such as type 2 diabetes, mainly when their diets are characterised by elevated refined carbohydrates and unhealthy fats, illustrative of a Western dietary pattern [16]. The data indicate that both hereditary and environmental variables, such as nutrition and lifestyle, significantly contribute to the elevated incidence of obesity and associated morbidities in South Asians. The TMEM18 Gene is another significant contributor to obesity

risk, and its expression has been shown to be associated with appetite and weight regulation. In South Asians, the presence of risk alleles in TMEM18 may amplify the likelihood of developing obesity even in the absence of other environmental triggers, such as a high-calorie diet.

The investigation into the genetics of metabolic disorders commenced with genome-wide association studies (GWASs), which identified several single nucleotide polymorphisms (SNPs) linked to obesity or metabolic syndrome predominantly. The proprotein convertase subtilisin/kexin type 1 (PCSK1) gene activates many neuropeptides and hormones that regulate thermogenesis and appetite. The PCSK1 SNP is the third most significant gene linked to obesity and is among the first identified as a monogenic cause of this condition. Research shows that PCSK1 deficiency is linked to early-onset obesity [17]. One study shows that single nucleotide polymorphisms rs6232 and rs6234–rs6235 in PCSK1 are linked to obesity [18]. Data explicitly addressing the use of PCSK1 inhibitors in South Asian populations is scarce; nonetheless, similar studies indicate their potential efficacy in the management of obesity and metabolic diseases. Most research on PCSK1 has concentrated on its impact on proinsulin and other prohormones essential for metabolic processes and energy management [19].

Although extensive research exists on PCSK9 inhibitors, especially their efficacy in cholesterol management and cardiovascular risk reduction, these studies frequently apply generalised findings across diverse groups. South Asians, prone to elevated risks of metabolic syndromes and cardiovascular illnesses, may benefit from PCSK inhibitors owing to their genetic predispositions. Research demonstrates that PCSK1 is linked to lipid and glucose metabolism, indicating possible treatment targets for obesity in ethnic populations with elevated metabolic risks [20].

A "thin fat" phenotype, where individuals have a relatively low BMI, but a high proportion of body fat, particularly visceral fat, is found more often in Asian populations. This unique body composition may be partially attributed to genetic factors, such as lower muscle mass and an increased propensity for fat storage. A recently published study from southern India found that about two-thirds of participants with a non-obese BMI (< 25 k/m^2) had a high body fat percentage [21]. Further, Current research suggests a correlation between the thin-fat phenotype and an environmental and lifestyle phenomenon affecting formerly thin individuals. This is especially predominant in India, considering the rapid transformation over the past twenty years [22]. Even individuals who appear lean by traditional BMI standards may have higher risks of obesity-related complications due to their increased fat-to-muscle ratio. This thin-fat phenotype is especially concerning because it often masks the underlying risk of metabolic diseases [23].

Screening and Therapeutics

As obesity results from a disruption of energy balance, screening for genes that regulate this can be very significant. Genetic screening allows for early detection of those prone to developing obesity and provides a better understanding of who is at risk; therefore, prevention measures can be implemented, such as lifestyle counselling on diet and physical activity. This could be particularly helpful in younger populations to reduce future health risks. Screening also allows us to see which variants an individual carries, and modifications can be tailored to an individual's specific needs. With genetic screening, physicians can apply more precise therapeutic strategies, leading to better outcomes.

Targeted therapies focusing on these genetic predispositions may prove more effective than generalised obesity interventions. Individuals possessing specific FTO gene variations can exhibit enhanced responses to lifestyle modifications when coupled with pharmacological interventions aimed at appetite regulation [24,25]. Other therapies, such as PCSK9 inhibitors, lower low-density lipoprotein (LDL) or 'bad' cholesterol, bettering lipid metabolism and reducing cardiovascular risk [26]. Implementing targeted therapy for obesity in South Asians via genetic screening and personalised medicine signifies a substantial advancement in targeted treatments in healthcare. By considering the distinct genetic characteristics of this population, healthcare practitioners can enhance treatment efficacy, mitigate obesity-related problems, and promote more sustainable weight management strategies.

Discussion

Studies suggest that South Asians are at risk of having a higher percentage of body fat, particularly visceral fat, which leads to metabolic abnormalities such as insulin resistance, dyslipidaemia, and hypertension. Notably, The International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) have recognised this risk by incorporating ethnic-specific cut-off points for WC into the definition of South Asian populations.

Despite lower BMI thresholds, central obesity and its related metabolic consequences are more prevalent in this population. This suggests that conventional BMI cut-offs may underestimate the cardiovascular risk in South Asians, underscoring the importance of developing tailored public health interventions.

The relationship between obesity, metabolic syndrome, and epigenetics in South Asian communities presents a multidimensional public health challenge. South Asians are disproportionately affected by metabolic disorders, with obesity and metabolic disorders manifesting at lower body mass index (BMI) and waist circumference (WC) values compared to Western populations. This phenomenon can be partially attributed to unique genetic, environmental, and epigenetic factors contributing to the thin-fat phenotype. In this, individuals appear lean but possess higher visceral fat levels, predisposing them to cardiovascular risks. Genetic research in South Asian populations has identified several obesity-related genes, such as FTO and MC4R, which have been implicated in regulating appetite and energy expenditure. However, research on South Asian populations is much less than that of Europeans. It is essential to accept that not all the data can

be replicated, particularly due to South Asians having differing risks and requiring increased focus on population-specific studies.

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