The Role of Innate Factors in The Aetiology of Obesity

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The Role of Innate Factors in The Aetiology of Obesity

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Abstract
Obesity is a complex, multi-aetiological and multifarious condition caused by the interaction of a number of factors including reduced physical activity, innate genetic make-up, ethnicity and a disadvantaged socioeconomic status. The aims of this review were to ascertain, through effective literature search, the innate factors that predispose an individual to developing obesity and to suggest recommendations for the prevention of obesity. These factors can be divided into biological and non-biological causes that includes genetics, hormones, education and income, lack of exercise, ethnicity and migration. It was found that certain genes may cause pathological alterations due to the alteration of proteins that regulate the appetite and satiety centres, while mutations in the polygenic genes inhibit the leptin-melanocortin pathway that regulates the energy homeostasis. Furthermore, changes to gut microbes could be associated with a higher risk of developing obesity due to a change in the absorption of nutrients. Education, behavioural changes and environmental approaches may be effective in promoting healthy lifestyle habits and in mitigating an obesogenic environment.

Key Words
Obesity; Leptin-melanocortin Pathway; Single Nucleotide Polymorphisms; Beta-arrestin Pathway; Epigenetics

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Introduction

Obesity, which is now considered as a non-communicable disease by the WHO, has become one of the greatest healthcare challenges of our times. According to the WHO, more than 1.9 billion adults (18 years and older) globally are overweight and about 650 million of these individuals are obese.[1, 2, 3] The medical and psychological sequelae of obesity contributes to a large proportion of current health-care expenditures leading to negative economic impact through loss of worker productivity, increased disability and premature loss of life. According to the 2017 Public Health England report, the annual spend of over £16 million on the treatment of obesity and diabetes is greater than the amount spent on the police, the fire service and the judicial system combined.[4, 5] It is estimated that by 2035 the increasing rate of diseases associated with obesity would cost the NHS an extra £2.5 billion per year.[6] Obesity results in various clinical manifestations such as Type 2 diabetes mellitus (T2DM), hypertension, cardiovascular diseases (CVD), visual problems, nerve impairment and renal failure. In addition, obesity may result in low self-esteem and despondency. Most complications related to obesity are long-term with no curative treatment, thus resulting in a significant detrimental effect on the Health-Related Quality of Life (HrQOL) of the individual.

Material and Methods

Selection Outline

This literature search analysed the factors that influenced and/or contributed to obesity in both children and adults. The literature was systematically analysed using a three-stage methodology of the following scientific databases: PubMed, Scopus, Google Scholar, CINAHL, EMBASE and Cochrane reviews. Established and well-recognised News and Health Service websites such as the BBC and NHS were used to obtain recent information that is not yet published in a scientific journal. To ensure that the sources I used were reliable and had sufficient scientific objectivity, I decided to use ***CAPOW*** (Currency, Accuracy, Purpose, Objectivity and Writing Style) criterion to evaluate them**.** This allowed for the most relevant and up-to-date literature to be analysed.

Analysis of Database Selection

The well-regarded and peer-reviewed databases such as PubMed, Scopus, Google Scholar, CINAHL, EMBASE and Cochrane reviews, along with

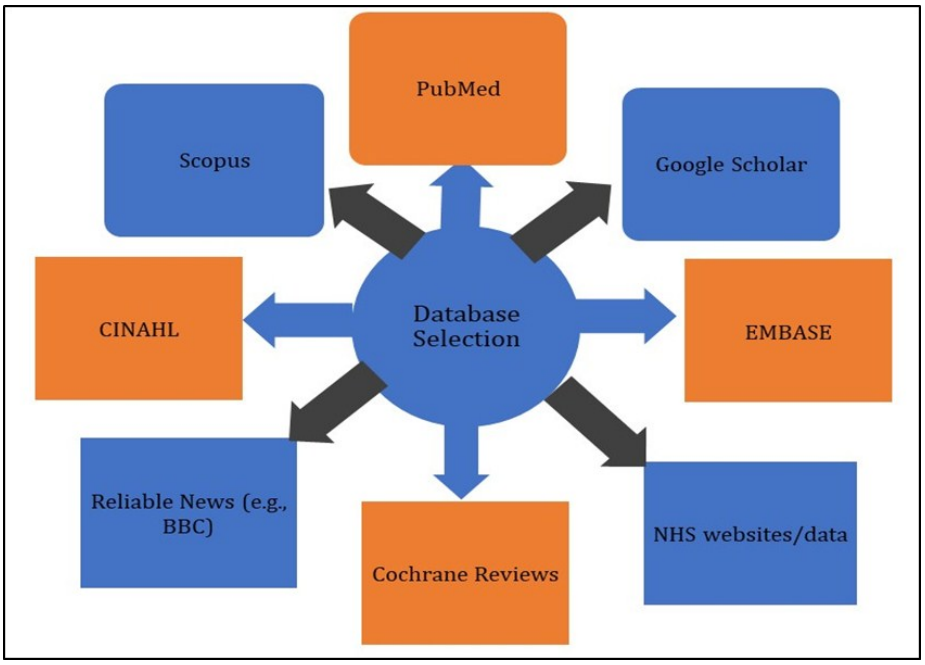

***Figure 1**: Summary of Databases Selected to Conduct Literature Search*

established News and Health Service websites such as the BBC and NHS, were considered ***(Figure 1)***.

An initial basic search about the topic was performed. PubMed has a strong filtering system as well as a 'See Related Citations' feature, which enables a wider study of the topic. Scopus, one of the largest citation database of peer-reviewed literature, has advanced filtering features, which is useful when narrowing down the results. Although Google Scholar has a limited ability to filter the search, the large number of publications in its repository allows a broad reading of the topic and covers a longer time-period. The records CINAHL provided were mostly citations and an author-provided abstract of the article but the full-text was available only for selected journals. Hence this database was not considered further. EMBASE, an Elsevier database available through subscription, was not used since all articles were available on PubMed. Cochrane review was used but no information was found in the search (due to a paucity of randomised controlled trials on this topic) and, therefore, not useful in the literature search. A criteria-based selection process allowed a short-list to be created by selecting the most appropriate literature ***(Figure 2)***.

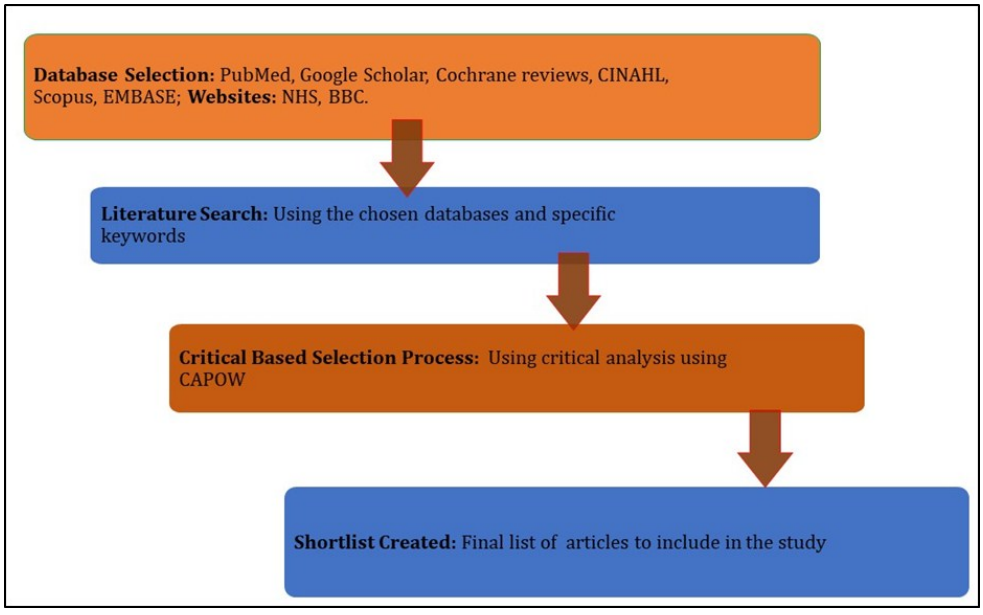

***Figure 2**: Overview of Methodology*

Literature Search

During the initial search, it became apparent that a plethora of information was available regarding the general topic of diet and obesity, and its associated complications and morbidities. This resulted in an unexpectedly large number of 'hits' during the literature search. In order to narrow down the relevant information, the chosen scientific databases were used to conduct a literature search using the key words *'income and obesity', 'education and obesity', 'childhood obesity and causes', ethnicity and obesity', 'immigration and obesity', 'genetic factors and obesity' and 'current research in genetics and obesity'* ***(Table 1)***.

Table 1*: Number of Results for Research Topics*

Number of results from key words: CASE 1	Scopus	PubMed	Google Scholar
Ethnicity and lack of exercise	11,000	48,800	117,000
Ethnicity and migration	12,500	37,800	125,000
Genetic factors and obesity	24,400	678,000	1,230,000
Education levels and obesity	26,900	1,050,000	1,660,000
Income and obesity	11,700	213,000	611,000
Current research in genetics and obesity	18,500	377,000	1,020,000

Results

Ethnicity and Lack of Exercise

Majority of the UK population is White Caucasian (87%), followed by people of Black Caribbean, Black African, Indian, Pakistani, Mixed and Bangladeshi descent. The prevalence of obesity among Black children aged 10–11 is about 30% compared to about 18% in Caucasian children ***(Figure 3)***. This disparity may be due to certain social factors, such as ethnic minority children engaging in lower levels of physical activity compared to their Caucasian peers.[7, 8, 9] Recent research (2019) published by Cambridge Scholar at the Centre for Diet and Activity Research (CEDAR) in the Medical Research Council (MRC) Epidemiology Unit at the University of Cambridge indicated that factors such as limited access to or the cost of participating in sports, parents working long and unsociable hours, and low socioeconomic status might influence this. Likewise, a combination of personal beliefs, socioeconomic, cultural and environmental barriers has been thought to discourage people from Black and other minority ethnic groups from engaging in physical activity. According to National Obesity Observatory, South Asian women report barriers such as dress codes and limited amount of single-sex facilities impede their physical activity. Likewise, studies have identified that some South Asian women have negative attitudes to physical activity instilled by their parents or grandparents who view sports and femininity to be incompatible.[10, 11] These views might be propagated to the future generations.

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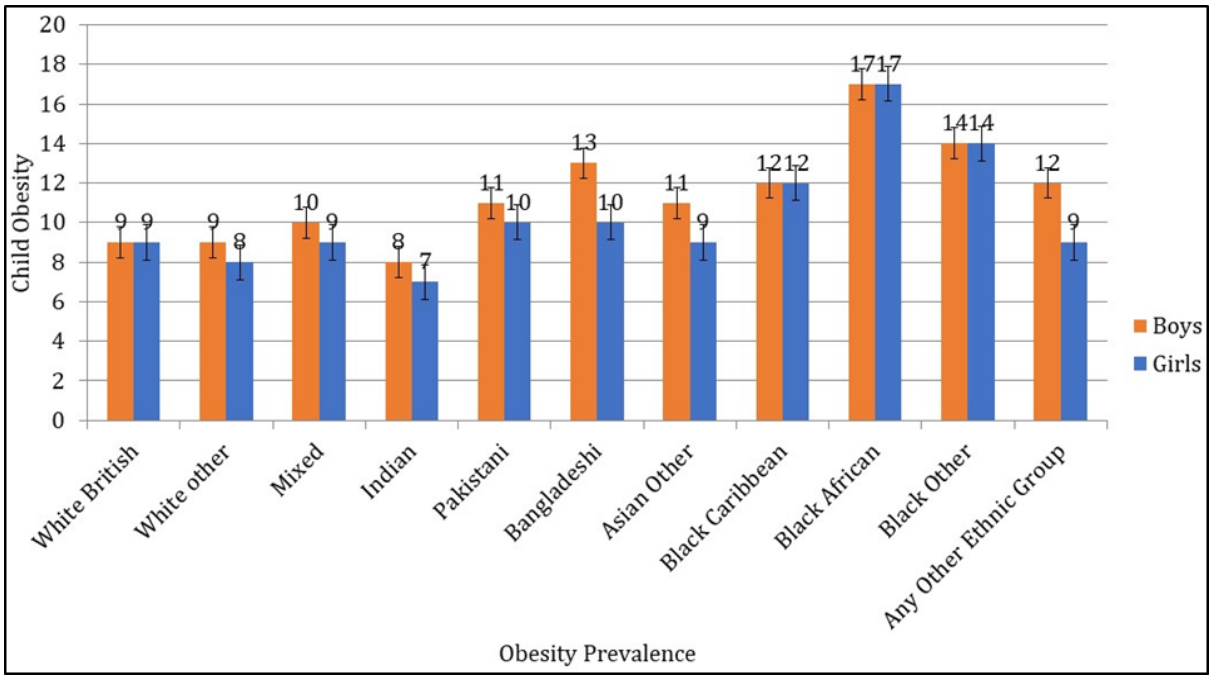

Figure 3: *Obesity Prevalence Amongst Different Ethnicities in the UK* [12]

Ethnicity and Migration

Research has identified that African-Americans have lower rates of lipolysis than Caucasians.[13, 14] Likewise, they may possess lower levels of adiponectin (a hormone that regulates glucose levels and fatty acid breakdown) during childhood and adolescence. This might explicate their increased preponderance towards T2DM and CVDs.[15] Migrant children are at higher risk of becoming overweight and obese due to acculturation and lifestyle changes: migrants tend to abandon their traditional food habits and adopt westernized dietary patterns containing high levels of fat, sugar and salt. In addition, migrants coming from developing countries may have a cultural preference for larger body sizes, as they are considered to be signs of good health and wealth. This may lead to the parents being unconcerned about their children becoming overweight or obese.[16] ***Figure 4*** illustrates the relationship between migration and obesity in American population.

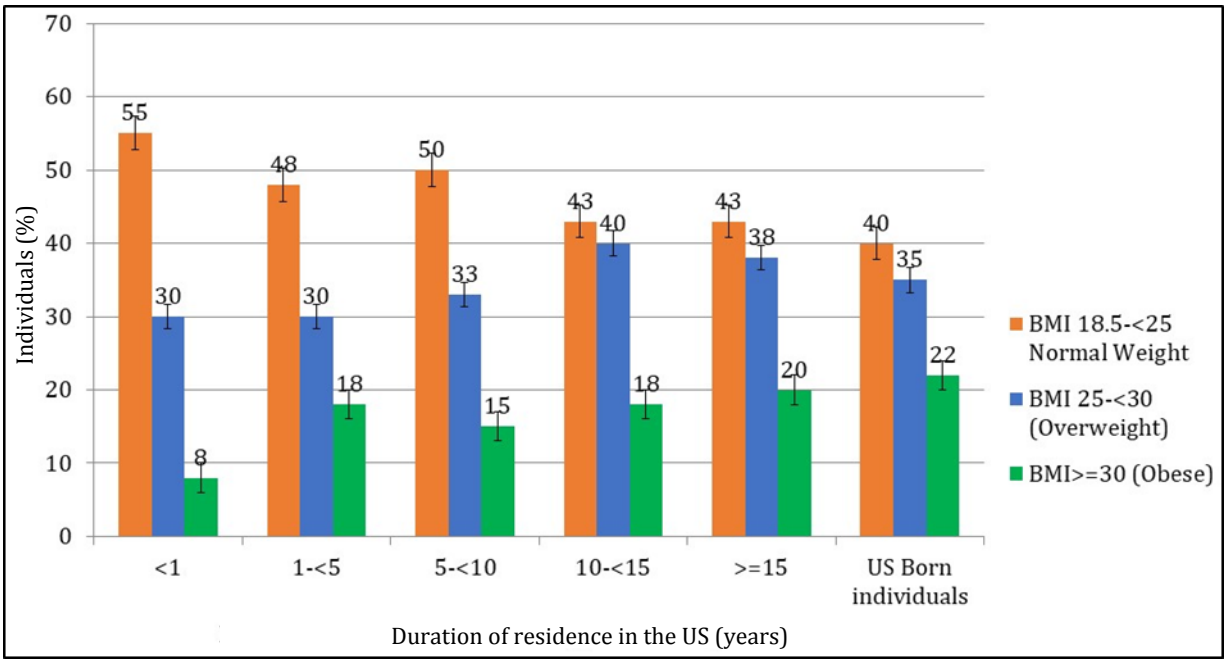

Figure 4: *Graph depicting the relationship between the Duration of residence in the US (Migration) and Obesity*[17]

Genetic Factors

Correlation has been established between an individual's genetic make-up and the risk of developing obesity. In 2010, Silventoinen and colleagues undertook a global study to determine the genetic and environmental influences on both twin and adopted children up to the age of 18 years.[18] They identified that the BMI of adopted children correlates strongly with biological parents and less with adoptive parents, thus corroborating a genetic predisposition.[18] About 50 obesity-associated genes loci have been identified, with both monogenic (5%) or polygenic (95%) inheritance patterns. In monogenic obesity, genes such as *FTO, PCSK1, MC4R, CTNNBL1* code for the proteins regulating the appetite and satiety centres cause pathological alterations, resulting in obesity.[19] Likewise, mutations in the polygenic genes inhibit the leptin-melanocortin pathway that regulates the energy homeostasis. Single Nucleotide Polymorphisms (SNPs) that occur on the first intron of the FTO gene, which is associated with fat mass and obesity, can result in a higher adiposity and, thus, obesity.[20] In 2016, Silventoinen and colleagues studied 88,000 twins (both monozygotic and polyzygotic) to understand the effect of genetics and the environment on BMI.[18] They concluded that the genetic factors could be influenced by environmental factors (such as availability of high calorie food, lack of exercise and social poverty).[21]

Role of Gut Microbiomes

Changes in the microbes of the gut (bacteria that influence the absorption of nutrients and the inflammatory responses of the body) could be associated with a higher risk of developing obesity.[22] The composition of microbiomes depends on the host, but it can also be modified by exogenous and endogenous factors. In infants, perinatal antibiotic exposure (destroys native gut flora), method of childbirth (vaginal birth is advantageous) and antibiotic usage during the first 2 years after birth could result in changes to the microbiomes. This can result in inefficient absorption of nutrients, altered regulation of fatty acid tissue composition and induce low-grade inflammation. In adults, excessive use of antibiotics can adversely affect the gut microflora that normally have a beneficial effect on digestion and absorption of nutrients. This can result in impaired metabolism and malabsorption of essential minerals and vitamins in the long-term.

Discussion

Health behaviours of a population can be influenced by geography, culture, ethnicity and socioeconomic factors. The incidence of obesity related complications such as T2DM and CVD differs in the various ethnic groups. Individuals from certain ethnic minorities in the UK often have lower socioeconomic status, which, in turn, can contribute to obesity especially in children and women (due to the difference in metabolism causing a greater increase in levels of fatty acids in blood and menopause affecting fat distribution).[23, 24, 25]

Sedentary lifestyle is also a major predisposing factor for the development of obesity and its associated morbidities. Study by Williams *et al*., (2010) has shown that, in the UK, individuals from South Asian population or descent have lower levels of physical activity.[11] The stigma that follows being obese leads to lack of confidence and low self-esteem. This could translate into these individuals not being able to get employment, thus continuing to remain within the low socioeconomic group. Minority ethnic groups tend to have greater levels of unemployment, experience less social mobility, lower income which causes them to reside in deprived areas within the UK. Migrants, refugees and asylum seekers from countries such as Congo, Somalia, Afghanistan and Eritrea face a high degree of exclusion form the job market.

In order to achieve health equity and to eliminate health disparity, the Government should strategically plan policies that are achievable and practical. Some recommendations include producing linguistically appropriate materials through inclusion of cultures and values that are specific to these ethnic minorities.[26] Another recommendation includes training individuals from these minorities to be 'community health ambassadors' for their community wherein they will be able to communicate with their own people and spread the knowledge and awareness regarding the importance of physical activity and good health.

Genetic or epigenetics (heritable phenotypic changes that do not involve alterations in the DNA sequence) cannot fully explicate the rapid rise in global obesity since the pool of different genes across a population remains fairly stable for many generations. It takes a long time for new mutations or polymorphisms to develop and manifest in a population. The answer is most likely in our societal factors: the physical, social, political, and economic surroundings that influence how much we eat and how active we are. Environmental changes that have made it easier for people to overeat and harder to get enough physical activity have played a key role in triggering the recent surge of overweight and obesity.[27] In 2008, for example, Andreasen and colleagues demonstrated that physical activity offsets the effects of one obesity-promoting gene, a common variant of FTO. The study, conducted in 17,058 Danes, found that people who carried the obesity-promoting gene and who were inactive had higher BMIs than people with the same gene variant

but were active. Although research on obesity-related gene-environment interactions is fairly recent and thus conclusive evidence limited, the indication so far suggests that genetic predisposition does not play a significant or proven role as many individuals who carry the so-called "obesity genes" do not become overweight. Consuming a healthy diet and getting enough exercise may counteract some of the gene-related obesity risk.

Ongoing Research

The leptin-melanocortin pathway is important to trigger the satiety centre in the hypothalamus. Absence of such inhibition leads to a desire to binge eat, increased feeling of hunger and polyphagia (increase intake of food).[28] In 2019, a team led by Professors Farooqi at the Welcome Trust-MRC Institute of Metabolic Science in Cambridge studied over half a million UK volunteers and found that MC4R can control the motivation for food in association with a brain reward system by 'switching the centre on-off' following eating through beta-arrestin pathway.[29] In obese individuals, the genetic variation is 'switched on' such that the individual consumes more calories than required. This is a breakthrough research and is thought to be a powerful aid in developing safer and effective treatment options for weight loss therapies.[30]

Dr Langenberg (2019) identified a genetic link between higher plasma glycine levels, and an increased incidence of T2DM and CHD. It is postulated that high levels of plasma glycine are associated with a higher blood pressure, thus reducing the risk of CHD. The study identified 27 genetic loci and concluded that glycine is genetically associated with higher CHD risk, possibly by increasing the blood pressure. They also found a strong association between genetically predicted hyperinsulinemia and higher levels of glycine (observed association between higher glycine and higher incidence of T2DM), and the glycine-T2DM association may be driven by a glycine-lowering effect of insulin resistance. Further understanding of the genetic link to glycine pathway could pave the way for novel treatment strategies to treat T2DM and CHD.

Future Directions

With continued advances in technology, micro-informatics and data analytics, there will be rapid strides in determining the role of genetics and epigenetics to determine the causation of obesity. Studies involving identical and biological twins might glean more information on the effect of nature and nurture in influencing obesity. Currently, there's a dearth of randomised controlled or blinded studies in the field of obesity and, thus, statistically significant objective evidence is limited. In might be beneficial to consider such studies in the future. Likewise, when undertaking population-based studies, it would be beneficial to carry out longitudinal or Cohort studies that follow a set of children through their development to see the impact of different contributing factors to obesity. Finally, when analysing studies in a structured manner as in a meta-analysis, it would be judicious to consider studies carried out in different parts of the world comprising a diverse population.

Conclusion

The prevention and treatment of obesity require commitment and collaboration of all relevant stakeholders at an individual, community, national and international levels.

Targeted education, behavioural changes and environmental approaches may be effective in promoting healthy lifestyle habits. For individuals to maintain these positive traits over longer periods of time and to have a long-lasting impact that negates an obesogenic environment, governments, industries, health care professionals and community members must consider the prevention of obesity to be of high priority. Specific strategies and delivery methods for the prevention and control of obesity at home, school, workplace, and healthcare settings should be established. Since factors such as genetic influence, hormonal variations, gut microbiomes, ethnicity and geographical migration are beyond an individual's control, at present, it might appear futile to influence this predisposition. However, with further advances in genetics, epigenetics and genomics, as well as novel technological developments, a more robust strategy may be implemented to target and attenuate some of these innate factors.

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