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A review on association and correlation of genetic variants with eating disorders and obesity

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Abstract

Background: Now, eating disorders and obesity and their correlations are danger signal in worldwide which is caused by multifactor and associated with significant mortality and morbidity.

Main body: Every aspect of a patient's life is influenced by eating disorders and obesity and their correlations. Due to frequent seeing of obese patients, eating disorders have been included in the review as they can sometimes be associated with obesity. However, it should be noted that most patients having eating disorder are at risk to be obese or overweight. This research explores the risk factors for the two disorders, as well as the assessment of medical complications and treatment recommendations for the disorders. In these two disorders, there is also a correlation. The essential consideration is that eating disorders are impulse-control disorders which are similar to addictive behaviors in some aspects. So it is a crying need to treat a patient with obesity and eating disorders simultaneously to ensure success. Genome-wide association studies (GWASs) have increased our knowledge of the pathophysiology of eating disorders (EDs) and obesity and their correlation.

Conclusion: This review enlightens on the summary of eating disorder, obesity, genotypic traits, molecular relations, interaction, correlation, and effect of eating disorder and obesity which outline potential future directions and clinical implications for patients with EDs and obesity.

Keywords: Eating disorders, Obesity, Genome, traits

Background

Eating disorders can be categorized into a class of mental illnesses that could result in numerous somatic and psychiatric complications and have penchant to perturb living quality as well as mortality in some cases. This psychiatric condition has increasingly been able to seek attention among world health fraternities over the past 20 years [1]. In accordance with the National Eating Disorder Association, not less than 70 million people across the world including both the male and female have been reported to experience eating disorders during their lifetime [2]. In every 62 min, the earth witnesses at least one of its inhabitants being deceased directly due to this nuisance [3]. The outbreak of these psychological disorder is on the rise in numerous countries and it was particularly predominant in females with young age [4], in Western and affluent countries [5] during the late twentieth century presumably by the virtue of factors related to economy and culture. Albeit globally, the ranking had been quite steady during the time period of 1990 to 2013 (shifting from 13th position in 1990 to 12th position in 2013); ranking of middle and low-income countries grew from 58th position in 1990 to 46th position in 2013 [6]. In recent time, eating disorders have been widely burgeoning among people dwelling in non-Western countries, mainly South Asia, China,

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and Middle East [7]. At present, worldwide pervasiveness of eating disorders is prominent, and hence Asia is also encountering overwhelming health burdens, though sparseness in terms of epidemiological information exists in Pacific Island and Asian countries [8]. The surges of EDs over the last 30 years have enlightened the intricate intertwining between pathology and culture. The propagation of EDs across various part of Asian region has combined with the time of unprecedented development and widespread economic and social revolution throughout much of the arena [9]. In Asia proper, only a few cases of EDs were recorded in certain countries before the 1990s, such as Singapore, India, Malaysia and among Chinese staying in Hong Kong (once under British control), but as a whole, EDs had been extensively absent in Asia except for Japan where EDs were reported to come into view in the mid-1970s [10]. Reportedly, by the end of the twentieth century, disorders in the eating behaviors and attitude enhanced considerably across Asian high-income young females, whereas clinical EDs crossed the boundaries of Japan to Hong Kong, Singapore, Taiwan, and Korea [11]. It is stated that EDs have proliferated among Asian population through the supposedly "Asian miracle" of economic revolution as it stretches across the territory [10]. Initially, EDs were found less prevalent in low-developed and relatively indigent Asian countries such as Myanmar, Thailand, India, Indonesia, Bangladesh, Philippines, Cambodia, China, Laos, and Vietnam [11]. However, evidence points out that there was a sharp increase in the cases of EDs across the territory varying explicitly with economic development and concomitant urbanization and industrialization. Obesity is one of the risk factors for the commencement of eating disorders as it is linked with high degree of body image discontentment and dieting pattern, and can certainly be also viewed as a tag of disordered eating. Accordingly, obesity, a comprehensive event of the twenty-first century is a pivotal causative factor for a lot of other metabolic disorders. WHO says, in 2014 over 1.9 billion people of 18 years old and above were found to be overweight; of these, more than 600 million people were obese, whereas about 15% women deemed obese across the globe [12]. In general, around the world, obesity and overweight kill more number of people in comparison with underweight. In 2016, 41 million children aged below 5 were obese or overweight while at the same year more than 340 million adolescents and children aged 5–19 were estimated to be obese or overweight [13]. Eating disorders and obesity are usually considered as two separate problems and are tackled by multidisciplinary professionals via the employment of distinctive clinical approaches and theoretical models. However, the current WHO standard data, garnered from a total of 79 developing countries along with some industrialized ones, reveals that the number of overweight children in the world are 110 million [14]. In several developing countries, the increasing number of overweight and obese children and adolescents has been well reported. Insufficiency in macro- and micronutrients has long been a major issue for children in low-income countries. Given a persistently high burden of malnutrition, Indo-Asian countries are now confronted with the peculiar challenge of a rapid increase in childhood obesity [15]. Over the last few decennaries, majority of Asian countries have noticed a drastic surge in the number of obese and overweight people, with the figures being soared up to many times and the degree of extension differs based on the diversification of various countries. One of the health surveys carried out in Bangladesh asserted that the presence of obesity and overweight (11.86% vs. 14.86%) were markedly greater in males (1.29-fold) in comparison to females. Unlike the average waist-circumference in male was prominently higher than in females, the ratio of waist to height (WHtR) was seen greater in females when correlated with males [16]. Teenaged girls have a potentiality to endure more than single disorder or to move from one disease to another with varied levels of severity [17, 18]. Conversely, a meta-analysis divulged that, pooled prevalence rate for obesity and overweight during the year of 2000 and 2015 among the adolescents and children was 9.7% and 7.9% respectively [19] and around 37.6% university going pupils in Bangladesh were deemed to be predisposed to eating disorder [20]. A variety of psychological hypotheses are available on eating disorders and out of them a hypothesis titled as "thrifty genotype" proposes that binge eating is sort of a psychological habituation that helps avoid malnutrition, regulated reproduction, and survival amid famines. Whereas, another hypothesis popularly known as "intra-sexual competition" has come up with the concept that the extreme intra-sexual contest for mates is the eventual reason for eating disorders. This hypothesis figures out that the shape of a woman's body is a marker of her reproductive potential, reproductive history, as well as mate value, partially signaled by BMI or body mass index and waist-to-hip ratio. It can be acknowledged that International conferences attended by the obesity researchers and specialists and arranged by the national and international associations of obesity often have dearth of contents on eating disorders. Notwithstanding that they have own community and professional group to eating disorder experts, they hardly manage to attract a great deal of commercial sponsorships in order to hold their meetings. This aberration is largely mirrored in varying public media perception to the disorders—blame or reluctance in obesity cases, and pity and awe concerning eating disorders. Antipathy between these two is generally

buttressed by the media through its overly simplified portrayal of scientific attainments and its extreme obsession with celebrity and body image. Women are often derided alternately for losing or gaining weight under the media limelight, with accompanying remarks which either rebuke them for their excessive self-indulgence or applaud them on their resiliently obtained thinness. Therefore, it has become an utmost priority to determine the long-standing characteristics of the both clinical problems of eating disorder and obesity.

Table 1 Classification, causes, sign and symptoms, treatment of eating disorders

Classification	Causes	Sign and symptoms	Treatment
Anorexia nervosa	Anorexia nervosa is linked to biological, cultural and social factors, family, parenting style, environmental influences, parental discord, and household stress.	marked weight loss, vomiting, chronicity, cardiac muscle wasting, psychiatric comorbidity, hypoglycemia, psychosocial problem, passive-aggressive and obsessive-compulsive disorder, heart failure, depression, hypoproteinuria, extended corrected QT interval, mineral and vitamin inadequacy, electrolyte disorder are common [23].	• Medication: (SSRI or selective serotonin reuptake inhibitors and antidepressants) [24], TCA or tricyclic antidepressant drugs [25, 26], antipsychotics [27], hormones [28], antiepileptics [29], nutritional supplement [30], weight restoration, and nutritional intervention. • Psychosocial interventions (CBT or cognitive behavioral therapy [31], CAT or cognitive analytic therapy [32]) • Family therapy [33] • Psychosocial interventions [34]
Bulimia nervosa	Mood disorder, physical and sexual abuse, obesity, parental obesity, low self-esteem, substance abuse, disturbed family dynamics, perfectionism, early menstruation in eating disorder patients, and parental shape/weight concern [35].	Bulimia nervosa has been observed to manifest binge eating symptoms, depression and anxiety, compensatory behavior, higher rates of obesity, sexual and physical abuse, mood disorder, perfectionism, low self-esteem, early menarche, disturbed family dynamics, and parental weight/shape concern [36].	• Medications: (SSRI, antidepressants, trazodone, 5-HT_3 antagonist, MAO inhibitors) [35]. • Psychosocial interventions [37] (dialectic behavior therapy , CBT). • Self-help trials, family therapy, 12-step programs/support group [38]. • Psychosocial interventions plus medication [38, 39] (CBT and tricyclic antidepressant, CBT and SSRI, CBT and multiple drugs). • Additional interventions (light therapy, guided imagery therapy, crisis prevention [37]).
Binge eating disorder	Though the exact reason of binge eating disorder has not been known up to date, several factors are assumed to play pivotal role in developing this disorder. Factors include the following [40]: • Biological: Biological abnormalities; for instance, genetic mutations or hormonal irregularities, may be implicated with addiction for food and impulsive eating. • Psychological: A profound relationship has been revealed between binge eating and depression. Low self-esteem, discontentment about body, and troubles in coping with emotions may also impart to the formation of binge-eating disorder. • Social and Cultural: Situations leading to trauma, e.g. a past event of sexual abuse, may enhance the risk of BN (binge eating). Social stresses to be slim, most commonly influenced by media can instigate emotional eating. People subjected to mean and hurtful remarks about their weight or body are especially susceptible to binge-eating disorder.	Binge eating is referred as the major symptom of BED; but, every individual who binge eats does not possess BED. A person can binge eat without acknowledging number of negative psychological, social or physical consequences of BED. The aforementioned example can, at the most, be regarded as eating problem except for a disorder. It is somewhat problematic to provide a precise definition of binge eating, however episodes of binge eating in BED usually have the following features [41, 42]: • Eating much quickly than the usual, may be within short time space. • Eating up to the time of perceiving uncomfortably full. • Eating a huge volume even when do not have appetite for food. • Losing control over what or how much is eaten • Binges could be premeditated associating with buying certain binge foods, allocation of particular time for binging, occasionally at night. • Eating confidentially or alone due to the feeling of discomfort over the volume of food taken. • There could be bewildered psychological state at the time of binge. • Being unable to recall what was consumed following the binge • Sense of guilt, disgust or shame after a food binge.	• Medications [43] (SSRI, anti-obesity, anticonvulsants) • Multidisciplinary sequential strategy [43] (Psychoeducational and behavioral interventions) • Psychotherapies [40] (DBT or dialectic-behavioral therapy, CBT) • Personal motivation and counseling • Bariatric surgery. • Administration of numerous SSRIs, e.g., sertraline, citalopram, fluvoxamine and fluoxetine, etc. [44]. • Other treatments available for BED are lifestyle interventions such as peer support groups, hormonal abnormalities investigation and weight training. Concentrating on optimistic mindset and self-love is effective for many [45].

Main text

Eating disorder and obesity

What does obesity and eating disorder mean?

Obesity is a long-term clinical condition which evokes plethora of other comorbid diseases and is accountable for medical morbidity to a great extent. With the global burst of corpulence, consciousness and research regarding obesity has heightened which ultimately leads to the ground breaking innovation of noble drugs, surgeries, and diets. Having stated that, yet the problem has kept hiking up at a substantial rate, particularly in adolescents. Eating disorders refer to illnesses that can be characterized by the presence of severe anguish or anxiety about one's own body mass or shape and undisciplined eating habits. Eating disruptions may involve insufficient or excessive consumption of food than the usual which is likely to inflict damage to individual's weal. Anorexia nervosa, binge eating disorder, and bulimia nervosa are the three most prevalent eating disorders. Anorexia nervosa, commonly termed as simple anorexia, is explicated as a type of eating disorder diagnosed by the presence of diminished body weight, fear of being chubby, dietary restriction, and an intense craving to become skinny [21]. Total death tolls caused by anorexia nervosa is the highest among all the psychiatric disorders [22] and about 0.3% young women have been found to be affected by it. Bulimia nervosa is a condition where someone becomes exceedingly preoccupied with his/her body shape and weight, with regular incidents of unrestrained gluttony accompanied by measures to subdue the appalled effects of eating in excess. Finally, binge eating disorder can be construed as a sort of severe eating disease characterized by frequent intake of abnormally large volume of diet and feeling of being incapable to put an end to eating. Treatment for eating disorders should necessarily be personalized on the basis of symptom severity (Table 1).

The relationship between obesity and eating disorders

Until the inclusion of BED (binge eating disorder) and compensatory behaviors of obesity, there had been conduction of extensive studies in the field of compulsion-induced over-eating and binge eating on clinical platform for some period of 50 years. In the decade of the 1990s, BED was formally subsumed in the categorization of diseases, and as a matter of fact even now researchers have an inclination to carry out studies on it compared to diagnostic status (Fig. 1). Recurrent self-indulgent overeating episodes characterize BED, with omitting the abuse of laxative or compensatory vomiting which actually represent bulimia nervosa. Despite majority of obese persons are not presented with BED, susceptibility to BED continues to rise with augmenting obesity. BED exists more commonly in females than the male counterparts. Surveys have managed to shed light upon the verity that, around 1–2% people expose to BED at some stages of their lifespan, with about 0.1–1% people being afflicted in a certain year. Among subjects who are seeking treatment for weight loss have been observed to show varied rates of 1.3–30% [46]. BED conceptualizations debate that it can be distinctly distinguished from anorexia; however, it is in no way a useful subclass of obesity [47]. Moreover, there has been a suggestion that treatments concentrated on BED could be succeeded but have a meager effect on the loss of individual's weight. Weight-loss treatments in obese people are effective in an equal manner (modestly) with the presence or absence of BED, but patients with a mood disorder (also referred as mood affective or affective disorder and is more common in BED) do not improve much. Gain speculation is a term which means abnormal dietary intake, Unhealthy diet, lifestyle, certain medication, and other medical problems. It is thought to be of a risk factor in terms of weight and BED might impart contribution to the escalation in obesity [48].

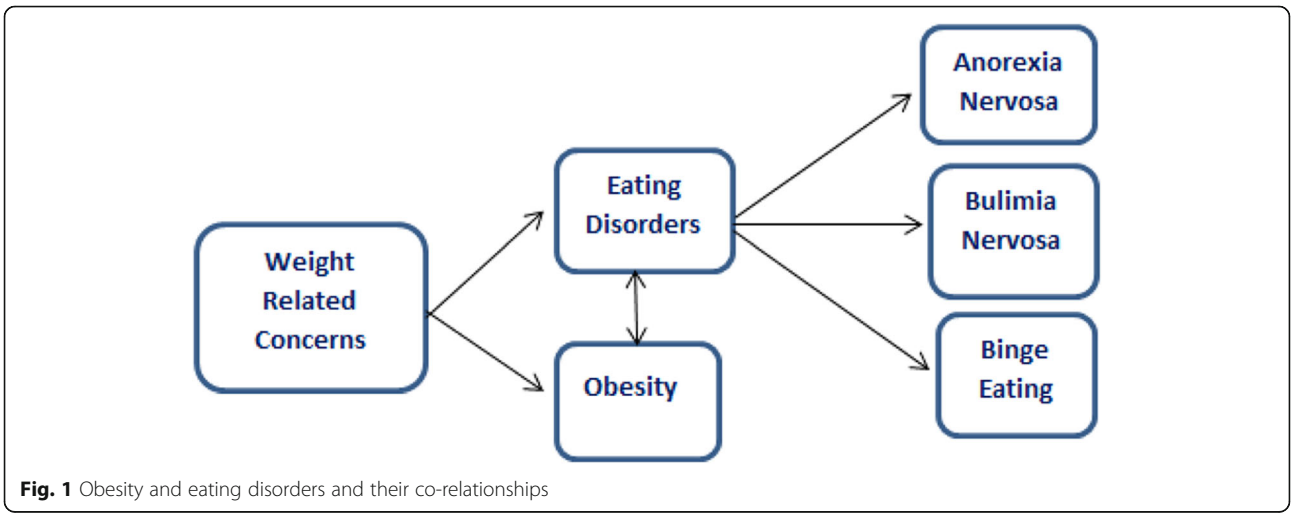

Fig. 1 Obesity and eating disorders and their co-relationships

Table 2 Overview of candidate gene findings in eating disorders

Gene	Description	rs Number	References
HTR1D	Serotonin receptor 1D	rs6300	[51]
		rs674386 rs856510	[52]
HTR2A	Serotonin receptor 2A	rs6311	[53–56]
HTR2C	Serotonin receptor 2C	rs6318	[57]
DRD2	Dopamine receptor D2	rs1799732	[58–60]
		rs6277	[59, 60]
		rs6278	[58]
		rs2283265	[60]
DRD3	Dopamine receptor D3	rs6280	[61]
DRD4	Dopamine receptor D4	rs1800955	[62]
COMT	Catechol-O-methyltransferase	rs4680	[63, 64]
ANKK1	Ankyrin repeat and kinase domain containing 1	rs1800497	[59, 60]
LEP	Leptin	rs13228377 rs7799039	[65]
LEPR	Leptin receptor	rs1137100 rs1137101	[65, 66]
		rs8179183	[66]
GHRL	Ghrelin	rs696217 rs4684677	[65, 67–69]
		rs34911341	[68, 69]
		rs2075356	[69]
MC4R	Melanocortin 4 receptor		
		rs52820871	[70, 71]
		rs17782313	[65, 72]
		rs489693	[65]
AGRP	Agouti related protein	rs5030980	[65, 73]
		rs13338499	[65]
POMC	Proopiomelanocortin	rs1042571	[65]
ESR1	Estrogen receptor 1	rs726281 rs2295193 rs3798577	[74]
		rs2234693 rs9340799	[75]
ESR2	Estrogen receptor 2	rs1256049	[75, 76]
		rs4986938	[75]
		rs928554	[77]
BDNF	Brain-derived neurotrophic factor	rs6265	[65, 78, 79]
		rs56164415	[65, 78]
CNR1	Cannabinoid receptor 1	rs1049353	[80, 81]
OPRD1	Opioid receptor delta 1	rs536706 rs760589 rs204081	[51]
		rs569356 rs521809 rs4654327	[52]
		rs536706 rs204081	[51]

Table 2 Overview of candidate gene findings in eating disorders *(Continued)*

Gene	Description	rs Number	References
OPRM	Opioid receptor mu 1	rs1799971	[82]
FTO	Fat mass and obesity associated	rs9939609	[83, 84]
GHRL	Preproghrelin gene	rs696217 rs2075356	[69]
TPH2	Tryptophan hydroxylase 2	rs1473473	[85]
POMC	Pro-opiomelanocortin	rs24831852	[86]
NTRK3	Neurotrophic tyrosine kinase receptor type 3	rs7180942	[87]
FAAH	Fatty acid amide hydrolase	rs932816 rs324420 rs324419 rs873978 rs2295632	[80]
NAAA	*N*-acylethanolamine-hydrolyzing acid amidase	rs2292534 rs4859567 rs10518142 rs6819442	[80]
MGLL	Monoglyceride lipase	rs893294	[80]

Molecular studies of eating disorder and obesity

The objective of linkage studies is to find out the genomic regions which are more likely to contain genes implicated with a particular disease or trait. For linkage analysis, experiment is carried out on samples related to individuals (for example, dense pedigrees, affected sibling pairs, parent-offspring trios), and no priori hypotheses formed on the basis of priori data or biological function are required. Candidate-gene association studies, commonly abbreviated as CGAS, have been vastly effective for disorders where relationship between the selected gene and pathogenesis of disease is already well grounded [49]. In case of psychiatric disorders with completely elucidated underlying pathophysiology, candidate-gene approaches employ more speculation in regard to pertinence of the concerned gene, and therefore, have less prior possibility in identifying true association [49]. Candidate gene studies in the field of eating disorders need to take the following clinical observations into account: (A) The existence of AN and BN in female is remarkably greater (ratio 9:1). (B) The clinical manifestation stage of BN and AN appears more frequently in late adolescence and puberty respectively. (C) Around 30% of AN patients develop BN in future; the reverse direction is less common. (D) Increased comorbidity rate has been seen with major depression, generalized anxiety disorder, and obsessive-compulsive disorder (OCD) [50]. Candidate-gene studies which have obtained popularity for studying genetics of obesity and EDs mainly focus on single-nucleotide polymorphisms (SNPs) with priori hypotheses grounded on biological function (as expressed in animal, in vivo or in vitro studies). Table 2 will succinctly outline the highlights that are attained from candidate-gene studies on EDs. GWAS has been carried out on obesity and EDs in order to estimate genetic relationships between various disorder and physical characteristics. Genetic correlations were calculated significantly positive between AN and neuroticism, schizophrenia, high-density lipoprotein cholesterol, OCD, and educational attainment. On the contrary, genetic correlations were calculated significantly negative between AN and insulin sensitivity, body mass index (BMI), lipid phenotypes, and glucose metabolism [88, 89]. We have experienced 3 successful waves of innovations backed up by high-density large-scale GWAS for obesity-linked traits (Table 3). In most of the studies, SNPs have been tested for correlation with BMI or body mass index as a continuous trait [97, 111]. BMI is regarded as a suitable proxy-measure of adult's adiposity which is quite convenient to obtain as well as available in numerous studies.

Emerging hypotheses, clinical implications, and future directions

Is dieting a risk for obesity?

Regardless of the fact that many people tout dieting as a solution for the upheaval of obesity epidemic, some prospective studies concluded that dieting is ineffective in thwarting weight gain [112]. On top of that, recent study has also resurrected the idea stating as "dieting makes someone fat" [113]. Neumark-Sztainer et al. [114], Field et al. [115], and Stice et al. [116] are some of the most intriguing researches which suggest that adolescent girls who undergo dieting have increased likelihood in gaining weight and becoming obese compared to their non-dieting companions. It is, however, somewhat ambiguous to decide if dieting is causal factor in this correlation, or could it be that, a largely futile strategy happened to come by people who tend to over-eat and gain weight. Evidence has been increasing in such a way that properly run and evaluated child obesity interventions reduce weight and pathology of eating disorder. This eventually

Table 3 Common gene variants are associated with obesity phenotypes

Gene	Description	rs Number	References
FTO	Alpha-ketoglutarate-dependent dioxygenase	rs9939609 rs9930506 rs1121980 rs1421085 rs8050136 rs1558902 rs17817449 rs12149832 rs9940128 rs62033400 rs9941349 rs3751812	[90, 91]
MC4R	Melanocortin 4 receptor	rs17782313 rs571312 rs12970134 rs2331841 rs6567160 rs8089364 rs7234864 rs723486 rs7227255 rs2229616 rs17782313 rs17700144 rs663129 rs571312 rs476828	[92, 93]
PCSK1	*Proprotein onvertase* subtilisin/kexin type 1	rs6232 rs6234	[94]
CTNNBL1	Catenin beta like 1	rs6013029	[95]
TMEM18	Transmembrane protein 18	rs6548238 rs2867125 rs4854344 rs7561317 rs11127485	[91, 96]
GNPDA2	Glucosamine-6-phosphate deaminase 2	rs10938397 rs13130484 rs348495	[97, 98]
SH2B1	Src homology 2B adapter protein 1	rs7498665	[97]
KCTD15	Potassium channel tetramerization domain containing 15	rs11084753 rs29941	[91, 97]
MTCH2	Mitochondrial carrier homolog 2	rs10838738 rs3817334	[97, 98]
NEGR1	Neuronal growth regulator 1	rs2815752 rs3101336 rs2568958	[91, 97]
NPC1	Niemann-pick disease, type C1	rs1805081	[99]
MAF	MAF BZIP transcription factor	rs1424233	[99]
PTER	Phosphotriesterase related gene	rs10598503	[99]
PRL	*Prolactin gene*	rs4712652	[99]
SEC16B	Endoplasmic reticulum export factor	rs10913469	[91]
ETV5	ETS variant 5	rs7647305 rs9816226	[91]
AIF1	Allograft inflammatory factor 1	rs2844479	[91]
BDNF	Brain-derived neurotrophic factor	rs6265 rs4923461 rs10767664 rs2030323 rs988712 rs925946	[91]
FAIM2	Fas apoptotic inhibitory molecule 2	rs7138803 rs7132908	[91]
SDCCAG8	Serologically defined colon cancer antigen 8	rs12145833	[96]
TNKS	Tankyrase	rs17150703	[96]
TFAP2B	Transcription factor AP-2 beta	rs987237 rs987237 rs734597 rs2272903	[98]
MSRA	Methionine sulfoxide reductase A	rs7826222	[100]
LYPLAL1	Lysophospholipase-like 1	rs4846567	[100]

Table 3 Common gene variants are associated with obesity phenotypes *(Continued)*

Gene	Description	rs Number	References
NRXN3	Neurexin 3	rs10146997 rs10150332	[98, 101]
HECTD4	HECT domain E3 ubiquitin protein ligase 4	rs2074356	[102]
GPRC5BB	G protein-coupled receptor, class C, group 5, member Bb	rs12444979	[103]
POMC	Pro-opiomelanocortin	rs713586 rs6545814 rs1561288 rs6752378 rs10182181	[98, 103]
MAP2K5	Mitogen-activated protein kinase 5	rs2241423 rs2241423 rs4776970 rs997295	[98, 103]
GIPR	*Gastric inhibitory polypeptide receptor*	rs2287019 s11671664	[103]
FANCL	Fanconi anemia complementation group L	rs887912 rs12617233	[103]
TNNI3K	TNNI3 interacting kinase	rs1514175 rs12142020 rs1040070 rs1514174	[98, 103]
TMEM160	Transmembrane protein 160	rs3810291	[103]
CADM2	Cell adhesion molecule 2	rs13078807	[103]
LRP1B	Low-density lipoprotein receptor	rs2890652	[103]
PRKD1	Protein kinase D1	rs11847697 rs12885454	[103]
MTIF3	Mitochondrial translational initiation factor 3	rs4771122	[103]
ZNF608	Zinc finger protein 608	rs48361333	[103]
PTBP2	Polypyrimidine tract binding protein 2	rs1555543	[103]
TUB	Tubby protein homolog	rs4929949	[103]
HMGA1	High mobility group AT-hook 1	rs206936	[103]
MC4R	*Melanocortin 4* receptor	rs7227255	[103]
RSPO3	R-spondin 3	rs9491696	[104]
VEGFA	Vascular endothelial growth factor A	rs6905288	[104]
TBX15	T-box transcription factor 15	rs984222	[104]
NFE2L3	Nuclear factor erythroid 2-like factor 3	rs1055144	[104]
GRB14	Growth factor receptor bound protein 14	rs10195252	[104]
DNM3	Dynamin-3	rs1011731	[104]
ITPR2/SSPN	Inositol 1,4,5-trisphosphate receptor type 2	rs718314	[104]
LY86	Lymphocyte antigen 86	rs1294421	[104]
HOXC13	Homeobox protein hox-C13	rs1443512	[104]
ADAMTS9	A disintegrin and metalloproteinase with thrombospondin motifs 9	rs6795735	[104]
ZNRF3	Zinc and ring finger 3	rs4823006	[104]
NISCH	Nischarin gene	rs6784615	[104]
CPEB4	Cytoplasmic polyadenylation element binding protein 4	rs6861681	[104]
RASAL2	RAS protein activator like 2	rs10913469 rs543874 rs574367 rs516636 rs591120	[91, 103]
LYPLAL1	Lysophospholipase-like protein 1	rs2605100	[104]
SLC39A8	Solute carrier family 39 member 8	rs13107325	[103]
NCR3	Natural cytotoxicity triggering receptor 3	rs2844479 rs2260000	[31]

Table 3 Common gene variants are associated with obesity phenotypes *(Continued)*

Gene	Description	rs Number	References
		rs1077393	
NUDT3	Nudix hydrolase 3	rs206936	[103]
RSPOS	roof plate-specific spondin	rs9491696	[104]
RPL27A	Ribosomal protein L27a	rs4929949	[103]
ITPR2	Nositol 1,4,5-trisphosphate receptor, type 2	rs718314	[104]
FAIM2	Fas apoptotic inhibitory molecule 2	rs7138803	[91]
MTIF3	Mitochondrial translational initiation factor 3	rs4771122	[103]
NRXN3	Neurexin 3	rs10146997	[101]
SH2B1	*SH2B* adaptor protein 1	rs7498665 rs8049439 rs4788102	[91]
MC4R	*Melanocortin 4* receptor	rs17782313 rs12970134 rs17700144	[91, 103]
GIPR	Gastric inhibitory polypeptide receptor	rs2287019	[103]
TMEM18	Transmembrane Protein 18	rs2867125 rs6548238 rs7561317 rs12463617 rs4854344	[91, 103]
QPCTL	Glutaminyl-peptide cyclotransferase like	rs2287019	[91, 103]
ADCY9	Adenylate cyclase 9	rs2531995	[98]
AGBL4	ATP/GTP binding protein like 4	rs657452	[105]
ASB4	Ankyrin repeat and SOCS box containing 4	rs6465468	[105]
CCDC171	Coiled-coil domain containing 171	rs4740619	[105]
CADM1	*Cell adhesion molecule 1*	rs12286929	[105]
CADM2	*Cell adhesion molecule 2*	rs13078807	[103]
CALCR	Calcitonin receptor	rs9641123	[105]
CBLN1	Cerebellin 1 precursor	rs2080454	[105]
CDKAL1	CDK5 regulatory subunit associated *protein* 1 like 1	rs2206734, rs9356744	[106]
CLIP1	CAP-Gly domain containing linker protein 1	rs11057405	[105]
CREB1	CAMP responsive element binding *protein* 1	rs17203016	[105]
EHBP1	EH domain binding protein 1	rs11688816	[105]
ELAVL4	ELAV like RNA binding protein 4	rs11583200	[105]
EPB41L4B	Erythrocyte membrane protein band 4.1 like 4B	rs6477694	[105]
ERBB4	Erb-B2 receptor tyrosine kinase 4	rs7599312	[105]
ETS2	ETS proto-oncogene 2	rs2836754	[105]
FIGN	Fidgetin, microtubule severing factor	rs1460676	[105]
FHIT	*Fragile histidine triad* protein	rs2365389	[105]
FOXO3	*Forkhead box O3*	rs9400239	[105]
GBE1	1,4-Alpha-glucan *branching enzyme* 1	rs3849570	[105]
GDF15	Growth/differentiation factor 15	rs17724992	[105]
GNAT2	G protein subunit alpha transducin 2	rs17024258	[98]
GP2	Glycoprotein 2	rs12597579	[106]
GRID1	Glutamate ionotropic receptor delta type subunit 1	rs7899106	[105]
GRP	Gastrin releasing peptide	rs7243357	[105]
GRP120	G-protein coupled receptor 120	rs116454156	[107]
HHIP	*Hedgehog interacting protein*	rs11727676	[105]
HIF1AN	Hypoxia inducible factor 1 subunit alpha inhibitor	rs17094222	[105]

Table 3 Common gene variants are associated with obesity phenotypes *(Continued)*

Gene	Description	rs Number	References
HIP1	*Huntingtin Interacting Protein* 1	rs1167827	[105]
HMGA1	High mobility group AT-hook 1	rs206936	[103]
HNF4G	Hepatocyte nuclear factor 4 Gamma	rs4735692	[98]
HOXB5	Homeobox B5	rs9299	[106]
HS6ST3	Heparan sulfate sulfotransferases	rs7989336	[98]
HSD17B12	Hydroxysteroid 17-beta dehydrogenase 12	rs2176598	[105]
IFNGR1	Interferon gamma receptor 1	rs13201877	[105]
KAT8	Lysine acetyltransferase 8	rs9925964	[105]
KCNK3	Potassium two pore domain channel subfamily K member 3	rs11126666	[105]
KCNMA1	Potassium calcium-activated channel subfamily M alpha 1	rs2116830	[108]
KLF9	Kruppel like factor 9	rs11142387	[109]
LEPR	*Leptin receptor*	rs11208659	[110]
LMX1B	LIM homeobox transcription factor 1-beta	rs10733682	[105]
BBS4	Bardet-biedl syndrome 4	rs7164727	[105]
RIT2	GTP-binding protein Rit2	rs7239883	[105]
MAPK3	Mitogen-activated protein kinase 3	rs4787491	[105]
MIR548A2	MicroRNA 548a-2	rs1441264 rs9540493	[105]
MRPS33P4	mitochondrial ribosomal protein S33 pseudogene 4	rs13041126	[98]
NAV1	*Neuron navigator 1*	rs2820292	[105]
NLRC3	NOD-like receptor family CARD domain containing 3	rs758747	[105]
NT5C2	5'-Nucleotidase, cytosolic II	rs11191560	[105]
NTRK2	Neurotrophic receptor tyrosine kinase 2	rs1211166	[105]
NUP54	Nucleoporin 54	rs17001654	[105]
OLFM4	Olfactomedin 4	rs9568856 rs9568867	[98]
PACS1	Phosphofurin acidic cluster sorting protein 1	rs564343	[110]
PARK2	parkin RBR E3 ubiquitin protein ligase	rs13191362	[99]
PLCD4	Phospholipase C delta 4	rs492400	[99]
PMS2L11	postmeiotic segregation increased 2-like 11	rs2245368	[99]
PRKCH	Protein kinase C Eta	rs1957894	[110]
RABEP1	Rabaptin, RAB GTPase binding effector protein 1	rs1000940	[105]
RALYL	RALY RNA binding protein like	rs2033732	[105]
RARB	Retinoic acid receptor beta	rs6804842	[105]
RASA2	RAS P21 protein activator 2	rs16851483	[105]
RMST	Rhabdomyosarcoma 2 associated transcript	rs11109072	[110]
RPTOR	Regulatory associated protein Of MTOR complex 1	rs7503807	[98]
SBK1	SH3 domain binding kinase 1	rs2650492	[105]
DMXL2	Dmx-like 2	rs3736485	[105]
SMG6	*SMG6* nonsense mediated MRNA decay factor	rs9914578	[105]
STXBP6	Syntaxin-binding protein 6	rs10132280	[105]
TAL1	T-cell acute lymphocytic leukemia protein 1	rs977747	[105]
TCF7L2	Transcription factor 7-like 2	rs7903146	[105]
TDRG1	Testis development related 1	rs2033529	[105]
TLR4	Toll-like receptor 4	rs1928295	[105]

Table 3 Common gene variants are associated with obesity phenotypes *(Continued)*

Gene	Description	rs Number	References
TOMM40	Translocase of outer mitochondrial membrane 40 homolog	rs2075650	[106]
UBE2E3	Ubiquitin conjugating enzyme E2 E3	rs1528435	[105]
ZBTB10	Zinc finger and BTB domain containing 10	rs16907751	[105]
ZZZ3	Zinc finger ZZ-type containing 3	rs17381664	[98]

makes work on improving and shaping up the dieting conceptualization an even more priority.

Management of obesity—implications for eating disorders

Many people, especially the health professionals who are engaged in treating obese and overweight children have frequently voiced their concern over the issue that active involvement in weight loss can sometimes lead to the development of an eating disorder in children (Fig. 2). This hurdle has been hard to leap over, since there have not been enough number of treatments regarding chronic child obesity in the literature. These particular children have been supervised for a period of 10 years or above, and over the time, eating disorders have been occasionally occurring in children who underwent these programs, with the rates close to those estimated in the community. In 2005, the review of a literature by Butryn and Brownwell found 5 researches related to this [117]. They summarized by mentioning that children and teenagers participating in weight-loss programs that were administered professionally did not have increased eating disorders symptoms. In fact, they were observed to develop significantly improved psychological well-being among them [118]. Thus, weight control management in no way carries hazard for eating disorders if done expertly and properly, but in contrast, it could be considered a risk without the presence of this control and organization. Secondly, as some particular groups of overweight teenagers and children are more prone to eating disorders than others, more attention are in need to explore these underlying risks and the method how those risks can be screened. Already, the propensity for launching negative health campaign on obesity has been raised with a view to mobilizing public to alter their behavior. Hence, any attempt that is likely to further stigmatize fat people and obesity may ferment adolescent and child weight concerns and thereby risking the increase of eating disorders [119].

Joint working in future

Both eating disorders and obesity would reap benefits from an education that teaches the malefactor aspect of both disorders. Women belonged to the high risk group for eating disorders might not have judged their physical outlook so desperately if the perceived value of being slim had not been so great. A common perspective that obese people should look at their weight negatively to stimulate them with a view to reducing bulkiness, is misplaced. It is a matter of fact that most people find it exceedingly hard to bring a huge and long-lasting transformation of their weight, and a high level of discontentment is not supposed to guarantee success for sure. Rather, a personal perception of futility and failure may be added in attempting to lose weight. Modest loss of weight (10%), as recommended by the heath professional, can paradoxically be achieved by depleting the negative delineation of obesity. Usually, personally taken goals for weight loss end up largely being in smoke, making people finally to give up. In the survey, there has been no mention of any statement concerning the weight loss behavior that the overweight people are giving more concentrated effort with the obese people

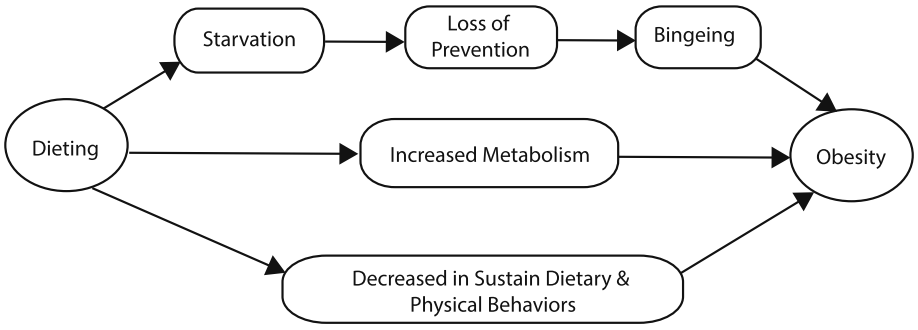

Fig. 2 Hypothesized associations and interrelationship between dieting and obesity

being less involved when it comes to trying. If it had been possible to make public understand about the intricacy of weight loss and weight regulation, enormous benefits would have obtained. Despite the truth that psycho-educational strategy is central for the treatments of numerous eating disorders, it has been disparaged in managing obesity. Without focusing on energy balance, an oversimplified message expressed in a phrase "Exercise more and eat less" is now widespread. We would not experience the present obesity levels if the solution was that facile. Therefore, the collaboration of the government, media, and health care professionals is an urgency to disseminate helpful, realistic, and consistent information [120]. Promotion of self-esteem in teenager and children should be one area to focus. This may also impart benefits to other health issues including conduct disorder and self-harm. Alternatively, surroundings that encourage and make young people eating healthily can be of mutual advantages to eating disorders and obesity. Therefore additional proof of long-term advantages of suchlike interventions is required.

Conclusion

Obesity and eating disorder perturb all ages, races, gender, sexual orientation, and ethnicities. People who suffer from health disorder or certain mental behavior problem undergo further complex medical condition later in their life. There are some particular genotypes which can make people more vulnerable to acquire those disorders. This review document explicated the complex genotypic correlation of eating disorders with obesity and overweight. It also delineated clinical implications, promising hypotheses, and future directions. It is high time we should talk and clarify it. Since this is a public health concern, making people well understand will definitely direct them through the exact way of tackling this epidemic. If early intervention, apposite treatment, and proper management are ensured, it is possible to gain complete recovery from this mental disorder.

Abbreviations

EDs: Eating disorders; BED: Binge eating disorder; BMI: Body mass index; AN: Anorexia nervosa; BN: Bulimia nervosa; GWASs: Genome-wide association studies

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Authors' contributions

SKA and AB equally participated in the conduction of the review. AFM, MK, and MSR did the initial literature search. UKR and AB participated in preparing the manuscript. SMNU designed the concept, analyzed the data. MAA redesigned the concept. SMNU and MAA revised the manuscript. All authors read and approved the final manuscript.

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