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LEPTIN RECEPTOR GENE AMONG OBESE SUBJECTS IN CARDIOVASCULAR DISEASES

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ABSTRACT

Leptin, a hormone synthesized by adipose tissue, serves a critical function in regulating both appetite and energy expenditure. Leptin resistance often occurs in obesity, which is characterized by excess adiposity. This impairment in leptin's signaling mechanism diminishes its efficacy in conveying feelings of satiety, potentially exacerbating the risk of cardiovascular diseases (CVDs) commonly associated with obesity. This review aims to investigate the complex link between leptin receptor gene variations and the heightened risk of cardiovascular diseases (CVDs) in people with obesity. By analyzing how genetic polymorphisms in the leptin receptor gene might disrupt leptin signaling pathways, we aim to shed light on their possible contribution to CVD development in this group. Synthesizing insights from pertinent studies, our objective is to consolidate the current understanding of the complex interplay between genetic predispositions, leptin resistance and cardiovascular health within the context of obesity.

Keywords: *Adipokines, Cardiovascular diseases, Leptin, Leptin resistance, Obesity*

INTRODUCTION

Cardiovascular disease (CVD) continues to be a major public health issue globally, particularly with an aging population [1]. In Europe and the United States, the prevalence of coronary heart disease (CHD) has significantly increased in recent years [1]. Joseph et al., pointed out that the onset of CVD is widely recognized to be influenced by a complex interaction of environmental and genetic factors [2,3]. Smith et al., reviewed that over 40 genetic loci have currently been associated with CVD susceptibility through genome-wide association studies (GWAS) [4].

DB, reported that obesity is a significant health challenge worldwide, driven by both genetic and environmental factors [5]. Ogawa et al., highlighted that obesity is characterized by an excessive accumulation of adipose tissue and is correlated with a heightened risk of conditions like diabetes mellitus, hypertension, hyperlipidemia and atherosclerotic diseases [6].

Ferrer described that leptin, a protein hormone weighing around 16 kDa, is crucial for regulating energy balance by controlling appetite and metabolism. Its circulation levels correspond with body fat mass, making it a primary hormone originating from adipose tissue. Leptin binds to and activates the long isoform of its receptor (LEPR-b) in the hypothalamus, triggering a specific molecular pathway that controls energy metabolism and body weight [7]. The human LEPR gene resides on chromosome 1p31.

Yiannakouris et al., recently highlighted extensive research focused on identifying variants within the LEPR gene that could have significant implications for the pathophysiology of human obesity [8]. Quinton et al., in their review, analyzed various single nucleotide polymorphisms (SNPs) within the LEPR gene, including the Q223R polymorphism. This variant affects the coding region for the extracellular domain of the leptin receptor, leading to the replacement of glutamine with arginine at position 223 of the LEPR protein. The Q223R polymorphism has been linked to reduced binding activity of leptin, which contributes to the development of leptin resistance [9].

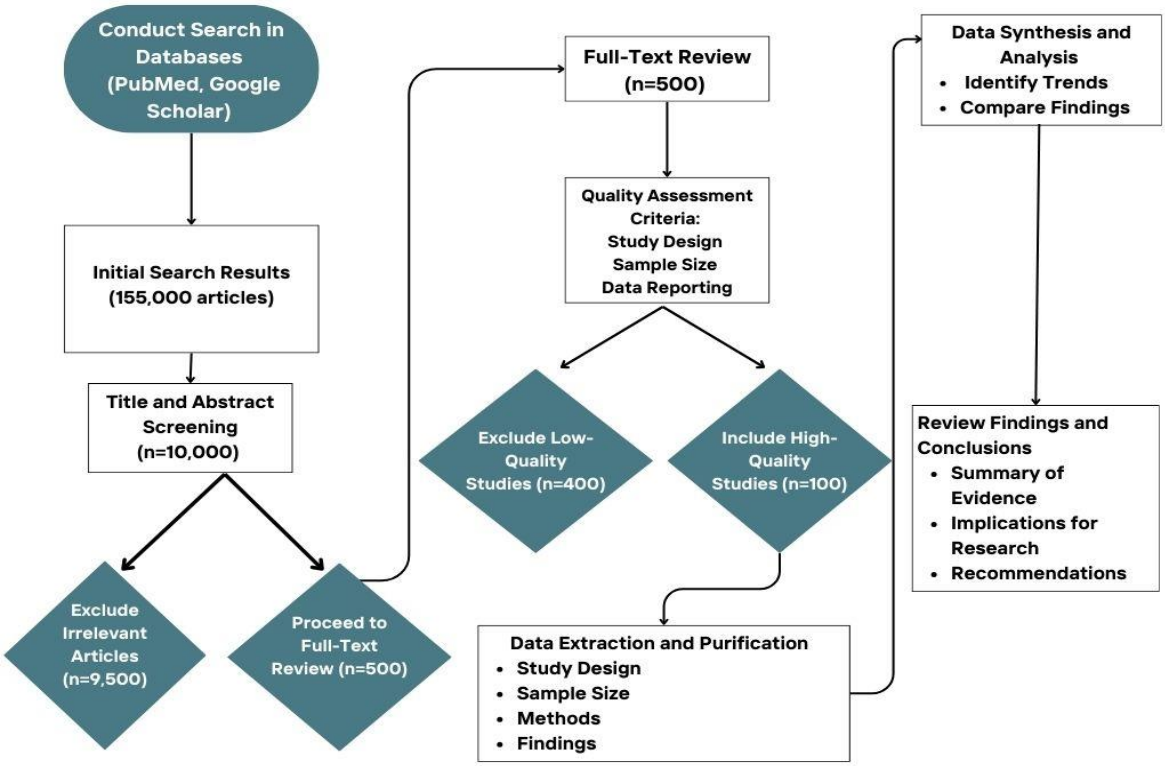
Schulze P C and Kratzsch, J observed that leptin is involved in regulating multiple cardiovascular effects, such as thrombosis, angiogenesis and cardiac hypertrophy [10]. Additionally, Tartaglia et al., reported that leptin influences metabolism, immunity and reproduction. Its physiological effects are mediated through the leptin receptor (LEPR), located on chromosome 1p31. LEPR is widely distributed across various tissues [11], serving as a critical mediator of leptin's essential role as a hormone in managing overall energy balance in the body.

Several studies have explored the association between LEPR gene polymorphisms and cardiovascular disease (CVD) risk, but findings have been inconsistent. Aziz et al., found a lower incidence of heart failure among individuals with the Gln/Gln genotype of the Gln223Arg polymorphism [12]. In contrast, studies by Li et al., and others suggested that the 223GG genotype is linked to a significantly higher risk of chronic heart failure or ischemic stroke [13,14]. Abd El-Aziz et al., studied with its small sample size of only 200 subjects, may have limited the generalizability of their findings [15]. Furthermore, differences in participant characteristics across these studies could contribute to conflicting conclusions.

METHODS

We extensively searched PubMed and Google Scholar for relevant studies. Our search included diverse keywords like "leptin receptor gene," "cardiovascular diseases" and "obesity." We focused on studies examining the link between leptin receptor gene variations

and cardiovascular diseases in obese individuals. We considered various study types, excluding those on non-human subjects or lacking full-text availability. This method ensured a comprehensive review, strengthening the reliability of our findings.



Obesity and Cardiovascular Diseases

Bombelli et al., found a link between obesity and changes in cardiac structure, particularly left ventricular (LV) hypertrophy. For each 1 kg/m² increase in body mass index (BMI), the risk of left ventricular hypertrophy (LV hypertrophy) rises by 5.1%, while each additional centimeter in waist circumference increases the risk by 2.6% [16]. Nilsson et al., explored how obesity contributes to vascular damage, including increased arterial stiffness, a higher incidence of carotid stenosis, elevated carotid intima-media thickness and coronary artery calcification, all of which accelerate vascular aging [17]. Lee et al., noted that obesity independently predicts coronary artery disease and doubles the risk of heart failure compared to individuals with a healthy weight [18]. Wanahita et al., discovered that stroke risk is linked to both BMI and waist-hip ratio, with obese individuals facing a 49% increased risk of arteriosclerosis compared to those who are not obese [19].

Horwich found that individuals with heart failure who are overweight or obese (BMI > 27.8 kg/m²) unexpectedly have higher survival rates [20]. Bozkurt B and Deswal A found in their analysis of 7,767 chronic heart failure patients that overweight or obese individuals had lower hazard ratios (HR, 0.81; 95% CI, 0.72–0.92) compared to those with normal weight (HR, 0.88; 95% CI, 0.80–0.96) [21]. Similarly, Matinrazm et al., observed a link between higher BMI and reduced mortality in cases of sudden cardiac arrest [22]. Goyal et al., and Braun et al., found that, contrary to popular belief, a higher BMI is linked to lower mortality rates in people with coronary artery disease, heart failure, and diabetes, whereas normal-weight individuals tend to have higher mortality rates than those who are obese [23, 24]. This phenomenon, known as the "obesity paradox," is frequently observed in patients with coronary artery disease or heart failure [25].

Leptin Receptor

The leptin receptor (LEP-R) gene encodes a key transmembrane receptor that plays a vital role in regulating body weight and energy balance by interacting with leptin, a hormone produced by adipocytes. The LEP-R receptor has a complex structure, beginning with an extracellular domain of over 800 amino acids that is essential for binding leptin. This domain includes conserved motifs such as four cysteine residues, which are critical for proper folding and stability and a WSXWS motif (Trp-Ser-Xaa-Trp-Ser sequence) typical of class I cytokine receptors, necessary for receptor dimerization and activation [26-30]. Additionally, the extracellular domain contains fibronectin type III (FN III) domains, important for maintaining receptor structure and facilitating protein-protein interactions [28-30].

The receptor is anchored to the cell membrane by a 34-amino-acid transmembrane domain, which is crucial for transmitting signals from outside the cell into the interior. The intracellular domain, which varies among the different LEP-R isoforms, is responsible for triggering signaling cascades after leptin binds to the receptor. The LEP-R gene produces several isoforms through alternative splicing, including LEP-Ra, LEP-Rb, LEP-Rc, LEP-Rd, LEP-Re and LEP-Rf, each possessing a unique intracellular domain that determines its specific signaling function [30].

These isoforms are categorized into three types: short, long and secreted. The long isoform, LEP-Rb, is the main signaling receptor, predominantly expressed in the hypothalamus, where it regulates food intake, energy expenditure and body weight [30]. LEP-Rb has an extended intracellular domain that interacts with various signaling molecules, activating pathways such as JAK-STAT, PI3K and MAPK, which are essential for metabolic regulation [30]. The short

isoforms, including LEP-Ra, LEP-Rc and LEP-Rd, have shorter intracellular domains and are involved in transporting leptin, regulating its availability to the long-form receptor and its clearance [30]. The secreted isoform, LEP-Re, lacks a transmembrane domain and likely acts as a soluble receptor, binding leptin in the bloodstream and controlling its bioavailability [30].

Understanding the structure and function of the LEP-R gene and its isoforms is crucial for addressing leptin resistance, a common issue in obesity where elevated leptin levels do not result in the expected physiological effects. This resistance is often linked to defects in LEP-R signaling or altered receptor expression, making LEP-R a significant target for therapeutic interventions aimed at treating obesity and related metabolic disorders [26-30].

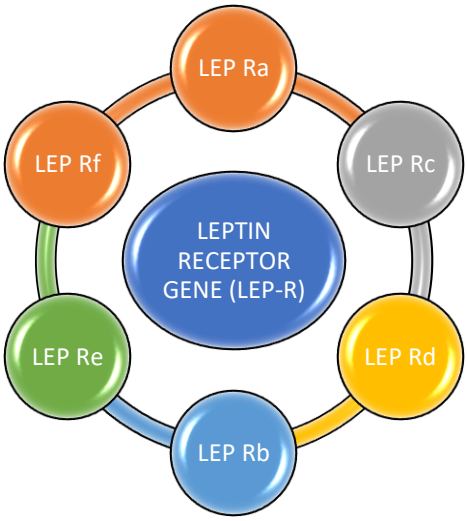


Figure.1: Leptin receptor gene isoforms

Role of Leptin in Cardiac Function

Shaw R M and Colecraft discussed the varied roles of calcium ions (Ca2+) entering the heart, which include regulating action potential duration, initiating muscle contraction, and influencing gene expression [31]. Bers and Shannon explained that β-adrenergic signaling activates Na+/Ca2+ exchange channels via protein kinase A (PKA) during excitation-contraction coupling, causing depolarization of the sarcolemma. This depolarization, as further elaborated by Kho et al., triggers the opening of L-type calcium channels, allowing Ca2+ to enter the cytoplasm and subsequently be released from the sarcoplasmic reticulum (SR) through ryanodine receptor channels, which leads to muscle contraction [32, 33]. Ibrahim et al., highlighted the critical roles of sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) and phospholamban (PLN) in regulating Ca2+ transport within myocytes and maintaining cytoplasmic Ca2+ levels, essential for normal cardiac function

[34]. Disrupted Ca2+ handling in the SR is a characteristic feature of cardiac disorders like heart failure and arteriosclerosis, significantly driving disease progression [34].

Dong et al., noted that leptin-deficient mice show reduced activation of SERCA2 and Na+/Ca2+ exchange channels. Conversely, administering leptin to ob/ob mice myocytes enhances β-adrenergic signaling, increases Gsα expression, activates PKA, and induces PLN phosphorylation [35]. Minhas et al. highlighted the significant relationship between leptin levels and cardiac function [36-39]. Additionally, R Kandadi et al., demonstrated that leptin treatment in cardiomyocytes of adult mice suppresses contraction through various pathways, including those involving the endothelin-1 receptor-nicotinamide adenine dinucleotide phosphate H oxidase, nitric oxide, JAK/STAT, interleukin-1β signaling, and induction of autophagy [40-42].

Table: 1 Role of Leptin in Cardiac Function

Aspects	Description	References
Leptin production	Produced primarily by adipocytes (fat cells) and released into the bloodstream.	[43]
Receptors	Leptin acts on leptin receptors (LEPR) present in various tissues, including the heart.	[44]
Cardiac Effects	Leptin influences cardiac function through several mechanisms, impacting heart rate, blood pressure, and myocardial metabolism.	[45]
Blood pressure regulation	Leptin can increase sympathetic nervous system activity, leading to elevated blood pressure.	[46]
Myocardial metabolism	Leptin influences myocardial fatty acid oxidation, glucose uptake, and overall energy metabolism in the heart.	[47]
Inflammation	Increased leptin levels are linked to heightened	[48]

	inflammatory responses, results cardiac function and leads to cardiovascular disease.	
Vascular Function	Leptin influences endothelial function and vascular smooth muscle cells, leads to atherosclerosis.	[49]
Cardiac Hypertrophy	Leptin signaling is implicated to cardiac hypertrophy in obesity.	[50]
Heart Failure	Leptin resistance or high leptin levels leads to heart failure.	[51]

Leptin and Cardiac Hypertrophy

Sente et al., observed that in obese individuals, the increased blood volume leads to elevated cardiac output, causing biomechanical stress and structural remodeling, which may contribute to cardiac hypertrophy [52]. Clinical studies by Zeidan et al., have shown that plasma leptin levels are associated with cardiac hypertrophy [53-56], with leptin directly inducing this condition in humans and mice through several pathways [48-50]. Rajapurohitam et al., identified key pathways involved, including mTOR signaling, calcineurin activation, PPAR-α activation, MAPK 14 (p38) nuclear transport, Rho activation, and increased intracellular ROS [57-60]. Zeidan et al., found that left ventricular hypertrophy is prevalent in genetically obese ob/ob and db/db mice [61], while Rajapurohitam et al., showed that maintaining sufficient leptin levels can normalize left ventricular thickness, irrespective of body weight [62]. Hou et al., identified hyperleptinemia in diet-induced obese mouse models, with the leptin receptor (LepR) actively responding to increased plasma or cardiac leptin levels [63]. Hu et al., reported that this response by LepR protects against cardiac hypertrophy by activating STAT3 and its downstream pathways, as well as influencing p38, p42/44 MAPK, and Akt, effects that are not present in LepR mutants or db/db mice [64].

Leptin and Cardiomyocytes Apoptosis

Leifheit-Nestler et al., reported that apoptosis, controlled by specific signaling pathways, acts as the primary mechanism of cell loss in the heart [65]. Cardiomyocyte apoptosis plays a

crucial role in heart failure progression and compensatory remodeling. According to Barouch et al., apoptotic cells display notable changes, including reduced size, membrane blebbing, nuclear condensation, and DNA fragmentation, and are subsequently removed by macrophages [66]. They further explained that apoptosis can proceed via two pathways: the extrinsic (death receptor) pathway, which is triggered by receptors containing death domains on the plasma membrane and the intrinsic (mitochondrial) pathway, which is activated by internal stressors such as growth factor deprivation, hypoxia, oxidative stress, and DNA damage. Apoptotic signals swiftly activate caspases and disrupt mitochondrial function, ultimately resulting in cell death [67].

Leptin and endothelial vascular dysfunction

Raju et al., discussed that leptin, known for its role in activating the sympathetic nervous system and increasing blood pressure, functions through various pathways [68]. Orogo and Gustafsson emphasized its ability to enhance endothelium-dependent vasodilation by boosting nitric oxide production, Akt phosphorylation and endothelial nitric oxide synthase (eNOS) activity [69]. Additionally, Lee and Gustafsson noted that leptin may induce vasodilation via endothelium-derived hyperpolarizing factor (EDHF) [70]. Zhang et al., pointed out that in conditions of leptin resistance, commonly observed in obesity and metabolic syndrome, its vasodilatory effects are compromised, contributing to the development of hypertension and atherosclerosis [71]. Understanding leptin's signaling pathways and its impact on endothelial cells holds promise for developing treatments for vascular diseases associated with obesity.

Furthermore, leptin plays a complex role in atherosclerosis by promoting monocyte infiltration into blood vessels, transforming macrophages into foam cells, and stimulating the proliferation of vascular smooth muscle cells. Despite recent findings suggesting a protective effect of leptin against atherosclerosis in low-density lipoprotein receptor–/–ob/ob mice, elevated leptin levels are associated with increased cardiovascular risk factors and may worsen atherosclerosis [71]. Therefore, gaining insights into liver cholesterol metabolism under physiological conditions and in the absence of leptin may provide strategies for mitigating the progression of atherosclerosis.

Relationship of leptin receptor with obesity

Farr et al., stated that early severe obesity often arises from rare genetic mutations disrupting leptin signaling [72], resulting in conditions like congenital leptin deficiency or ineffective

leptin function and resistance [73]. Liu et al., reported that in typical obesity, there is a tendency towards elevated leptin levels and resistance to weight loss [74], with heightened leptin expression observed at the gene level in adipose tissue (86). Plasma leptin levels strongly correlate with body fat percentage. Studies by Ravussin et al., indicated leptin resistance; initially, plasma leptin levels and ob mRNA content decline during weight loss in obese individuals but rebound during continued weight loss efforts [75]. Interestingly, halting leptin therapy does not lead to weight regain or increased leptin levels and hyperleptinemia in diet-induced obese (DIO) mice does not replicate the central nervous system effects seen with chronic weight gain [75].

Leptin's influence on brain function in the context of nutrient excess involves various brain regions, including the arcuate nucleus (ARC) and ventral tegmental area (VTA). Ravussin et al., reported that these areas can develop resistance to leptin signaling when exposed to high-fat diets [76]. Studies by Bian et al., have shown that reducing Ob-Rb expression in the ARC promotes obesity in rats [77]. Sensitivity to leptin varies across brain regions, influenced by diet and experimental conditions, revealing intricate interactions and potential compensatory mechanisms [77].

Genetic mutations in mice affecting the ob gene cause severe obesity due to disrupted leptin function. Similarly, mutations in the LEP-R gene alter leptin signaling, contributing to obesity. Riestra et al., noted that LEP -2548 G/A polymorphism in the leptin gene's 5’-untranslated region shows inconsistent associations with obesity in humans [78]. Research by Nesrine et al., also highlighted epigenetic factors like DNA methylation affecting leptin and LEP-R expression in obesity, along with non-coding RNAs and regulatory elements influencing leptin gene regulation [79].

Leptin resistance and obesity

Leptin resistance, a concept introduced post the 1994 discovery of leptin, refers to the compromised response of leptin in obese states, diminishing its therapeutic potential [80]. This condition arises from impaired leptin transport to target cells, reduced receptor expression or disrupted signaling pathways. While rare loss-of-function mutations affect leptin and its receptors, more common issues involve pathways regulating leptin synthesis, influenced by adiposity and external factors like diet and circadian rhythms [81]. Reduced transport across the blood-brain barrier limits leptin's central effects despite elevated plasma levels, complicating metabolic dysregulation in obesity and forms of selective leptin resistance [83].

Recent studies have uncovered that the brain renin-angiotensin system (RAS) plays a pivotal role in mediating leptin's effects on renal function and brown adipose tissue (BAT) thermogenesis independently of its influence on food intake. This suggests that manipulating brain RAS activity could modulate leptin's impacts on blood pressure and energy expenditure without affecting its ability to reduce food intake. Leptin primarily stimulates BAT thermogenesis through central leptin receptors (LEP-R) via the sympathetic nervous system, involving key hypothalamic and extra-hypothalamic regions [83].

Seoane-Collazo et al., reveled that selective leptin resistance (SLR) has been observed in specific extra-hypothalamic brain areas in diet-induced obese (DIO) mice, while other hypothalamic and extra-hypothalamic nuclei remain responsive to leptin. This type of resistance appears unique to DIO and differs from the generalized resistance observed with constant high leptin exposure across all brain regions [84].

Kwon et al., reviewed that sexual dimorphism influences the sympathetic response to leptin and insulin in obesity, showing significant differences between males and females. In obese males, there is an increased sympathoexcitatory response to insulin and leptin, whereas disruptions in the reproductive cycle in obese females limit the sympathoexcitatory response to leptin, possibly due to variations in NPY and POMC signaling to the PVN [85].

The mechanisms underlying these sexually dimorphic alterations induced by obesity, particularly concerning NPY and POMC responses to insulin and leptin in the ARC, remain incompletely understood. Variations in NPY suppression via hypertensive RAS pathways and POMC excitation in obese males compared to females underscore the complex gender-specific metabolic responses to leptin and insulin in obesity [86].

Relevance of leptin in obesity associated cardiovascular diseases

Adipose tissue is classified into visceral and subcutaneous types, each playing distinct roles in health and disease. Tchernof and Després stated that visceral adiposity, characterized by fat accumulation around abdominal organs, significantly increases cardiometabolic risk due to its higher pro-inflammatory nature compared to subcutaneous fat [87]. Age, gender, genetics and hormonal factors contribute to the accumulation of visceral fat, alongside specific mechanisms like local cortisol production and endocannabinoid activity [87]. Oikonomou and Antoniades reported that this classification highlights the diverse physiological impacts of different adipose tissue depots, with visceral obesity defined by an increased waist-to-hip ratio strongly linked to cardiovascular risk [88].

Chang et al., releaved that adipokines derived from various fat depots, including perivascular and epicardial fat, play crucial roles in cardiovascular health [90]. Their secretion, influenced by systemic factors such as inflammation and insulin resistance, varies by depot and affects local vascular and myocardial functions through both endocrine and paracrine mechanisms. The expansion of adipose tissue in obesity leads to morphological changes, hypertrophy and hyperplasia, exacerbating metabolic dysfunction and cardiovascular risk [91]. These changes involve heightened inflammation, cell death and fibrosis within adipose tissue, closely associated with the metabolic consequences of obesity.

Obesity changes how adipokines are released, including acute-phase reactants, cytokines, chemokines, DAMPs, pro-inflammatory factors like leptin, resistin and anti-inflammatory factors such as adiponectin and omentin [91]. This disruption is linked to higher cardiovascular risk related to dysfunctional adipose tissue [89].

CONCLUSION

In conclusion, our exploration of the intricate interplay involving leptin resistance, genetic variations in the leptin receptor gene, and the increased susceptibility to cardiovascular diseases (CVDs) among individuals with obesity underscores the complexity of this health challenge. Obesity, characterized by excess adipose tissue, disrupts the finely tuned mechanisms through which leptin regulates appetite and energy balance. This disruption often results in leptin resistance, diminishing the body's responsiveness to leptin and impairing its ability to effectively signal feelings of fullness. Within the context of obesity, these disruptions in leptin signaling pathways significantly impact cardiovascular health. The compromised signaling associated with leptin resistance may contribute to heightened food consumption and weight gain, exacerbating the metabolic irregularities that predispose individuals to CVDs. Moreover, genetic variations within the leptin receptor gene further complicate matters, influencing the susceptibility to CVDs among those affected by obesity.

Our investigation into the link between genetic variations in the leptin receptor gene and the risk of CVDs has provided valuable insights into the underlying molecular mechanisms driving cardiovascular complications in obesity. This deeper understanding opens up new possibilities for therapeutic interventions, potentially leading to more personalized approaches in managing CVDs associated with obesity. By employing personalized medicine strategies tailored to the specific genetic and metabolic profiles of individuals with obesity, we can strive to reduce the burden of CVDs and improve long-term cardiovascular health outcomes.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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