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The thin fat paradox: Understanding normal weight obesity and its clinical relevance

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Abstract

Obesity, defined by the World Health Organization (WHO) as an excess accumulation of body fat or body fat percentage (BFP) associated with clear health risks, presents a significant global challenge. While Body Mass Index (BMI) serves as a conventional metric for identifying obesity, it fails to account for body composition variations, such as distinguishing between fat-free mass and adipose tissue. Consequently, individuals with normal BMI may exhibit excessive body fat (BFP≥30%), termed Normal Weight Obesity (NWO). In contrast, others with normal BMI and normal body fat are termed Normal Weight Lean (NWL).

NWO significantly elevates the risks of various metabolic disorders, including hyperglycemia, diabetes, hypertension, dyslipidemia, and reduced HDL levels. Moreover, NWO is associated with an increased risk of cardiovascular diseases (CVD), hypertension, low HDL, central obesity, and muscle weakness. Individuals with NWO face a heightened risk of developing cardiometabolic diseases, including atherosclerosis, coronary artery disease, stroke, and heart failure, due to the adverse effects of excess body fat on cardiovascular health. Furthermore, NWO is associated with insulin resistance, inflammation, and endothelial dysfunction, further exacerbating the risk of metabolic disorders and cardiovascular complications.

Early identification of NWO is crucial for implementing preventive measures and lifestyle interventions to mitigate these health risks. Integrating body fat percentage measurements into nutritional screening protocols in healthcare facilities is essential for identifying individuals at risk of NWO and initiating appropriate interventions to prevent the onset of cardiometabolic diseases. This study aims to provide comprehensive insights into Normal-Weight Obesity (NWO) and its potential health implications.

Keywords: Body Fat Percentage; Cardiovascular Risk; Metabolic Disorders; Normal Weight Obesity

1. Introduction

The World Health Organization (WHO) defines obesity as the accumulation of body fat or excess body fat percentage (BFP) associated with clear health risks. WHO establishes a Body Mass Index (BMI) >25 kg/m2 to identify obesity. However, BMI cannot depict body composition as it does not differentiate between lean mass and adipose tissue. Therefore, an individual with a normal BMI (18.5–24.9 kg/m^2) may have an appropriate or excessive body fat percentage obscured by a normal BMI. As a result, De Lorenzo defines a condition where individuals with a normal BMI have high body fat (BFP ≥30%) as Normal Weight Obesity (NWO). This is distinct from individuals with a normal BMI and normal body fat (BFP <30%), also referred to as Normal Weight Lean (NWL) (1–3).

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The meta-analysis conducted by Khonsari et al. revealed a 50% and 42% increased risk of hyperglycemia and diabetes, respectively, in individuals with Normal Weight Obesity (NWO) compared to Normal Weight Lean (NWL). Individuals with NWO exhibited a 40%, 83%, and 32% increased risk of hypertension, dyslipidemia, and decreased levels of High-Density Lipoprotein (HDL), respectively. Moreover, individuals with NWO also showed a 90% increased risk of hypertriglyceridemia (3). Research conducted by Rodriguez et al. demonstrated that NWO is associated with an elevated risk of cardiovascular diseases, high blood pressure, low HDL, central obesity, and weak muscle strength in young adults (4,5).

Early identification of NWO is crucial for implementing preventive measures and lifestyle interventions to mitigate these health risks. Based on the above background, this study aims to provide comprehensive insights into Normal-Weight Obesity (NWO) and its potential associated health implications.

2. Material and Methods

2.1. Study Design

The study utilized a narrative review approach to gather, analyze, and synthesize information about Normal Weight Obesity (NWO) from various literature sources.

2.2. Literature Source Identification

Relevant literature sources were identified through systematic searches in electronic databases such as PubMed and Google Scholar and official health organization websites like the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).

2.3. Inclusion and Exclusion Criteria

Articles meeting inclusion criteria, including discussions on NWO's definition, prevalence, health risks, and consequences, and articles published within a specific timeframe (e.g., the last ten years), were included. Articles that were irrelevant or not available in English were excluded.

2.4. Data Collection

Relevant information about the definition, concept, laboratory profiles, prevalence, and health risks associated with NWO was extracted from the selected articles. This data was then organized and synthesized to form coherent conclusions.

2.5. Data Analysis

The collected data was qualitatively analyzed by identifying patterns, trends, and emerging conclusions from the literature included in the review. The interrelation between findings was analyzed to understand the topic comprehensively.

2.6. Report Compilation

The results of the data analysis were compiled into a well-structured narrative review report, including sections such as introduction, methodology, key findings, discussion, and conclusion. This report underwent review and revision as needed to ensure completeness and accuracy of information.

3. Result and Discussion

3.1. Normal Weight Obesity (NWO)

The World Health Organization (WHO) defines obesity as "a condition in which body fat percentage (BFP) increases to a level where health and well-being are adversely affected." This definition emphasizes the expansion of adipose tissue rather than defining it solely based on weight gain (6). Although BMI has high specificity for detecting excess weight, its sensitivity is low. BMI cannot differentiate between fat-free and fat mass; thus, it cannot assess body fat distribution. Gender, age, genetics, and environmental factors influence body fat distribution, and visceral fat is a risk factor for developing non-communicable diseases, irrespective of total body fat content (1,2).

Normal Weight Obesity (NWO) is a condition with a normal BMI but a high body fat percentage. However, there is still no consensus on the threshold for body fat percentage and the percentage of body fat through a measurement method. Among body composition assessment methods, Bioelectric Impedance Analysis (BIA) is suitable for studying body composition due to its adequate precision, non-invasiveness, ease of application, safety, and relative affordability. Studies conducted by Amarat et al. have already demonstrated the accuracy of BIA and established a threshold of BFP ≥ 30%, consistent with Lorenzo's proposal. However, the WHO has not yet established a high body fat percentage threshold to determine obesity and still uses BMI to determine nutritional status (7–9).

De Lorenzo et al. describe the global prevalence of NWO at around 10%, with a higher prevalence among women than men. Wijayatunga et al. report that among adults with average weight, the prevalence of NWO ranges from 29% to 46% in various countries. Research conducted in Asian countries reveals diverse NWO prevalences. Kapoor et al. report a 31.7% prevalence of NWO in Indian adults, Moy et al. in Malaysia report a 19.8% prevalence of NWO in adult women, Ji et al. report a 10.7% prevalence of NWO in adults in China, and research in Korea indicates a majority of 32%, with a breakdown of 27% in adult men and 31% in adult women (1,2,10,11).

Research on the prevalence of NWO in children remains limited. NWO in children is relatively high, estimated at around 10% in children aged 3-6 years and 42-46% in children aged 9-18. Morais et al. observed that, among 274 Brazilian adolescents aged 14-19 years, 15% were overweight based on BMI, but 53.9% had excess body fat. In a longitudinal study conducted over approximately seven and a half years, Wiklund et al. evaluated 396 girls with an average age of 11. They found that the cardiometabolic risk scores were higher in adolescents with normal weight and high fat percentage compared to the control group (2,12).

3.2. Risk Factors of NWO

3.2.1. Genetic

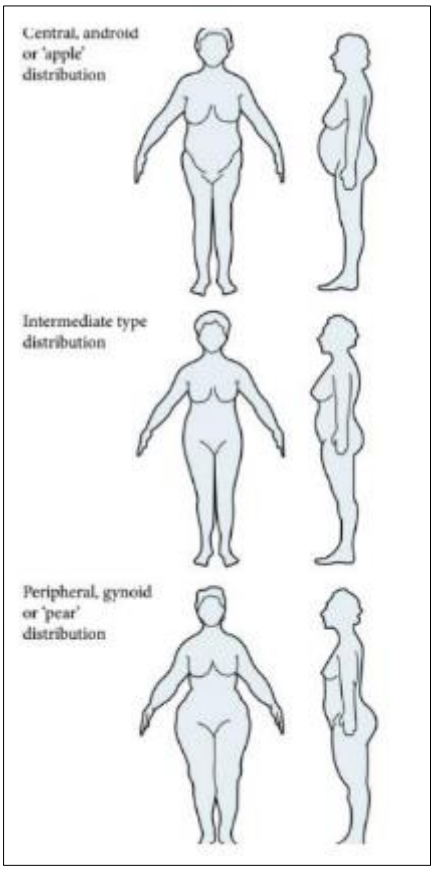

Figure 1 The Difference in Obesity Based on Body Fat Distribution (14)

Individuals with NWO and obesity exhibit significant phenotypic heterogeneity, directly associated with molecular, genetic, and cellular participation and environmental, social, and economic factors. For instance, central obesity (visceral obesity) is evident in an apple or android body shape and poses a greater risk for metabolic complications

(Figure 1). Conversely, peripheral obesity, or fat accumulation in the gluteofemoral region, presents a pear-shaped body with a gynoid phenotype associated with reduced metabolic risk (1,13).

Genetic polymorphisms associated with inflammation and cardiovascular disease have been studied in NWO. Cytokines related to obesity-induced inflammation and insulin resistance include interleukin (IL)-1, IL-6, IL-15, and tumor necrosis factor-alpha (TNFα). Polymorphisms in the interleukin-1 receptor antagonist (IL-1Ra), alpha receptor IL-15 (IL15-Rα), and G/C promoter gene of Interleukin (IL) 6 are associated with NWO in Caucasian women. However, significant differences in the genetic polymorphism of TNF Gen G/A-308 promoter were not found in Caucasian women with NWO compared to other body composition groups (1,13).

About 4% of individuals with NWO experience sarcopenia, and around 2% of individuals with overweight/obesity have sarcopenia. Other genetic polymorphisms related to cardiovascular disease have also been studied in NWO. Genetic polymorphisms in MTHFR 677C→T are associated with NWO in Caucasian women. Differences in genotypes in NWO can explain the higher plasma homocysteine levels in NWO compared to NWL, and increased homocysteine levels are associated with an increased risk of cardiovascular disease. However, De Lorenzo et al. did not measure folate or homocysteine levels with genotypes in the study, as mentioned earlier. Apolipoprotein E (APOE) is another genetic polymorphism related to cardiovascular disease. In Brazilian adults with NWO, there is an interaction between diet and APOE genetic polymorphisms that increases the risk of dyslipidemia (1,2,15).

3.2.2. Sociodemographic and Prenatal Factors

Prenatal factors are known to be associated with overweight. However, early life variables, including maternal education, parity, type of delivery, maternal smoking during pregnancy, birth weight, or gestational age at birth, are not related to NWO in young adults in Brazil. Sociodemographic factors such as gender, age, income, education, and marital status also did not differ in NWO compared to NWL in the same study. However, higher education is associated with a lower risk for NWO than NWL. Population studies with Swedish adults aged 45 to 75 stated that marital status is unrelated to NWO. Still, a study in China showed that being married has a significant association with central obesity in adults with average weight (2,16).

Wijayatunga states that gender is another factor that may be associated with NWO. According to large-scale population studies in Europe, NWO is more common in women than in men, and the male gender is associated with a lower risk for NWO compared to women. A study conducted by Hadaye et al. in India stated that the prevalence of NWO in women is twice as high as in men. Scientific reports from China over two decades reported that advanced age, female gender, marital status, and urban residency have a higher risk for central obesity with average weight (2,15,16).

Age becomes a risk factor associated with NWO. For instance, when the >30% cutoff for body fat is used, almost all women with normal BMI above 65 years old and two-thirds aged between 45 and 65 years are NWO. At the same time, only about 1-3% of women in the age groups of 18–25 years and 25–35 years have NWO. Retirement is also associated with a higher risk for NWO than NWL. However, some studies reported that NWO is also found in children and adolescents, with NWO prevalence up to 46% among children/adolescents with normal weight in Colombia (2,17,18).

Ethnicity and race are determinants of different adipose tissue distribution and responses to cardiometabolic risk, as highlighted by Deurenberg et al., who observed ethnic differences in BMI at the same level of BFP in Chinese, Indonesian, and Thai ethnic groups compared to Caucasians (American, Australian White and European Whites were analyzed as one group). In Asians and Indians, fat accumulation primarily occurs in the visceral area. BFP per unit of BMI is higher for Chinese, Hispanic, and South Asian populations compared to Whites. South Asian ethnicities have the highest amount of visceral fat compared to other ethnicities. Similarly, Indian women with NWO have the highest amount of body fat at certain BMI levels, followed by Malay and Chinese women, according to a study conducted in Malaysia. However, research on racial and ethnic groups is still limited so that no firm conclusions can be drawn about the association of race with NWO (1,2,11).

Higher diet quality is associated with lower body fat and Visceral Adipose Tissue (VAT). Diet-related factors such as high-protein, high-fiber diets, fish, green vegetables, and regular breakfasts have been proven to prevent obesity. Lack of physical activity, inadequate sleep, and alcohol consumption can lead to obesity and NWO. Several unhealthy dietary patterns observed in adult NWO compared to NWL include higher fat and sugar intake but lower intake of fish, cereals, vegetables, and tubers. Fruit, legume, nut, seed, beta-cryptoxanthin, and lycopene intake are significantly lower in young men with NWO than NWL in Iran. Additionally, calorie intake is higher in NWO and obesity than in NWL. Adolescents in Iceland with NWO are less likely to have breakfast or consume vegetables more than four times a week than NWL. However, NWO is not associated with soda, candy, and fast food consumption. Smoking or alcohol consumption habits

do not differ between NWO and NWL in young adults in Brazil. Similarly, smoking and alcohol consumption frequencies do not differ in NWO compared to NWL in the past in adults aged 45-75 years in Sweden. However, a meta-analysis conducted by Rakhmat et al. showed a significant relationship between NWO and alcohol consumption (2,18,19).

3.3. Pathogenesis of NWO

3.3.1. Changes in Body Fat Distribution

Body fat distribution is a vital risk factor for cardiometabolic conditions. The mechanisms underlying differences in body fat distribution among individuals are highly complex and still need to be studied. However, several studies have already indicated that sex hormones, glucocorticoid use, genetics, and epigenetic mechanisms determine the distribution of excess calories from food storage. Each individual consumes up to one million calories on average every year. Disruptions in energy balance will lead to weight gain or loss. The composition of weight gain during positive energy balance is mainly in fat (70%-80%), with the remainder being lean body mass (20%-30%) (20,21).

Adipose tissue serves as the primary storage depot for lipids in the body and plays a crucial role in buffering the daily influx of dietary fat into the bloodstream. The body's ability to adapt to changes in (chronic) calorie intake heavily relies on the capacity of adipose tissue to accommodate potential calorie excess. In obesity, subcutaneous adipose tissue may fail to expand adequately to store excess energy. This, in turn, can lead to ectopic fat accumulation in other tissues involved in metabolic homeostasis (such as skeletal muscle, liver, and visceral adipose tissue), potentially resulting in insulin resistance (Figure 2) (20,21).

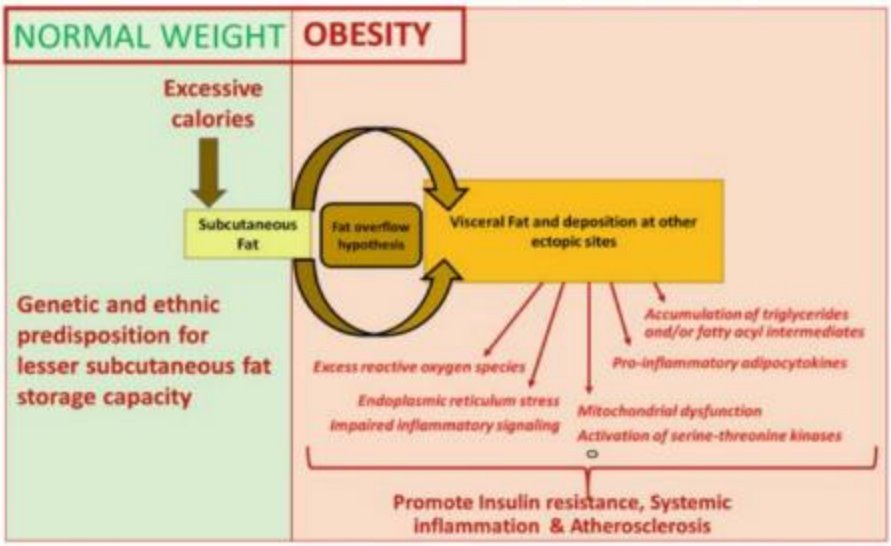

Figure 2 Pathogenesis of NWO (20)

Lipids are stored in subcutaneous adipose tissue before expansion of storage into visceral adipose tissue, although there are variations in fat storage patterns among individuals in the population. The inability to increase adipose tissue mass through adipocyte hyperplasia will result in adipocyte hypertrophy during prolonged positive energy balance. Adipocyte enlargement is a crucial characteristic of adipose tissue dysfunction. Hypertrophic adipocytes have a significantly reduced capacity to rapidly store dietary fat due to an excess lipid storage burden, leading to lipid diversion to other metabolic organs. Additionally, hypertrophic adipose tissue is characterized by adaptive and innate immune cell infiltration and changes in adipokine secretion. These disturbances can lead to peripheral insulin resistance (20,21).

Accumulation of adipose tissue in the upper body region is associated with the development of comorbidities and cardiometabolic-related mortality. Intra-abdominal adipose tissue (IAAT), or visceral adipose tissue (VAT), plays a crucial role in insulin resistance and cardiovascular disease risk, unlike gluteal-femoral adipose tissue, associated with protective lipid and glucose profiles. IAAT is predominantly located in the mesentery and omentum, flowing directly through the portal circulation to the liver. One reason for the differential risk of cardiometabolic disease between upper and lower body obesity is that abdominal fat deposition is marked by rapid absorption and storage of energy from food and increased lipid turnover (lipolysis). In contrast, lower body obesity has lower rates of lipid turnover and reduced diversion of lipids to non-adipose tissues. In other words, lower body fat appears to have a higher lipid buffering capacity and effectively sequesters fatty acids, acting as a protective metabolic sink (20–22).

3.4. Mitochondrial dysfunction and Endoplasmic Reticulum Stress

Mitochondria participate in a series of metabolic processes as a platform for ATP production. Mitochondrial dysfunction can be defined as reduced mitochondrial content, decreased mitochondrial activity, and oxidative phosphorylation, and it is involved in insulin resistance. Mechanisms primarily involve the production of lipid metabolite toxins. The ability to oxidize fatty acids declines when mitochondrial dysfunction occurs. Free fatty acids are converted into fatty acyl-CoA and diacylglycerol, which inhibit insulin signaling pathways. Another potential mechanism of mitochondrial dysfunction leading to insulin resistance is associated with increased production of reactive oxygen species (ROS). Mitochondria are the major organelles that generate ROS within cells. Mitochondrial dysfunction significantly increases ROS, causing oxidative stress and insulin resistance (20,23).

Obese patients with excessive nutrient intake may experience disruption of endoplasmic reticulum homeostasis, leading to endoplasmic reticulum stress (ERS). Otoda et al. reported that the release of non-esterified fatty acids in individuals with obesity triggers ERS and activates the unfolded protein response (UPR), which increases the regulation of inflammatory factor expression, where elevated cytokine levels contribute to the development of insulin resistance. ERS is also involved in apoptosis and pancreatic beta-cell failure (20,23).

3.5. Inflammation and Reactive Oxygen Species (ROS)

High-calorie, high-salt, high-fat, animal protein-rich diets and low fiber intake can alter intestinal barrier function and increase metabolic endotoxemia, reactive oxygen species (ROS), and inflammation. These disturbances contribute to dysfunction of the cardiometabolic system, organ damage, and high blood pressure (24,25).

3.6. Clinical Manifestation of NWO

3.6.1. Altered Body Fat Distribution

Individuals with NWO are heavier and have an IMT of about 1–2 kg/m2 higher than NWL. Both visceral and subcutaneous fat content are higher compared to NWL. NWO individuals report higher waist circumference or waist-to-hip ratio than NWL. When adjusted for age and ethnicity, the likelihood of central obesity among NWO women is 2.6 times higher in Malaysia. This indicates abnormal fat distribution in NWO with higher visceral fat and less low limb fat. Visceral fat in the intra-abdominal compartment is associated with increased metabolic risk, while subcutaneous fat in the body offers a protective effect. Thus, changes in fat distribution occurring in NWO may be related to metabolic disturbances. In addition to increased visceral fat, ectopic fat distribution in the liver and muscles, leading to lipotoxicity and insulin resistance, has been observed in NWO compared to NWL (2,26).

3.6.2. Inflammation

Inflammation is higher in NWO compared to NWL. Plasma proinflammatory cytokine levels are higher in NWO, such as IL-1α, IL-1β, IL-6, IL-8, TNFα, and IL-15, compared to NWL in Caucasian women. Complement 3, another inflammation marker and an independent risk factor for metabolic syndrome, is higher in NWO women than NWL. There is also a higher level of type-I procollagen carboxy-terminal propeptide in NWO compared to NWL, indicating a profibrotic status in NWO. CRP is significantly higher in NWO compared to NWL in most studies. Leptin, a proinflammatory adipokine secreted from adipose tissue, is higher in plasma in NWO than in NWL. However, other studies evaluating IL10, IL2, IL12p70, IL18, and IFNg state no significant difference between NWO and NWL (2,5,27).

3.6.3. Oxidative Stress

Oxidative stress found in NWO is similar to that of obesity and metabolic syndrome. Mitochondrial dysfunction, reactive oxygen species (ROS) activation, nitrogen species-generating enzymes, and antioxidant system dysfunction lead to oxidative stress. Decreased glutathione (GSH) and lower nitrate oxide metabolites levels, while higher levels of lipid hydroperoxides are observed in Caucasian women with NWO and obesity compared to NWL. Furthermore, GSH negatively correlates with cytokines IL-1α, IL-6, IL-10, and IL-15, indicating a relationship between oxidative stress and inflammation. Total antioxidant capacity is lower in NWO women than NWL but lowest in obese women. Research on the association between oxidative stress and NWO is still limited (1,2).

3.6.4. Cardiometabolic Risk

The risk of cardiovascular disease is higher in adult NWO compared to NWL. For example, young Latin Americans aged 18-30 with NWO have a threefold higher cardiometabolic risk than NWL. Finnish women with NWO in childhood will persist into adulthood (18 years old) and have a higher cardiometabolic risk even without a family history of cardiometabolic disease compared to NWL. This highlights the importance of early detection of NWO, even in children,

to prevent future cardiovascular disease. Individuals with NWO have a four times higher prevalence of metabolic syndrome than NWL in the United States. The risk of metabolic syndrome in Brazilian adults is 6.8 times higher, while in Chinese adults, NWO is 2.2 times higher compared to NWL (2,18).

Adults with NWO have a 1.5–1.6 times higher likelihood of hypertension compared to NWL. Both systolic and diastolic blood pressure are significantly higher in NWO individuals of both genders. Rakhmat et al. reported in a meta-analysis that men with NWO have a 1.5 times higher risk, while women have a 1.72 times higher risk compared to NWL (2,18).

NWO individuals tend to experience dyslipidemia. Serum levels of low-density lipoprotein (LDL) and triglycerides are higher, while high-density lipoprotein (HDL) is lower in adult NWO than NWL. Men with NWO have a 2.22 times higher risk, while women have a 1.33 times higher risk than NWL. Furthermore, the ratio of apolipoprotein B to apolipoprotein B/A-I is higher in NWO than in NWL (2,18).

Vascular changes in NWO include subclinical vascular inflammation, subclinical atherosclerosis with fragile plaques, and vessel stiffness compared to NWL. However, the prevalence of further cardiovascular diseases, such as acute coronary syndrome or coronary artery stenosis, does not differ between NWO and NWL. Thus, subclinical vascular and cardiac changes seem to occur in NWO, which may not be detected during routine assessment. This underscores the importance of screening for NWO for primary prevention of cardiometabolic diseases (2,18).

The risk of diabetes is higher in NWO compared to NWL. NWO is associated with insulin sensitivity disorders and impaired pancreatic beta cell function with higher serum insulin and fasting blood sugar compared to NWL. Insulin resistance in NWO individuals is approximately 45% higher than in adults with NWL in the United States, and even higher insulin resistance is observed in 18-year-old adolescents with NWO in Iceland. Therefore, diabetes and insulin resistance screening are essential in adults and children/adolescents with NWO. As body fat percentage increases, cognitive performance declines in individuals with normal weight in the United States. Further imaging analysis is needed to understand changes in cognitive function in NWO. The risk of cardiometabolic diseases may increase in NWO for several reasons. As previously explained, oxidative stress and inflammation are higher in NWO than in NWL, and oxidative stress and inflammation contribute to cardiometabolic diseases. There may be a genetic predisposition to increased cardiometabolic risk in NWO due to several gene polymorphisms related to inflammation, homocysteine production, and plasma lipids associated with NWO. The health behaviors discussed above may also contribute to cardiometabolic diseases in NWO (2,18).

3.6.5. NWO and Cancer

Previous literature on the relationship between cancer and NWO is limited. A population-based study in the US with a median follow-up of 16 years observed that postmenopausal women with normal weight but higher body fat had a higher risk of invasive breast cancer. Carcinogenesis and cancer development may be increased due to visceral adiposity, inflammation, hyperglycemia, hyperinsulinemia, changes in growth factors such as insulin-like growth factor I (IGF-I) pathway, and estrogen signaling in NWO. However, further research is needed to explore this association between NWO and cancer (2,18,23).

3.6.6. NWO and muscle mass and strength

The relationship between NWO and muscle mass and strength has been explored in various studies. Caucasian women with NWO show significantly lower appendicular skeletal muscle mass, while adults in Korea with NWO exhibit lower muscle mass than their NWL counterparts. Similarly, older adults aged 60 and above with NWO in the US have lower muscle mass than NWL individuals. Czech children aged 9 to 12 with NWO also have lower muscle mass compared to NWL or overweight/obese peers. Finnish girls with NWO also have a lower lean mass per body weight than their NWL counterparts. Skeletal muscle density is lower in NWO than in NWL, indicating higher fat content in skeletal muscles. Regarding muscle strength, Latin American children and adolescents with NWO have significantly lower grip strength adjusted for body weight than NWL peers. Similarly, Latin American young adults with NWO are 3.3 times more likely to have weaker grip strength than NWL individuals. Furthermore, the association between NWO and muscle function has been explored, indicating that Latin American young adults with NWO are 3.3 times more likely to have weaker grip strength than NWL individuals. However, the relationship between NWO and physical activity limitations in older adults remains unclear, as one study reported that NWO is associated with limited physical activity in older women (2,28).

4. Conclusion

Normal-Weight Obesity (NWO) is a global phenomenon that poses a public health issue. Genetics, lifestyle, and dietary patterns contribute to the risk of NWO. Its pathophysiological mechanisms involve changes in body fat distribution,

mitochondrial dysfunction, inflammation, and oxidative stress. Clinical manifestations of NWO include changes in body fat distribution, inflammation, oxidative stress, and an increased risk of cardiovascular diseases and diabetes, as well as alterations in muscle mass and strength. Prevention and management of NWO require a holistic approach involving lifestyle modifications, including healthy dietary patterns and regular physical activity. Furthermore, further research is needed to understand NWO's pathophysiological mechanisms better and develop effective prevention strategies.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest is to be disclosed.

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