



Comparison of the Castelli-II Index Between Normal Weight Obesity and Obese Medical Students

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ARTICLE INFO

Keywords:

Normal weight obesity
Obesity
Castelli-II index
Cardiovascular
Young adults

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All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.32539/BJI.v12i1.309>

Received 21 December 2025;

Accepted 8 February 2026

ABSTRACT

Introduction. Cardiovascular disease remains the leading cause of mortality in Indonesia, with obesity recognized as a major risk factor. Excess body weight not only contributes to obesity but also alters lipid metabolism, thereby accelerating atherosclerosis. Interestingly, not all individuals with metabolic risk exhibit excess weight. This condition, termed normal weight obesity (NWO), describes individuals with a normal BMI (18.5-24.9 kg/m²) but an elevated body fat percentage (men >25%, women >30%). One of the important predictors of cardiovascular risk is the Castelli-II Index, defined as the LDL/HDL ratio, which reflects the balance between atherogenic and protective lipoproteins. This study aimed to evaluate the Castelli-II Index as a predictor of cardiovascular disease in individuals with NWO and obesity among medical students at the Faculty of Medicine, Universitas Pattimura. **Methods.** An analytic observational design with a cross-sectional approach was employed. A total of 52 respondents were recruited, comprising 26 individuals with NWO and 26 with obesity. BMI and body fat composition were assessed using a bioelectrical impedance analyzer (BIA), while LDL and HDL levels were determined through direct enzymatic testing. **Results.** Bivariate analysis using the chi-square test demonstrated no statistically significant difference in the Castelli-II Index between the NWO and obesity groups ($p = 0.235$). **Conclusion.** In conclusion, despite differences in body composition, the Castelli-II Index did not significantly differ between students with NWO and those with obesity. Further studies with larger and more diverse samples are recommended to validate the role of the Castelli-II Index in predicting cardiovascular risk among young adults.

1. Introduction

One of the major risk factors for cardiovascular disease is obesity.¹ According to data from the World Health Organization (WHO) in 2024, more than 890 million people worldwide were affected by obesity, including individuals over the age of 18, with approximately 16% classified as obese.² Obesity not only increases body weight but also alters the blood lipid composition, which plays a critical role in the development of atherosclerosis. Excessive accumulation of body fat, particularly visceral fat, can lead to metabolic disturbances such as dyslipidemia, which is also a risk factor for cardiovascular disease.³ Dyslipidemia is an abnormality in blood lipid levels that is frequently observed in individuals with obesity.⁴ It is characterized by elevated levels of total cholesterol, LDL, and triglycerides, along with reduced HDL levels.¹ This combination, known as atherogenic dyslipidemia, is strongly associated with an increased risk of cardiovascular disease, even in

individuals without obvious clinical symptoms. However, not all individuals with metabolic disorders appear visually obese.^{1,4,5}

De Lorenzo *et al.* introduced the term *Normal Weight Obesity* (NWO), which refers to a condition in which an individual has a normal body mass index (BMI) but a high body fat percentage.⁶ Individuals with NWO often present with dyslipidemia that is not detected through BMI assessment, as BMI cannot accurately reflect body composition or health risks due to its inability to differentiate between muscle mass and fat mass. Routine clinical risk assessments often fail to detect NWO; therefore, early identification of this condition is crucial, particularly in individuals who appear healthy but have underlying metabolic disturbances that may increase the risk of cardiovascular disease.⁷ Consequently, although they may appear physically healthy, these individuals still carry a high risk of developing cardiovascular problems.^{3,5,8}

Normal weight obesity is commonly observed in young adults, one of whom is the university student population, who often adopt a sedentary lifestyle due to academic demands.⁹ Among this group, medical students represent a subgroup with particularly high vulnerability to sedentary behavior, as the heavy academic workload and extensive study hours are predominantly spent sitting.¹⁰ In addition to spending a considerable amount of time engaged in sedentary activities, young adults, particularly university students, often experience difficulty obtaining sufficient sleep.¹¹ Sleep deprivation can increase the risk of body fat accumulation. As explained in a study by Grander and Krike (cited in Ma'ruf *et al.*),¹¹ Short sleep duration may lead to an imbalance in the hormones ghrelin and leptin. This hormonal disruption increases appetite, particularly at night, and contributes to an energy imbalance that promotes body fat gain, which in turn is associated with cardiovascular disease.¹¹ To identify the hidden potential risk of cardiovascular disease in individuals with NWO, several predictors can be considered.^{12,13}

The Castelli Risk Index-I (total cholesterol/HDL) and Castelli Risk Index-II (LDL/HDL) are relatively easy to calculate and apply. However, the Castelli Risk Index-I has limitations in its sensitivity to atherogenic risk compared to the Castelli Risk Index-II.^{13,14,15} According to a study conducted by Yilmaz *et al.*,¹⁶ the Castelli Risk Index-II provides a more comprehensive and in-depth assessment of atherogenic risk and is superior in predicting mortality from cardiovascular disease.¹⁶ This index accurately reflects the balance between lipid parameters that promote atherosclerosis and those that protect against it. In their study, Yilmaz *et al.* reported that among all indices, the Castelli Risk Index-II (LDL/HDL) had the best predictive value, showing a strong correlation with in-hospital mortality. This is significant because the Castelli Risk Index-II is a reliable indicator of cardiovascular risk influenced by total lipid levels, as it effectively represents both atherogenic cholesterol (LDL) and protective cholesterol (HDL). The Castelli Risk Index-II categorizes risk as low (<2.5), moderate (2.5–3.4), and high (≥3.5).¹⁷

Early detection of NWO using the Castelli Risk Index-II enables earlier interventions, such as dietary modifications and regular physical activity, to prevent future cardiovascular disease and metabolic disorders. This study is particularly important given the limited research on NWO, especially among university students, who are considered vulnerable to sedentary lifestyles that may contribute to an increased risk of cardiovascular disease.

2. Methods

This study was an analytical observational research employing a cross-sectional design. The research was conducted at the Clinical Pathology Laboratory, Faculty of Medicine, Universitas Pattimura, and the sample examinations were

performed at the Health Laboratory and Medical Equipment Calibration Center of Maluku Province. The study population consisted of active medical students from the faculty of medicine, Universitas Pattimura. Participants were selected using purposive sampling and divided into two groups: the normal weight obesity (NWO) and the obesity group. A total of 52 students were screened using a bioelectrical impedance analysis (BIA) device (Omron Karada Scan HBF 375) to determine their body composition.

The inclusion criteria for both study groups were active undergraduate students of the Faculty of Medicine, Universitas Pattimura Ambon, aged 18–25 years, and willingness to participate in the study by providing written informed consent. Participants were classified into two groups based on anthropometric measurements. The normal weight obesity group consisted of individuals with a normal body mass index (BMI) ranging from 18.5 to 24.9 kg/m² and a body fat percentage ≥30% for females and ≥25% for males. The obesity group consisted of individuals with a body mass index (BMI) >25 kg/m² without assessment of body fat percentage.

The exclusion criteria for both groups included individuals with a history of chronic diseases such as diabetes mellitus or hypertension, participants undergoing medication that may affect lipid metabolism, active smokers, and individuals who consumed alcohol at least once per week within the last three months. In addition, individuals classified as athletes or those who routinely engaged in high-intensity physical training were excluded from the normal weight obesity group, while participants who were enrolled in a weight loss program within the last three months were excluded from the obesity group.

Venous blood samples were collected from all participants using standard phlebotomy equipment, including non-sterile gloves, a 3 cc syringe, a tourniquet, alcohol swabs, adhesive plaster, and plain tubes. The blood samples were centrifuged to separate serum from blood cells, and the serum was analyzed for LDL and HDL levels using the Biosystem BA200 analyzer with the Direct LDL Test and Direct HDL Test methods.

Low-density lipoprotein (LDL) cholesterol levels were categorized according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria as follows: optimal (<100 mg/dL), near optimal (100–129 mg/dL), borderline high (130–159 mg/dL), high (160–189 mg/dL), and very high (≥190 mg/dL).¹⁸ High-density lipoprotein (HDL) cholesterol levels were classified as low (<40 mg/dL), normal (40–59 mg/dL), and high (≥60 mg/dL).¹⁸ The Castelli-II Index (LDL/HDL ratio) was subsequently calculated to determine the cardiovascular risk level, categorized as low (<2.5), moderate (2.5–3.4), or high (≥3.5).¹⁷

In this study, the independent variables were normal weight obesity and obesity, while the

dependent variable was the Castelli-II Index as a predictor of cardiovascular disease risk. Anthropometric measurements, including height and weight, were obtained using a microtoise and a body weight scale, while body fat percentage was measured through BIA.

Data normality was assessed using the Shapiro-Wilk test. All variables were normally distributed; therefore, the data are presented as mean $\pm$ standard deviation. Data analysis was performed in two stages. The univariate analysis described the characteristics of the participants, including age, sex, body weight category, LDL, HDL, and Castelli-II Index. Frequency and percentage were presented for categorical variables (age, group, sex, and body weight category), while the mean and standard deviation were calculated for continuous variables (LDL, HDL, and Castelli-II Index). The bivariate analysis compared the Castelli-II Index between the NOW and obesity groups. Initially, the Chi-square test was applied; however when the test assumptions were not met, Fisher's Exact test was used instead.

Ethical clearance for this study was granted by the Ethics Committee of the Faculty of Medicine, Universitas Pattimura (Approval No. 097/FK-KOM.ETIK/VI/2025). All participants gave their written informed consent prior to participation by signing the consent form.

3. Results

The distribution of the study sample characteristics by age, sex, and BMI is presented in Table 1; the sample consisted of 52 medical students from Faculty of Medicine, Universitas Pattimura, comprising 26 students with NOW and 26 students with obesity. The largest group was 19 years old, with 12 participants (23.1%). Most participants were female (40 students, 76.9%), while males accounted for 12 students (23.1%) (Table 1).

The results in Table 2 show the distribution of NWO and obese students by sex. In the NWO group, the majority were female (92.3%), with males accounting for only 7.7%. A similar pattern was observed in the obesity group, where females comprised 62.5% and males 38.5% (Table 2).

The analysis in Table 3 shows the median age distribution in the NWO and obesity groups. Both groups had median ages of 20 and 21 years, respectively, with the same age range of 18 to 23 years (Table 3).

The results in Table 4 show the LDL level distribution in the NWO and obesity groups. In the NWO group, most students were in the borderline-high category (38.5%), and none had very high LDL levels. In the obesity group, the largest proportion was in the near-optimal category (34.6%), with only 3.8% having optimal LDL levels (Table 4).

Table 1. General description of research sample characteristics

Groups	n	%
IMT		
Normal weight obesity	26	50.0
Obesity	26	50.0
Total	52	100.0
Age		
18	8	15.4
19	12	23.1
20	10	19.2
21	11	21.2
22	7	13.2
23	4	7.7
Total	52	100.0
Sex		
Women	40	76.9
Men	12	23.1
Total	52	100.0

Table 2. Frequency distribution of NOW and obesity groups by sex

Groups	Women		Men		Total	
	n	%	n	%	n	%
NWO	24	92.3	2	7.7	26	100.0
Obesity	16	62.5	10	38.5	26	100.0

Table 3. Age distribution per group

Groups	Median (Minimum - Maximum)
NWO	20 (18 - 23)
Obesity	21 (18 - 23)

Table 4. Frequency distribution of LDL levels in NWO and obesity groups

Groups	Mean ± SD	Optimal		Near optimal		Borderline		High		Very high		Total	
		n	%	n	%	n	%	n	%	n	%	n	%
NWO	122 ± 27.77	7	26.9	7	26.9	10	38.5	2	7.7	0	0.0	26	100.0
Obesity	142 ± 31.66	1	3.8	9	34.6	6	23.1	8	30.8	2	7.7	26	100.0

Table 5. Frequency distribution of HDL levels in NWO and obesity groups

Groups	Mean ± SD	Low		Normal		High		Total	
		n	%	n	%	n	%	n	%
NWO	64 ± 11,85	0	0.0	10	38.5	16	61.5	26	100.0
obesity	60 ± 11,43	1	3.8	13	50.0	12	46.2	26	100.0

Table 6. Frequency distribution of Castelli-II Index in NWO and obesity groups

Groups	Mean ± SD	Low risk		Moderate risk		High risk		Total	
		n	%	n	%	n	%	n	%
NWO	1.99±0.57	21	80.8	5	19.2	0	0	26	100.0
Obesity	2.46±0.76	14	53.8	9	34.6	3	11.5	26	100.0

Table 7. Analysis of Castelli-II Index values in NWO and obesity groups

Groups	Mean ± SD	Low-Moderate		High		Total		P-value
		n	%	n	%	n	%	
NWO	1.99±0.57	26	100.0	0	0.0	26	100.0	0.235*
Obesity	2.46±0.76	23	88.5	3	11.5	26	100.0	

*Fisher Exact Test

The results in Table 5 show the HDL level distribution in the NWO and obesity groups. In the NWO group, the majority had high HDL levels (61.5%), and no students had low HDL levels. In the obesity group, most were in the normal category (50.0%), with only one student (3.8%) having low HDL levels. (Table 5)

The results in Table 6 show the distribution of Castelli Risk Index-II values in the NWO and obesity groups. In the NWO group, most students fell into the low-risk category (80.8%), and none were classified as high-risk. In the obesity group, the majority also had low Castelli Risk Index-II values (88.5%), but three students (11.5%) were in the high-risk category. (Table 6)

In this study, the initial bivariate analysis used the Chi-square test; however, its assumptions were not met. An attempt was made to fulfill the requirements by combining two Castelli Risk Index-II categories—low and moderate risk—but the minimum frequency criteria for the Chi-square test were still not satisfied. Therefore, the analysis proceeded with Fisher's Exact test to obtain the p-value. The bivariate analysis results in Table 4.7 show a p-value of 0.235 (>0.05), indicating no significant difference in Castelli Risk Index-II between the NWO and obesity groups. (Table 7)

4. Discussion

This study found a higher proportion of female

subjects in both groups compared to males. Physiologically, women have a higher body fat percentage than men, with fat distribution tending to be subcutaneous. This is primarily influenced by the hormone estrogen, which regulates the location and manner of fat storage.¹⁹ Estrogen is known to promote fat accumulation in subcutaneous tissue, particularly in the gluteo-femoral region (hips and thighs), which is metabolically more protective than visceral fat.¹⁹ The mechanism by which estrogen promotes subcutaneous fat storage involves increasing lipoprotein lipase (LPL) activity and reducing hormone-sensitive lipase (HSL) activity, thereby facilitating fat accumulation in metabolically protective areas.²⁰

In men, testosterone plays a role in limiting fat storage in abdominal tissue by suppressing LPL activity, a mechanism that contributes to reduced visceral fat accumulation.²¹ This is consistent with reviews on the role of androgens in adipose tissue and obesity.²¹ Furthermore, the metabolic effects of testosterone metabolites are depot-specific: estradiol (produced through testosterone aromatization) inhibits visceral fat growth, whereas dihydrotestosterone (DHT) tends to inhibit subcutaneous fat growth, as demonstrated in experimental studies and discussed in human analyses.²²

This study found that the median ages of the two groups were 20 and 21 years, which fall into the

young adult age category. The young adult phase is a transitional period from late adolescence to full independence, during which lifestyle changes may affect body composition.²³ Studies have shown that the decline in physical activity from adolescence to the early twenties is associated with an increase in body fat mass, even though total body weight does not always change significantly.²³ Dietary patterns in this age group are often dominated by snacks high in sugar and saturated fat, such as cakes, biscuits, and ice cream.²⁴ One study found that these types of snacks contribute a large proportion of total energy intake among young adults, and excessive consumption is associated with an increase in both visceral and subcutaneous fat.²⁴

This study found that in the NWO group, LDL levels were still relatively within the near-optimal range. This can be attributed to protective factors such as the hormonal status in young adulthood, during which endogenous estrogen levels remain sufficiently high to help maintain low LDL levels.²⁵ A recent meta-analysis reported that estradiol lowers LDL levels by increasing hepatic LDL receptor activity and stimulating favorable lipid metabolism in premenopausal women.²⁵ Furthermore, the tendency for fat to be predominantly distributed in subcutaneous rather than visceral depots during the early phase of fat accumulation may also delay a significant rise in LDL, as reported by Telle-Hansen *et al.* in 2021 and Malodobra-Mazur *et al.* in 2022.^{26,27}

As age increases or body fat accumulation continues without intervention, these protective mechanisms may weaken, leading to a significant increase in LDL levels and the formation of atherogenic small dense LDL (sdLDL).²⁸ Therefore, early detection and lifestyle interventions are necessary even among young adults to prevent the deterioration of lipid profiles and the future risk of cardiovascular disease.

The HDL levels observed in both the NWO and obesity groups were within the normal-to-high range. This finding appears to contradict the common assumption that body fat accumulation is always accompanied by a decrease in HDL levels.⁴ This can be explained by the hormonal status of the study participants, who were still within reproductive age, during which endogenous estrogen levels remain sufficiently high to maintain a favorable lipid profile.²⁵ Estrogen plays a particularly significant role in this regard, as it can enhance Apo-A1 expression and sustain lipoprotein lipase activity.²⁹ The relatively high HDL levels are likely the result of a combination of an unaltered metabolic profile and the hormonal status of the study participants.²⁹

Various studies have shown that premenopausal women have significantly higher HDL levels and lower LDL levels compared to postmenopausal women.^{25,29} This finding supports the notion that, during the early metabolic or compensatory phase, HDL function remains largely unaffected.^{25,29} In

addition, an active lifestyle also contributes to maintaining HDL levels, including light daily activities such as walking, standing, or performing household chores.³⁰ Nevertheless, the currently favorable HDL levels may not be sustained indefinitely. Continuous fat accumulation, coupled with aging, can decrease both the quantity and quality of HDL, thereby increasing the risk of cardiovascular disease in the future.¹⁹ Therefore, maintaining a healthy body weight and engaging in physical activity from an early age remains important, even for young adults.

More important than individual LDL or HDL values, the LDL/HDL ratio has been shown to be a stronger indicator of atherosclerotic risk.¹⁶ This study found that the NWO and obesity groups had the same cardiovascular disease risk, as assessed by the Castelli Index-II, namely low risk. Several studies have demonstrated that this ratio more accurately predicts the severity of coronary heart disease compared to LDL or HDL alone, making it a clinically valuable predictive parameter.^{16,31} Furthermore, a 2024 meta-analysis reported that the LDL/HDL ratio was significantly higher in patients with coronary heart disease than in individuals without the disease, reinforcing the relevance of this ratio in cardiovascular risk screening.³²

The characteristic visceral fat accumulation in NWO contributes to elevated LDL levels and reduced HDL levels, ultimately influencing the Castelli Index-II ratio.^{4,16,33} In this study, no significant difference in the Castelli Index-II was found between the NWO and obesity groups, indicating that both groups share a comparable level of cardiovascular risk. This finding supports the hypothesis that individuals with NWO, despite appearing anthropometrically normal, exhibit a risk profile similar to that of obese individuals. Therefore, the use of the Castelli Index-II is crucial for identifying hidden risks not captured by conventional BMI parameters.^{13,15,33}

The strengths of this study lie in its focus on young adults, a population often overlooked in cardiovascular risk studies, and in the use of the Castelli-II Index which provides a more sensitive assessment of lipid-related atherogenic risk than conventional lipid parameters. The inclusion of both NWO and obesity groups allows for a meaningful comparison of metabolic risk across different body composition profiles. However, this study has several limitations, the relatively small sample size and cross-sectional design limit the ability to establish causal relationships between normal weight obesity and lipid profile alterations. In addition, hormonal levels such as estrogen and testosterone were not directly measured, which may have provided further insight into the underlying physiological mechanisms. The study population, consisting of medical students, may also limit the generalizability of the findings to broader populations with different lifestyles and activity patterns.

5. Conclusion

This study found no significant difference in the Castelli Risk Index-II between students with normal weight obesity and those with obesity. Despite having a normal body mass index, individuals with normal weight obesity exhibited a lipid-related cardiovascular risk profile that did not differ from that observed in obese students. These findings highlight the limitation of body mass index as a sole indicator of cardiometabolic risk and underscore the importance of assessing body fat composition and lipid ratios in young adults. Further studies involving larger and more diverse populations, as well as longitudinal designs, are needed to better elucidate the role of the Castelli Risk Index-II in early cardiovascular risk stratification.

6. Author Contribution

F.A. collected the data sample and wrote the manuscript with support from F.d.L. and V.L. F.d.L. and V.L. carried out the experiment and helped supervise the project. R.A, R.L, and I. helped supervise the project.

7. Acknowledgements

The authors would like to thank all participants who willingly took part in this study and all individuals who contributed to the preparation of this manuscript.

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