



Relationship of normal weight central obesity on comorbid diseases: Systematic Review

Hubungan obesitas sentral dengan berat badan normal terhadap penyakit komorbid: Tinjauan Sistematis

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Article History:

Received: January 06, 2024; Revised: January 29, 2024; Accepted: April 05, 2024; Published: June 17, 2024.

Publisher:



Politeknik Kesehatan Aceh
Kementerian Kesehatan RI

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Abstract

Normal-weight central obesity (NWC0) has a significant effect on Cardiovascular Disease (CVD) and mortality, which are modulated by comorbidities. This systematic review aimed to identify comorbid diseases associated with NWC0. Search for articles published in 2013-2023 using the PubMed, Science Direct, and Scopus databases. Articles were selected based on the inclusion criteria, specifically articles about the relationship between NWC0 and comorbid diseases, using English language, observational study design, and can be accessed in full text. Each article was assessed based on sample size, study design, response rate, outcome measurement, statistical analysis, confounding factors, ethics, and research limitations. The results of this study show that NWC0 increases the risk of comorbid diseases such as hypertension, CVD, Diabetes Mellitus (DM), Metabolic Syndrome (MS), dyslipidemia, stroke, and hyperuricemia. Hypertension, MS, and dyslipidemia play a role in the incidence of CVD and DM. This study can increase awareness and attention to groups with normal body weights to improve lifestyle, routine health screening, and immediate intervention to prevent comorbid diseases.

Keywords: Cardiovascular disease, central obesity, comorbid

Abstrak

Obesitas sentral berat badan normal berpengaruh signifikan terhadap penyakit kardiovaskular dan kematian yang dimodulasi oleh penyakit komorbid. Tinjauan sistematis ini bertujuan untuk mengetahui penyakit komorbid yang berhubungan dengan obesitas sentral berat badan normal. Pencarian artikel yang terbit tahun 2013-2023 menggunakan *database* PubMed, Science Direct, dan Scopus. Artikel dipilih berdasarkan kriteria inklusi, yaitu terkait hubungan obesitas sentral berat badan normal terhadap penyakit komorbid, berbahasa Inggris, desain penelitian observasional, dan dapat diakses *full text*. Penilaian artikel berdasarkan ukuran sampel, desain penelitian, tingkat respon, pengukuran hasil, analisis statistik, faktor perancu, etika, dan keterbatasan penelitian. Hasil penelitian ini menunjukkan bahwa obesitas sentral dengan berat badan normal meningkatkan risiko berbagai penyakit komorbid, seperti hipertensi, penyakit kardiovaskular, diabetes melitus, sindrom metabolik, dislipidemia, stroke, dan hiperurisemia. Hipertensi, sindrom metabolik, dan dislipidemia berperan terhadap kejadian penyakit kardiovaskular dan diabetes melitus. Studi ini dapat meningkatkan kesadaran dan perhatian lebih khususnya kelompok berat badan normal untuk memperbaiki gaya hidup, pemeriksaan kesehatan rutin, dan intervensi segera dalam mencegah penyakit komorbid.

Kata Kunci: Komorbid, obesitas sentral, penyakit kardiovaskular

Introduction

Globality, an epidemic of obesity and overweight, is a global and national challenge for health systems (Mohamed et al., 2019). Obesity can be assessed by measuring the Body Mass Index (BMI) for general obesity, Waist Circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) for central obesity. Most epidemiological studies have used BMI because it is simple and easy to perform, and has shown a link between increased BMI and mortality (Global BMI Mortality Collaboration et al., 2016). However, BMI has limitations in terms of measurement accuracy (Alqarni et al., 2023).

Body Mass Index cannot differentiate between body composition and distribution of adipose tissue and fat-free mass (Merchant et al., 2021). To address this limitation, central obesity measurements were used because they more precisely depict the distribution of body fat to predict health risks (Ashwell & Gibson, 2016; Park et al., 2017). Combining measures of general and central obesity provides a more precise identification of the risk factors for CVD. The prevalence of MS in the normal-weight group was 8,6% but it had the highest mortality rate (Shi et al., 2020).

Normal weight central obesity refers to normal body weight but central obesity (Choi et al., 2023). Sahakyan et al., show a positive relationship between NWCO and cardiometabolic risk and mortality (Sahakyan et al., 2015). NWCO prevalence increased from 6,7% to 13,2% (with WC), 13,2% to 17,1% (with WHtR), and 16,1% to 19% (with WHR) in China from 1993-2011 (Song et al., 2019). The reported NWCO prevalence ranging from 26,9-36,9%, depending on the criteria used (Owolabi et al., 2017). The difference in NWCO prevalence can be attributed to variations in population, ethnicity, cut-off values for general and central obesity, and the measurement methods used (Montenegro Mendoza et al., 2022; Song et al., 2019).

Normal-weight central obesity can indicate an early risk of CVD (Ashwell & Gibson, 2016). However, the NWCO group has received less attention because it has a normal BMI despite central obesity (Owolabi et al., 2017). Few studies have addressed NWCO. Furthermore, the literature concerning NWCO primarily focuses on CVD and mortality and neglects other diseases. Therefore, a systematic study is needed to explain comorbid diseases in more detail before more

severe conditions or death. This study aimed to determine the types of comorbid diseases affected by NWCO.

Plain Language Summary

Normal weight central obesity is associated with increased mortality and cardiometabolic risks. This study systematically collected and assessed comorbid diseases associated with NWCO. Several comorbid diseases (hypertension, CVD, DM, MS, dyslipidemia, stroke, and hyperuricemia) impact NWCO conditions, and most of them increase the risk of CVD. The findings from this study can raise awareness of health maintenance through various preventive efforts to prevent more serious diseases.

Methods

This systematic review aimed to identify comorbid diseases influenced by NWCO. The PubMed, Science Direct, and Scopus databases were used to identify relevant articles. The search included articles published in 2013-2023 using a combination of keywords (impact OR effect OR relationship OR association) AND (normal weight central obesity OR NWCO) AND comorbid. The articles selected for inclusion were as follows: 1) discussing the relationship between NWCO and comorbid diseases, 2) written in English, 3) observational study design, and 4) available in full text. Conversely, articles with the following criteria were excluded: 1) discussion of normal-weight obesity, 2) systematic review, literature review, or proceedings, and 3) experimental study design.

The preparation for this study involved identification, screening, eligibility, and acceptable results. The first author independently performed the screening, selection, and assessment of the studies. Identification was performed with an initial search from several databases to identify the keywords or synonyms used. Retrieved articles were imported into the Zotero software to manage references, remove duplicates, and screen. The next stage was to remove articles that met the exclusion criteria and assess eligible articles after reviewing the title and abstract. The articles were extracted using a table that included the author, methods, results, and quality assessment. Only relevant data of interest were extracted.

The authors will discuss the articles that will be involved. Study quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, which includes 22 assessment points. Eight key items were selected for evaluation: the number of subjects that met the minimum sample size (sample size), explained the study design used (study design), reported the number of responses from the selected sample (response rate), explained the outcome assessment method (outcome measurement), the statistical method used (statistical analysis), the confounding factors in the analysis (confounding factors), the safety of research on subjects guaranteed through ethical approval (ethics), and research limitations such as bias and imprecision (research limitations) (Cuschieri, 2019). This assessment helps reduce potential bias. Each fulfilled item received a score of 1 and these scores were summed to determine the overall study quality. The study quality was categorized as poor (0-3), moderate (4-6), or good (≥ 7) (Kurniati et al. 2022). This study synthesized all the data related to NWCO and comorbid diseases.

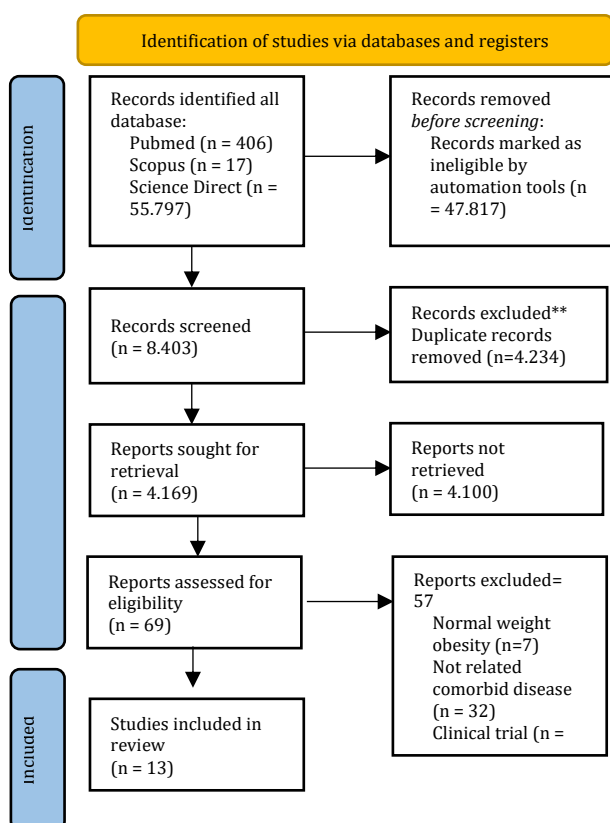


Figure 1. Article selection flow

Result and Discussion

A total of 56,220 articles published in the PubMed, Science Direct, and Scopus databases from 2013-2023. After eliminating duplicates and refining the inclusion and exclusion criteria, 13 articles were finally included. These studies spanned multiple countries: five in China, three in Japan, and one each in the United States (US), Thailand, Korea, Panama, and South Africa. Nine cross-sectional and four cohort studies were included in this review, with sample sizes ranging from 499 to 1,687,903 individuals from different populations. Eleven studies focused on the adult population, and two other studies on postmenopausal women and adolescents. Figure 1 illustrates the study's search and screening processes.

The study reported that the comorbid diseases affected by NWCO included hypertension (n=6), CVD (n=4), DM (n=3), MS (n=3), dyslipidemia (n=2), stroke (n =1), and hyperuricemia (n=1). Table 1 summarizes the study's characteristics and main results. Hypertension, DM, MS, stroke, and dyslipidemia increase the risk of CVD and mortality. This study also explains how comorbid diseases associated with NWCO contribute to CVD.

Individuals with NWCO have higher amounts of visceral adipose tissue and lower muscle mass (Wang et al., 2022). Visceral fat accumulation is closely related to cardiometabolic disorders, DM, dyslipidemia, hypertension, and MS markers (González et al., 2017; Li et al., 2022). This finding is supported by the results of this review, which identified the comorbidities and diseases associated with NWCO, including hypertension, CVD, DM, MS, dyslipidemia, stroke, and hyperuricemia.

Relationship between NWCO and Hypertension

Hypertension, which is characterized by a persistent increase in arterial pressure, is the most common chronic medical condition. Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure > 80 mmHg were diagnosed (Iqbal & Jamal, 2023). The risk of hypertension gradually increases with various types of central obesity measurements.

The NWCO group had a higher prevalence of hypertension (19,5%) than the normal weight and WC groups (10,4%) or the overweight obese group with normal WC (16,6%) (H. Ren et al., 2023). In males with normal BMI and abnormal WHR (Qi et al., 2015). Among adolescents,

systolic and diastolic blood pressure was higher in the NWCO group than in the non-NWCO group (Ying-Xiu et al., 2014). Other studies have shown an association between NWCO and hypertension (Thaikruea & Thammasarot, 2016; Owolabi et al., 2017; Shirasawa et al., 2019).

Several potential mechanisms may explain the interaction between central obesity and development of hypertension. First, hypertension and obesity share hemodynamic patterns that may be linked to various mechanisms, including increased cardiac output, volume expansion, increase in systemic vascular resistance that is not reduced enough to counteract increased cardiac output, and stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone system. Second, fat cells produce adipokines that may contribute to the association between obesity and hypertension (Boutcher, 2014).

Relationship between NWCO and Cardiovascular Disease

Numerous studies have shown that NWCO is associated with CVD. Normal weight central obesity can represent a high body fat percentage and is predisposed to cardiac dysfunction, even when BMI is normal. The NWCO group faces an elevated risk of heart failure and atrial fibrillation compared to those without NWCO, with a higher incidence of heart failure (62,2 per 10.000 person-years) than individuals with normal weight and WC (48 per 10.000 person-years) (Ueno et al., 2022). Normal weight central obesity is associated with new-onset Coronary Heart Disease (CHD) and stroke (Z. Ren et al., 2022). Patients with a normal BMI but a high WHR are at the highest risk of coronary artery calcification (Lee et al., 2016). Patients with diabetes with NWCO have the highest risk of cardiovascular atherosclerosis after 10 years of follow-up (Zheng et al., 2023).

Visceral fat has a higher lipolytic activity than subcutaneous fat. An increased risk of CVD through the excessive release of free fatty acids (FFA) triggers insulin resistance, dyslipidemia, and modification of systemic lipid metabolism. In addition, disruption of molecules secreted by fat, that is, hormones (adiponectin, leptin, and resistin) and proinflammatory factors, such as C-Reactive Protein (CRP), Tumor Necrosis Factor (TNF)- α , interleukin (IL)-6, and IL-8, triggers oxidative stress and inflammation (D'Oria et al., 2022).

This condition contributes to prothrombosis of the cardiocerebrovascular smooth muscle and endothelium. Excessive subcutaneous fat deposition in vital organs such as the cerebral and cardiac arteries contributes to lipotoxicity and arteriosclerosis (Koliaki et al., 2019).

Relationship between NWCO and Diabetes Mellitus

Diabetes mellitus (DM) is closely related to various types of obesity, particularly central obesity. Visceral fat contributes to diabetes development because it releases fat into the liver, impacting the ability of insulin to transport blood sugar to the cells of the body for energy. Excessive visceral fat reduces insulin sensitivity and increases the risk of diabetes mellitus and other serious diseases (Boutcher 2014).

Normal weight central obesity is associated with DM and becomes stronger with increasing BMI (Qi et al., 2015). Based on nutritional status classification, NWCO with DM ranks second in prevalence for men (9,6%) and third for women (3,6%) (Shirasawa et al., 2019). A study in Thailand with a healthy worker population also reported an increased risk of DM associated with NWCO (Thaikruea & Thammasarot, 2016).

Elevated visceral fat levels promote inflammation by increasing the production of inflammatory cytokines and by decreasing the levels of protective adipokines and adiponectin. Chronic inflammation, driven by changes in adipokine secretion, can impair glucose tolerance and increase the risk of DM (Katsiki et al., 2018). The association between central obesity, glucose intolerance, and type 2 DM can be attributed to excessive glycerol from excess visceral fat and FFA, which reduces insulin extraction by the liver and increases hepatic glucose production (Shirasawa et al., 2019).

Relationship between NWCO and Metabolic Syndrome

General and central obesity lead to abnormalities in adipose tissue and cell dysfunction, resulting in abnormal levels of cytokines and other hormones that cause metabolic disorders. Metabolic syndrome is one of the factors directly associated with an increase in CHD and type 2 DM. The main causes of MS are insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension (Fahed et al., 2022).

Table 1. Study characteristics and results

Author	Methods	Results	Quality Assessment
Ren et al. (2023)	Study design: cross sectional Sample: 10,719 people aged ≥18 years Country: China Measurements: WC and WHR	The NWCO group has higher risk of hypertension than people with normal BMI without central obesity.	7
Owolabi et al. (2017)	Study design: cross sectional Sample: 998 people aged ≥18 years Country: South Africa Measurements: WC, WHR, and WHtR	Normal weight central obesity is associated with hypertension based on measurements with WHR and WHtR.	7
Ying-Xiu et al. (2014)	Study design: cross sectional Sample: 38,826 people aged 7-17 years Country: China Measurement: WC	Children and adolescents with NWCO have a greater chance of experiencing increased blood pressure.	5
Ueno et al. (2022)	Study design: cohort Sample: 1,687,903 people aged ≥ 20 years Country: Japan Measurement: WC	People with NWCO have a higher risk of heart failure and atrial fibrillation than non-NWCO people.	2.
Ren et al. (2022)	Study design: cohort Sample: 9,856 people aged ≥45 years Country: China Measurement: WC	Normal weight central obesity is related to the new onset of CHD and stroke events.	7
Lee et al. (2016)	Study design: cohort Sample: 1,078 people Country: Korea Measurement: WHR	Patients with normal BMI with high WHR are at the highest risk of coronary artery calcification compared to those with normal BMI with low WHR.	7
Zheng et al. (2023)	Study design: cohort Sample: 6,997 people Country: China Measurement: Visceral Fat Area (VFA)	Diabetic patients with NWCO have the highest risk of cardiovascular arteriosclerosis compared to overweight or obese patients but not central obesity.	7
Mendoza et al. (2022)	Study design: cross sectional Sample: 5,066 people aged ≥18 years Country: Panama Measurements: WC and WHtR	Normal weight central obesity increased cardiovascular risk factors, especially with increased triglyceride concentration.	7
Qi et al. (2015)	Study design: cross sectional Sample: 16,415 people aged 18-74 years Country: US Measurements: WC and WHR	Normal weight central obesity increased cardiovascular risk factors, especially with increased triglyceride concentration. is associated with DM and	7

Liu et al. (2017)	Study design: cross sectional Sample: 634 people postmenopause women Country: China Measurements: WC and WHtR	dyslipidemia in women and hypertension and dyslipidemia in men based on WC. Diabetes, hypertension, and dyslipidemia were linked with NWCO based on WHR. Normal weight central obesity is significantly associated with metabolic disorders; high triglycerides, blood pressure, blood glucose, low High Density Lipoprotein (HDL), and ≥ 2 non-adipose components.	7
Shirasawa et al. (2019)	Study design: cross sectional Sample: 117,163 people aged 40-64 years Country: Japan Measurements: WC and WHtR	The NWCO group had significantly more diabetes, dyslipidemia, and hypertension.	7
Thaikruea & Thammasarot (2016)	Study design: cross sectional Sample: 499 people Country: Thailand Measurements: WC and WHR	Health workers with NWCO were at greater risk of having at least one CHD factor associated with hypertension, DM, cholesterol, triglycerides, HDL, and Low Density Lipoprotein (LDL).	7
Shirasawa et al. (2020)	Study design: cross sectional Sample: 93,863 people aged 40-64 years Country: Japan Measurement: WHtR	Normal weight central obesity was significantly related to hyperuricemia and was not influenced by alcohol consumption status.	7

Individuals with normal BMI but abnormal WHR had substantially higher diastolic blood pressure (in men), LDL cholesterol (in men), triglyceride, two-hour blood sugar, and fasting insulin ($p < 0,05$) as well as lower HDL cholesterol ($p < 0,01$) than those with normal BMI and WHR (Qi et al., 2015). Children with NWCO also show significantly increased LDL, triglyceride, and insulin levels, and a risk of significantly lower HDL levels (Ying-Xiu et al. 2014). Normal weight central obesity is associated with hypertension, DM, insulin resistance, low HDL, and elevated triglycerides, indicating the importance of central obesity monitoring in individuals with a normal BMI (Song et al., 2019).

Ectopic fat accumulation is related to insulin resistance, which is a general factor in MS. Visceral fat accumulation leads to the

enlargement of fat cells that secrete pro-inflammatory biomarkers, including CRP, prostaglandins, and cytokines such as interleukin (IL), leptin, and TNF- α . Adipose tissue inflammation contributes to the development of type II DM, hyperlipidemia, and CVD. Excessive consumption of carbohydrate-rich foods results in postprandial hyperglycemia, which contributes to chronic inflammation, increases oxidative stress, and decreases metabolic flexibility, thereby maintaining MS (Paley & Johnson, 2018).

Relationship between NWCO and Dyslipidemia

Dyslipidemia is a quantitative change in total cholesterol concentration, its respective fractions, and triglycerides in the plasma. Dyslipidemia is one of the main risk factors of

atherosclerosis and CHD. Approximately 80% of lipid disorders are attributed to diet, lifestyle, or genetics. Dyslipidemia can be classified into high LDL, low HDL, hypertriglyceridemia, excess lipoprotein, mixed lipid disorders, and atherogenic dyslipidemia (Moini et al., 2020). Individuals with NWCO have a higher prevalence and risk of DM, hypertension, and dyslipidemia than those with a normal body weight (Shirasawa et al., 2019). In addition, people with normal BMI but abnormal WHR had higher LDL cholesterol (in men) and triglycerides, and lower HDL cholesterol ($p < 0,01$) than those with normal BMI and WHR (Qi et al., 2015).

Central obesity affects dyslipidemia by inhibiting fatty acid release from adipose tissue through lipolysis. This excess fatty acid load reaches the liver, leading to the synthesis of very-low-density lipoproteins and an increase in triglyceride production. Central obesity also affects apolipoprotein levels and reduces LDL receptor expression. The fat tissue acts as an endocrine gland, secreting various adipokines, such as adiponectin, IL-1, IL-6, TNF- α , and Serum Amyloid A along with an increased number of macrophages, all of which play a crucial role in dyslipidemia development (Lu et al., 2021).

Relationship between NWCO and Stroke

Stroke is a rapidly developing clinical sign of impaired brain function for more than 24 h, causing death (Aho et al., 1980). Stroke is the second leading cause of death and the largest cause of disability worldwide, affecting health costs (Katan & Luft, 2018). Approximately 30–50% of patients experience severe disabilities, leading to a high degree of dependence on others (Pesantes et al., 2017).

Several mechanisms have been proposed to explain the association between visceral fat and stroke. First, excess pro-inflammatory cytokines trigger oxidative stress and endothelial dysfunction. Second, visceral fat can promote insulin resistance, which causes endothelial damage and atherosclerosis. Third, visceral fat accumulation disrupts the balance between leptin and adiponectin expression levels. Increased leptin levels cause arterial stiffness, and decreased adiponectin levels increase the risk of stroke via oxidative stress and endothelial injury. Fourth, accumulated visceral fat can produce excess oxidized LDL,

which plays an important role in atherosclerosis (Zhang et al. 2023).

Relationship between NWCO and Hyperuricemia

Hyperuricemia is characterized by elevated uric acid levels in the blood, with a normal limit set at 6,8 mg/dl and levels exceeding 7 mg/dl are considered saturated, potentially leading to symptoms. Increased uric acid levels can result from enhanced production, reduced uric acid excretion, or both. Hyperuricemia is associated with gout and nephrolithiasis, which are indicators of comorbid diseases such as MS (George and Minter, 2023). Studies on the association between NWCO and hyperuricemia are limited, with only one article on this topic.

In another central obesity study, Shirasawa et al. reported that NWCO was associated with an increased risk of hyperuricemia (Shirasawa et al., 2020). A study in Korea also found a positive association between central obesity and hyperuricemia, with the risk of hyperuricemia increasing with increasing BMI and WC (Bae et al., 2023).

Visceral fat increases the risk of hyperuricemia, which is related to the dysfunction of visceral fat, such as in the liver and kidneys, causing excessive uric acid production or impaired excretion. The amount of perirenal fat can increase the serum uric acid levels. Thickening of the perirenal fat causes dysfunction of the glomerular filtration rate, which causes uric acid accumulation (Hang et al., 2023).

This study provides knowledge and awareness for maintaining health by focusing on body weight and waist circumference to prevent comorbid diseases. The NWCO group is important to pay attention because the rate of central obesity continues to increase and is very common in society; therefore, health risks are clinically assessed (Jin et al., 2023). Our findings also show that NWCO is strongly associated with comorbid diseases, especially CVD.

The NWCO group is important for lifestyle modification and other preventive strategies. Lifestyle modification by improving diet and regular physical activity to reduce waist circumference and increase metabolism. Routine and comprehensive health screening for the early detection of potential comorbid diseases and immediate intervention.

The strength of this research lies in it being the first systematic review to explore the impact of NWCO on comorbid diseases. These results provide comprehensive information regarding NWCO and comorbid diseases. However, this study has several limitations. First, it only used three databases and specified inclusion criteria, thereby reducing the scope of relevant literature and thus having the potential for evidence selection bias. Second, the inclusion criteria were too general and did not consider other factors that influence the relationship between NWCO and comorbid diseases. Fourth, variations in anthropometric measurement methods between studies could have influenced the results. NWCO research must progress given its importance in preventing various comorbidities and mortality. Furthermore, conducting a meta-analysis of NWCO studies is beneficial.

Conclusion

This systematic review reports that NWCO conditions increase the risk of comorbid diseases, such as hypertension, CVD, DM, MS, dyslipidemia, stroke, and hyperuricemia. Hypertension, MS, and dyslipidemia can explain their roles in CVD and DM in greater detail.

By understanding its pathophysiology, early intervention can be performed to prevent worse conditions. More attention is needed from health workers and the community to carry out regular and detailed health screening, and to pay more attention to the NWCO group as a form of preventive effort.

Acknowledgments

The authors thank Universitas Indonesia for their academic support and everyone who helped with this study.

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